2,6-DIAMINO-PYRIMIDIN-5-YL-CARBOXAMIDES AS SYK OR JAK KINASES INHIBITORS

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application is claims the benefit of U.S. Provisional Patent Application No. 61/120,348, filed December 5, 2008; U.S. Provisional Patent Application No. 61/120,346, filed December 5, 2008; U.S. Provisional Patent Application No. 61/045,406, filed April 16, 2008; and U.S. Provisional Patent Application No. 61/045,499, filed April 16, 2008; the entire disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] This invention is directed to pyrimidine-5-carboxamide compounds which act as inhibitors of Spleen tyrosine kinase (syk) and/or `JAK kinases. This invention is also directed to pharmaceutical compositions containing the pyrimidine-5-carboxamide compounds and methods of using the compounds or compositions to treat a condition characterized by other indications. The invention is also directed to methods of making the compounds described herein.

State of the Art

[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within cells (see, e.g., Hardie and Hanks, The Protein Kinase Facts Book, I and II, Academic Press, San Diego, Calif., 1995). Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases can be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these families (see, e.g., Hanks & Hunter, (1995), FASEB J. 9:576-596; Knighton et al., (1991), Science 253:407-414; Hiles et al., (1992), Cell 70:419-429; Kunz et al., (1993), Cell 73:585-596; Garcia-Bustos et al., (1994), EMBO J. 13:2352-2361).

[0004] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies, asthma, alzheimer's disease and hormone-related diseases. As a consequence, there has been substantial efforts in medicinal chemistry to find inhibitors of protein kinases for use as therapeutic agents.

[0005] Immunoreceptor tyrosine activation motif (ITAM)-mediated signaling has emerged as a primary event in signaling pathways responsible for human pathologies. ITAM-mediated signaling is responsible for relaying activation signals initiated at classical immune receptors such as T-cell receptors, B-cell receptors, Fc receptors in immune cells and at GPVI and FcγRIIa in platelets to downstream intracellular molecules such as syk and ZAP-70 (Underhill, D.M and Goodridge, H. S., *Trends Immunol.*, 28:66-73, 2007).

[0006] The binding of a ligand to an ITAM-containing receptor triggers signaling events which allows for the recruitment of proteins from a family of nonreceptor tyrosine kinases called the Src family. These kinases phosphorylate tyrosine residues within the ITAM sequence, a region with which the tandem SH2 domains on either syk or ZAP-70 interact.

[0007] Syk, along with Zap-70, is a member of the syk family of protein tyrosine kinases. The interaction of syk or ZAP-70 with diphosphorylated ITAM sequences induces a conformation change in the kinases that allows for tyrosine phosphorylation of the kinase itself. Phosphorylated Syk family members activate a multitude of downstream signaling pathway proteins which include Src homology 2 (SH2) domain containing leukocyte-specific phosphoprotein of 76 kDa (SLP-76), Linker of Activation of T-cells (LAT) and PLC (phospholipase C)γ2.

[0008] Human pathologies attributed to dysfunctional ITAM-mediated signaling include autoimmune diseases such as rheumatoid arthritis, systemic lupus, multiple sclerosis, hemolytic anemia, immune-thrombocytopenia purpura, and heparin-induced thrombocytopenia and arteriosclerosis. Interestingly, many of the above mentioned diseases are thought to occur through crosslinking of Fc receptors by antibodies which, via syk, activate a signaling cascade in mast, basophil and other immune cells that result in the release of cell mediators responsible for inflammatory reactions. The release of mediators and the production of cytokines in IgE stimulation-dependent allergic and inflammatory reactions from mast cells and basophiles can be controlled by inhibiting the tyrosine kinase activity of syk (Rossi, A.B. et al., *J Allergy Clin Immunol.*, 118:749-755, 2006). In immune-thrombocytopenia, antibody bound platelets are cleared by the spleen by an Fc receptor/ITAM/syk-mediated process (Crow, A.R. et al., *Blood*, 106:abstract 2165, 2005). Drug-induced thrombocytopenia, caused by heparin- platelet factor 4 immune complexes that activate platelet FcγRIIa, also involve syk signaling downstream of receptor engagement (Reilly, M.P., *Blood*, 98:2442-2447, 2001).

[0009] Platelet agonists induce inside-out integrin signaling resulting in fibrinogen binding and platelet aggregation. This initiates outside-in signaling which produces further stimulation of platelets. syk is activated during both phases of integrin signaling, and inhibition of syk is shown to inhibit platelet adhesion to immobilized proteins (Law, D.A. et al., *Blood*, 93:2645-2652, 1999). Release of arachidonic acid and serotonin and platelet aggregation induced by collagen are markedly inhibited in platelets derived from syk deficient mouse (Poole, A. et al., *EMBO J.*, 16:2333-2341, 1997). Thus syk inhibitors may also possess anticoagulation action.

[0010] Because of the role syk plays in Ig-induced platelet activations, it is likely to be important in arteriosclerosis and restenosis. Arteriosclerosis is a class of diseases characterized by the thickening and hardening of the arterial walls of blood vessels. Although all blood vessels are susceptible to this serious degenerative condition, the aorta and the coronary arteries serving the heart are most often affected. Arteriosclerosis is of profound clinical importance since it can increase the risk of heart attacks, myocardial infarctions, strokes, and aneurysms.

[0011] The traditional treatment for arteriosclerosis includes vascular recanalization procedures for less-serious blockages and coronary bypass surgery for major blockages. A serious shortcoming of intravascular procedures is that, in a significant number of treated individuals, some or all of the treated vessels restenose (*i.e.*, re-narrow). For example, restenosis of an atherosclerotic coronary artery after PTCA occurs in 10-50% of patients undergoing this procedure and subsequently requires either further angioplasty or a coronary artery bypass graft. Furthermore, restenosis of an atherosclerotic coronary artery after stenting occurs in 10-20% of patients undergoing this procedure and subsequently requires repeat treatments to maintain adequate blood flow through the affected artery. Restenosis generally occurs in a relatively brief time period, *e.g.*, roughly less than six months, after treatment.

[0012] While the exact hormonal and cellular processes promoting restenosis have not been determined, restenosis is thought to be due in part to mechanical injury to the walls of the blood vessels caused by the balloon catheter or other intravascular device. For example, the process of PTCA, in addition to opening the obstructed artery, also injures resident coronary arterial smooth muscle cells (SMCs). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells themselves release cell-

derived growth factors such as platelet-derived growth factor (PDGF), with subsequent proliferation and migration of medial SMCs through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMCs and, most significantly, production of large amounts of extracellular matrix over a period of three to six months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct blood flow.

[0013] In addition to the role syk plays in Ig-induced platelet activations, syk plays a very important role in collagen-mediated signaling. The primary adhesive protein responsible for platelet adhesion and activation is collagen. Collagen is a filamentous protein contained within the fibrotic caps of atheromas which becomes exposed to blood during plaque rupture. Collagen functions initially by binding von Willebrand factor which tethers platelets through binding platelet membrane GPIb. Collagen functions secondarily by engaging the two collagen receptors on platelets, GPVI and integrin $\alpha 2\beta 1$.

[0014] GPVI exists in platelet membranes as a complex with FcRγ, an interaction required for the expression of GPVI. Activation of FcγRIIa on platelets results in platelet shape change, secretion and thrombosis. Signaling by the GPVI/FcRγ complex is initiated by tyrosine phosphorylation of the ITAM domain of FCRγ followed by the recruitment of syk. Activation of GPVI leads to induction of multiple platelet functions including: activation of integrins $\alpha 2\beta 1$ to achieve firm platelet adhesion, and GP IIb-IIIa which mediates platelet aggregation and thrombosis growth; platelet secretion, allowing for the delivery of inflammatory proteins such as CD40L, RANTES and TGFβ to the vessel wall; and the expression of P-selectin which allows for the recruitment of leukocytes. Therefore, it is believed that syk inhibitors can inhibit thrombotic events mediated by platelet adhesion, activation and aggregation.

[0015] It has been reported that the tyrosine phosphorylation of intracellular protein (activation) induced by stimulation of a receptor for IgG antibody, FcγR, and the phagocytosis mediated by FcγR are considerably inhibited in macrophages derived from syk deficient mouse (Crowley, M.T. et al., *J. Exp. Med.*, 186:1027-1039, 1997). This suggests that syk has a markedly important role in the FcγR-mediated phagocytosis of macrophages.

[0016] It has also been reported that an antisense oligonucleotide of syk suppresses the apoptosis inhibition of eosinophils induced by GM-CSF (Yousefi, S. et al., *J. E. Med.*, 183:1407-1414, 1996), showing that syk is essential for the life extending signal of

eosinophils caused by GM-CSF and the like. Since life extension of eosinophils is closely related to the transition of diseases into a chronic state in allergic disorders, such as asthma, syk inhibitors can also serve as therapeutic agents for chronic eosinophilic inflammation.

[0017] Syk is important for the activation of B-cells via a B-cell antigen receptor and is involved in the phosphatidylinositol metabolism and increase in the intracellular calcium concentration caused by the antigen receptor stimulation (Hutchcroft, J E. et al., *J. Biol. Chem.*, 267:8613-8619, 1992; and Takata, M. et al., *EMBO J.*, 13:1341-1349, 1994). Thus, syk inhibitors may be used to control the function of B-cells and are, therefore, expected to serve as therapeutic agents for antibody-related diseases.

[0018] Syk binds to a T-cell antigen receptor, quickly undergoes tyrosine phosphorylation through crosslinking of the receptor and synergistically acts upon intracellular signals mediated by Src tyrosine kinases such as Lck (Couture, C. et al., *Proc. Natl. Acad. Sci. USA,* 91:5301-5305, 1994; and Couture, C. et al., *Mol. Cell. Biol.,* 14:5249-5258, 1994). syk is present in mature T-cell populations, such as intraepithelial γδ T-cells and naïve αβ T-cells, and has been reported to be capable of phosphorylation of multiple components of the TCR signaling cascade (Latour, S. et. al., *Mol Cell Biol.*, 17:4434-4441, 1997). As a consequence, syk inhibitors may serve as agents for inhibiting cellular immunity mediated by T-cell antigen receptor.

[0019] Recent comparative genomic hybridization studies have identified syk as another gene important in the pathogenesis of Mantle Cell Lymphoma (MCL) (Chen, R. et al. *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition).Vol 25, No 18S (June 20 Supplement), 2007: 8056). MCL represents 5–10% of all non-Hodgkins lymphomas and it is a difficult form of lymphoma to treat. It has the worst prognosis among the B cell lymphomas with median survival of three years. It has been reported that Syk is overexpressed in MCL (Rinaldi, A, et.al, *Br. J. Haematol.*, 2006; 132:303–316) and that Syk mediates mTOR (mammalian target of Rapamycin) survival signals in follicular, mantel cell, Burkitt's, and diffuse large B-cell non-Hodgkin's lymphomas (Leseux, L., et. al, Blood, 2006; 108:4156-4162).

[0020] Several lines of evidence suggest that many B-cell lymphomas depend upon B-cell receptor (BCR)-mediated survival signals. BCR signaling induces receptor oligomerization and phosphorylation of Igα and β immunoreceptor tyrosine-based activated motifs by SRC family kinases. ITAM phosphorylation results in the recruitment and activation of syk that

initiates downstream events and amplifies the original BCR signal. Given the role of tonic BCR signaling in normal B cell and syk-dependent survival of non-Hodgkins lymphoma cell lines in vitro (Chen, L., et.al, *Blood*, 2006; 108:3428–3433), syk inhibition is a promising rational treatment target for certain B-cell lymphomas and chronic lymphocytic leukemia (CLL) (Stefania Gobessi, Luca Laurenti, Pablo Longo, Laura Carsetti, Giuseppe Leone, Dimitar G. Efremov, Constitutive activation of the protein tyrosine kinase Syk in Chronic Lymphocytic Leukemia B-cells, Blood, 2007, 110, Abstract 1123). Recent data shows that administration of a multikinase inhibitor which inhibits syk, may have significant clinical activity in CLL patients (Friedberg JW et al, *Blood* 2008; 112(11), Abstract 3).

[0021] The oncogenic potential of the spleen tyrosine kinase (Syk) has been described in a number of different settings. Clinically, Syk over-expression is reported in Mantle Cell Lymphoma (Rinaldi, A, et.al, *Br. J. Haematol.*, 2006; 132:303–316) and the TEL-Syk fusion protein (Translocated ETS Leukemia) generated by a chromosomal translocation (t(9;12)(q22;p12)) leads to increased Syk activity and is associated with myelodysplastic syndrome (Kuno, Y., et.al, *Blood*, 2001; 97:1050–1055). Leukemia is induced in mice by adoptively transferring bone marrow cells that express human TEL-Syk (Wossning, T., JEM, 2006; 203:2829-2840). Further, in mouse primary bone marrow cells, over-expression of Syk results in IL-7 independent growth in culture (Wossning, T., et.al, JEM, 2006; 203:2829-2840).

[0022] Interestingly, Syk signaling appears to be required for B-cell development and survival in humans and mouse. Inducible loss of the B-cell receptor (Lam, K., et.al, Cell, 1997; 90:1073-1083) or Igα (Kraus, M., et.al, Cell, 2004; 117:787-800) results in loss of peripheral B-cells in mice. Over-expression of the protein tyrosine phosphatase PTP-RO, which is known to negatively regulate Syk activity, inhibits proliferation and induces apoptosis in cell lines derived from non-Hodgkin's lymphomas (Chen, L., et.al, *Blood*, 2006; 108:3428–3433). Finally, B-cell lymphomas rarely exhibit loss of BCR expression, and anti-idiotype therapy rarely leads to resistance (Kuppers, R. Nat Rev Cancer, 2005; 5:251-262).

[0023] Engagement of the antigen-specific B cell receptor (BCR) activates multiple signaling pathways that ultimately regulate the cells activation status, promoting survival and clonal expansion. Signaling through the BCR is made possible by its association with two other members of the immunoglobulin super-family; Igα and Igβ, each bearing an immuno-tyrosine based activation motif (ITAM) (Jumaa, Hendriks et al. Annu Rev Immunol 23: 415-

45 (2005). The ITAM domain is directly phosphorylated by Src family kinases in response to BCR engagement. The spleen tyrosine kinase (Syk) docks with and phosphorylates the ITAM, a process that enhances its kinase activity, resulting in Syk autophosphorylation and tyrosine phosphorylation of multiple downstream substrates (Rolli, Gallwitz et al. Mol Cell 10(5): 1057-69 (2002). This signaling pathway is active in B cells beginning at the transition from pro- to pre-B cell stage of development, when the newly formed pre-BCR is expressed. In fact, B cell development arrests at the pro-B cell stage in Syk knockout mice (Cheng, Rowley et al. 1995; Turner, Mee et al. Nature 378(6554): 303-6 (1995). Inducible loss of the B cell receptor (Lam, Kuhn et al. Cell 90(6): 1073-83 (1997) or Igα (Kraus, Alimzhanov et al. Cell 117(6): 787-800 (2004) results in loss of peripheral B cells in mice. Human B cells also appear to require Syk for proliferation and survival. Over-expression of the protein tyrosine phosphatase PTP-RO, a negative regulator of Syk activity, inhibits proliferation and induces apoptosis in cell lines derived from non-Hodgkin's lymphomas (NHL) (Chen, Juszczynski et al. Blood 108(10): 3428-33 (2006). Knock down of Syk by siRNA in the NHL line SUDHL-4 led to a block in the G1/S transition of the cell cycle (Gururajan, Dasu et al. J Immunol 178(1): 111-21 (2007). Together, these data suggest that Syk signaling is required for the development, proliferation, and even survival of human and mouse B cells.

[0024] Conversely, the oncogenic potential of Syk has been described in a number of different settings. Clinically, Syk over-expression is reported in Mantle Cell Lymphoma (Rinaldi, Kwee et al. Br J Haematol 132(3): 303-16 (2006) and the TEL-Syk fusion protein (Translocated ETS Leukemia) generated by a chromosomal translocation (t(9;12)(q22;p12)) leads to increased Syk activity and is associated with myelodysplastic syndrome (Kuno, Abe et al. Blood 97(4): 1050-5 (2001). Leukemia is induced in mice by the adoptive transfer of bone marrow cells that express human TEL-Syk (Wossning, Herzog et al. J Exp Med 203(13): 2829-40 (2006). Further, in mouse primary bone marrow cells, over-expression of Syk results in IL-7 independent growth in culture (Wossning, Herzog et al. 2006). Consistently, Syk was reported to mediate mTOR (mammalian target of Rapamycin) survival signals in follicular, mantle cell, Burkitt's, and diffuse large B-cell NHL (Leseux, Hamdi et al. Blood 108(13): 4156-62 (2006). Additional recent studies also suggest that Syk-dependant survival signals may play a role in B-cell malignancies, including DLBCL, mantle cell lymphoma and follicular lymphoma (Gururajan, Jennings et al. 2006; Irish, Czerwinski et al. J Immunol 176(10): 5715-9 (2006). Given the role of tonic BCR signaling in normal B

cells and Syk-dependent survival of NHL cell lines in vitro, the specific inhibition of Syk may prove promising for the treatment of certain B-cell lymphomas.

[0025] Recently, R406 (Rigel Pharmaceuticals) was reported to inhibit ITAM signaling in response to various stimuli, including FcεR1 and BCR induced Syk activation (Braselmann, Taylor et al. J Pharmacol Exp Ther 319(3): 998-1008(2006). Interestingly, this ATP-competitive inhibitor of Syk was also active against Flt3, cKit, and JAK kinases, but not against Src kinsase (Braselmann, Taylor et al. 2006). Activating mutations to Flt3 are associated with AML and inhibition of this kinase is currently under clinical development (Burnett and Knapper Hematology Am Soc Hematol Educ Program 2007: 429-34 (2007). Over-activation of the tyrosine kinase cKit is also associated with hematologic malignancies, and a target for cancer therapy (Heinrich, Griffith et al. Blood 96(3): 925-32 (2000). Similarly, JAK3 signaling is implicated in leukemias and lymphomas, and is currently exploited as a potential therapeutic target (Heinrich, Griffith et al. 2000). Importantly, the multi-kinase inhibitory activity of R406 attenuates BCR signaling in lymphoma cell lines and primary human lymphoma samples, resulting in apoptosis of the former (Chen, Monti et al. Blood 111(4): 2230-7 (2008). Further, a phase II clinical trial reported favorable results by this compound in refractory NHL and chronic lymphocytic leukemia (Friedberg JW et al, *Blood* 2008; 112(11), Abstract 3). Although the precise mechanism of action is unclear for R406, the data suggest that inhibition of kinases that mediate survival signaling in lymphocytes is clinically beneficial.

[0026] Additional recent studies also suggest that syk-dependant survival signals may play a role in B-cell malignancies, including DLBCL, mantle cell lymphoma and follicular lymphoma (see e.g., S. Linfengshen et al. *Blood*, Feb. 2008; 111: 2230-2237; J. M. Irish et al. *Blood*, 2006; 108: 3135-3142; A. Renaldi et al. *Brit J. Haematology*, 2006; 132: 303-316; M. Guruoajan et al. *J. Immunol*, 2006; 176: 5715-5719; L. Laseux et al. *Blood*, 2006; 108: 4156-4162.

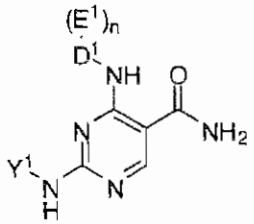
[0027] Patents and patent applications describing substituted pyrimidinediamine compounds include: U.S. application Ser. No. 10/355,543 filed Jan. 31, 2003 (US2004/0029902A1), international application Serial No. PCT/US03/03022 filed Jan. 31, 2003 (WO 03/063794), U.S. application Ser. No. 10/631,029 filed Jul. 29, 2003, international application Serial No. PCT/US03/24087 (WO 04/014382), U.S. application Ser. No. 10/903,263 filed Jul. 30, 2004, and international application Serial No. PCT/US2004/24716

(WO 05/016893), the disclosures of which are incorporated herein by reference. Substituted pyrimidinediamine compounds are also described in international patent application publication numbers: WO 02/059110, WO 03/074515, WO 03/106416, WO 03/066601, WO 03/063794, WO 04/046118, WO 05/016894, WO 05/122294, WO 05/066156, WO 03/002542, WO 03/030909, WO 00/39101, WO 05/037800 and U.S. Pat. Pub. No. 2003/0149064.

[0028] While progress has been made in this field, there remains a need in the art for compounds that inhibit syk kinase, as well as for methods for treating conditions in a patient, such as restenosis, thrombosis, and/or inflammation that can benefit from such inhibition. Moreover, the availability of compounds that selectively inhibit one of these kinases as compared to other kinases would also be desirable. The present invention satisfies this and other needs.

BRIEF SUMMARY OF THE INVENTION

[0029] The present invention provides novel compounds having activity as inhibitors of syk activity (also referred to herein as "syk inhibitors") kinase activity (also referred to herein as "JAK inhibitors"), as well as to methods for their preparation and use, and to pharmaceutical compositions containing the same. Such compounds have the following structure (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein D^1, E^1 and Y^1 are as defined below.

[0030] The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I, or a pharmaceutical acceptable salt thereof, and a pharmaceutically acceptable carrier and/or diluent.

[0031] The compounds of the present invention have utility over a wide range of therapeutic applications, and may be used to treat a variety of conditions, mediated at least in

part by syk activity, in both men and women, as well as a mammal in general (also referred to herein as a "subject"). For example, such conditions include, but are not limited to, those associated with cardiovascular disease, inflammatory disease or autoimmune disease. More specifically, the compounds of the present invention have utility for treating conditions or disorders including, but not limited to: restenosis, thrombosis, inflammation, heparin induced thrombocytopenia, dilated cardiomyopathy, sickle cell disease, atherosclerosis, myocardial infarction, vascular inflammation, unstable angina, acute coronary syndromes, allergy, asthma, rheumatoid arthritis, B-cell mediated diseases such as Non Hodgkin's lymphoma, anti-phospholipid syndrome, lupus, psoriasis, multiple sclerosis, end stage renal disease, hemolytic anemia, immune thrombocytopenic purpura, and chronic lymphocytic leukemia. Thus, in one embodiment, methods are disclosed which include the administration of an effective amount of a compound of formula (I), typically in the form of a pharmaceutical composition, to a subject in need thereof.

[0032] The conditions associated with cardiovascular disease is selected from the group consisting of acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombosis occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolism, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

[0033] The present invention also provides a method for inhibiting the syk kinase activity of a blood sample comprising contacting said sample with a compound of the present invention.

[0034] The present invention further provides compounds in purified forms, as well as chemical intermediates.

[0035] These and other aspects, objects, features and advantages of the invention will be apparent upon reference to the following detailed description and figures. To this end, various references are set forth herein which describe in more detail certain background

information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] **Figure 1** shows how Syk serves as a key mediator of Fc receptor mediated signaling in cellular biology and multiple diseases.

[0037] **Figure 2** shows how gene targeting of Syk indicated that Syk serves as a key mediator in arterial platelet biology and a selective target for treating arterial thrombosis.

[0038] **Figure 3** shows a general synthesis of compounds of the present invention.

[0039] **Figures 4A, B** and **C** provides tables 2A, B and C illustrating compounds of the present invention and syk IC_{50}s.

[0040] **Figure 5** provides table 3 illustrating compounds of the present invention and syk IC_{50}s.

[0041] **Figure 6** provides table 4 illustrating compounds of the present invention and syk IC_{50}s.

[0042] **Figure 7A and 7 B** provide table 5 A and B illustrating compounds of the present invention and syk IC_{50}s.

[0043] **Figure 8** shows a series of compounds that were identified to selectively inhibit Syk in purified kinase assays. **Figure 8A**) Compounds (example 596 and example 87 and P420-89) were screened at 300nM against the Millipore purified kinase panel (270 kinases tested with 10μM ATP) to determine potency and selectivity for Syk. Data are represented as a heat-map, defined at the bottom. **Figure 8B**) Subset of the purified kinases that had >80% inhibition by any of the three compounds. example 596 only inhibited Syk and MLK1. example 87 at 50nM (~10x greater than its Syk IC50) only inhibited Syk. P420-89 inhibited multiple kinases, including Syk, JAK2 and JAK3. The IC50 of Syk inhibition is reported for each compound on the left of the heat map. Percent kinase inhibition is given in each panel within the heat-map.

[0044] **Figure 9** shows the selective inhibition of Syk in non-Hodgkin's Lymphoma cell lines. B cells were stimulated with anti-BCR antibody in the presence of the indicated

concentrations of Syk specific inhibitors example 596 and example 87 (**Figure 9A** and **Figure 10B**) or the dual Syk/JAK inhibitor P420-89 (**Figure 9C**). Western blot analyses of whole cell lysates were then performed to evaluate Syk kinase activity (pBLNK Y84 and total BLNK; top two gels) and Src kinase activity (pSyk Y352 and total Syk; bottom two gels). Experiments were performed 2-3 times each, bar graphs represent mean ± S.D. of pBLNK Y84. The calculated IC50s of Syk kinase inhibition are presented above the graphs.

[0045] **Figure 11** provides a comparison of Syk-Specific and Dual Syk/JAK Inhibition in NHL Cell Lines. B cells were stimulated with anti-BCR (**Figure 11A**), or IL-4 (**Figure 11B**) for 15min in the presence of various concentrations of each inhibitor, as indicated. Cells were then evaluated for inhibition of signaling pathways by phospho-flow cytometry. **Figure 11A**) bar graphs (mean ± S.D., n=3) representing Src activity (pSyk Y352 MFI) and Syk activity (pERK Y204 MFI) following BCR stimulation under the various treatment conditions. **Figure 11B**) Bar graphs depicting pSTAT-6 Y641 MFI (mean ± S.D., n=3) following stimulation with IL-4 in the presence of various concentrations of each inhibitor, as indicated.

[0046] **Figure 12** shows how Syk-specific inhibitors disrupt proliferation and survival of and induces apoptosis in NHL cell lines . The Syk-dependent "BCR type" and Syk-independent "non-BCR type" NHL cell lines were previously described (Polo, Juszczynski et al. Proc Natl Acad Sci U S A 104(9): 3207-12 (2007). **Figure 12A**) Cells were treated for 72h with 1 and 3μM of the Syk-specific inhibitor example 87. Apoptosis was determined by FACS analysis of active caspase 3; data is represented as histograms. **Figure 12B**) Additional cell lines were tested for sensitivity to Syk specific (example 596 and example 87) versus dual Syk/JAK (P420-89) inhibition. Bar graphs represent mean ± S.D. (n=3) of the percent of caspase 3 positive cells following each condition.

[0047] **Figure 13** shows how selective inhibition of Syk prevents BCR-induced activation of mouse primary B cells. **Figure 13** provides a comparison of Syk-Specific and Dual Syk/JAK Inhibition in NHL Cell Lines. B cells were stimulated with anti-BCR (**Figure 13C**) for 15min in the presence of various concentrations of each inhibitor, as indicated. Cells were then evaluated for inhibition of signaling pathways by phospho-flow cytometry. **Figure 13C**) Flow cytometry plots (mean ± S.D., n=3) representing Src activity (pSyk Y352 MFI) and Syk activity (pERK Y204 MFI) following BCR stimulation under the various treatment conditions.

[0048] **Figure 14** shows the efficacy in a mouse arthritis model by specific inhibition of Syk

[0049] **Figure 15** shows how the histopathology in a mouse model confirms the clinical score for a Syk specific inhibitor.

[0050] **Figure 16** shows the dose dependent effect of inhibition of Syk/JAK in a Mouse Arthritis Model:

[0051] **Figure 17** provides a mouse immune thrombocytopenia model

[0052] **Figure 18** shows how Syk Inhibition prevents NHL tumor formation in a xenograft mouse model with a NHL cell line. Selective Syk inhibitor example 87 prevents tumor formation. Syk inhibition prevents NHL tumor formation in xenograft mice. Mice were dosed twice daily with 10, 15, or 20mg/kg example 87 or vehicle control beginning the day of tumor cell inoculation. A) Tumor weights were determined at 4 weeks post-inoculation for each treatment condition. Statistical differences relative to vehicle control are depicted as P values within the graph. B) Bar graphs depict normal blood cell counts (mean ± S.D., n=13 to15) of mice treated with each concentration of example 87 or vehicle control.

DETAILED DESCRIPTION OF THE INVENTION

[0053] As used herein, the below terms have the following meanings unless specified otherwise:

1. Abbreviations and Definitions

[0054] The abbreviations used herein are conventional, unless otherwise defined. The following abbreviations are used: AcOH = acetic acid, AIBN = azobisisobutyronitrile (also azobisisobutylonitrile), aq. = aqueous, Boc = t-butylcarboxy, Bz - benzyl, BOP = benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate, BPO = benzoyl peroxide, nBuOH = n-butanol, CBr_4 = tetrabromomethane, mCPBA = m-chloroperoxybenzoic acid, CH_2Cl_2 or DCM = dichloromethane, Cs_2CO_3 = cesium carbonate, $CuCl_2$ = copper chloride; DPPA = diphenyl phosphoryl azide; DIBAL = diisobutylaluminum hydride, DIEA = Hunig's base or diisopropyl ethylamine, DME = dimethyl ether, DMF = dimethyl formamide, DMSO = dimethyl sulfoxide, Et_3N =

triethylamine, EtOAc = ethyl acetate, g = gram, HATU = 2-(1H 7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, H_2 = hydrogen; H_2O = water; HBr = hydrogen bromide; HCl = hydrogen chloride, HIV = human immunodeficiency virus, HPLC = high pressure liquid chromatography, h = hour, IgE = immunoglobulin E, IC_{50} = The concentration of an inhibitor that is required for 50% inhibition of an enzyme in vitro, IPA = isopropyl alcohol, kg = kilogram, KCN = potassium cyanide, KOH = potassium hydroxide, K_2PO_4 = potassium phosphate, LDA = lithium diisopropylamine, $LiAlH_4$ = lithium aluminum hydride = LiOH: lithium hydroxide; MeCN = acetonitrile; MS = Mass Spec, m/z = mass to charge ratio, MHz = Mega Hertz, MeOH = methanol, μM = micromolar, μL = microliter, mg = milligram, mm = millimeter, mM = millimolar, mmol = millimole, mL = milliliter, mOD/min = millioptical density units per minute, min = minute, M = molar, Na_2CO_3 = sodium carbonate, ng = nanogram, $NaHCO_3$ = sodium bicarbonate; $NaNO_2$ = sodium nitrite; NaOH = sodium hydroxide; $Na_2S_2O_3$ = sodium bisulfate; Na_2SO_4 = sodium sulfate; NBS = N-bromosuccinamide; NH_4Cl = ammonium chloride; NH_4OAc = ammonium acetate; NaSMe = sodium methylthiolate, NBS = N-bromosuccinamide, n-BuLi = n-butyl lithium, nm = nanometer, nM = nanomolar, N = Normal, NMP = N-methylpyrrolidine, NMR = nuclear magnetic resonance, Pd/C = palladium on carbon, $Pd(PPh_3)_4$ = Tetrakis-(triphenyl-phosphine)-palladium, pM = picomolar, Pin = pinacolato, PEG = polyethylene glycol, PPh_3 or Ph_3P = triphenyl phosphine, RLV = Raucher leukemia virus, Ra-Ni = Rainey Nickel, $SOCl_2$ = thionyl chloride, RT = room temperature, TEA = triethylamine, THF = tetrahydrofuran, TFA = trifluoroacetic acid, TLC = thin layer chromatography, TMS = trimethylsilyl, Tf = trifluoromethylsulfonyl and TSC = trisodium citrate.

[0055] It is noted here that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0056] "Alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, fully saturated aliphatic hydrocarbon radical having the number of carbon atoms designated. For example, "C_{1-8}alkyl" refers to a hydrocarbon radical straight or branched, containing from 1 to 8 carbon atoms that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. The phrase "unsubstituted alkyl" refers to alkyl groups that do not contain groups other than fully saturated aliphatic hydrocarbon radicals. Thus the phrase includes straight chain alkyl groups such as methyl,

ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups such as isopropyl, t-butyl, isobutyl, sec-butyl, and the like. Representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. Further representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms.

[0057] "Alkenyl" by itself or as part of another substituent refers to a straight or branched chain, which may be mono- or polyunsaturated, having the number of carbon atoms designated. For example, "C_2–C_8 alkenyl" means an alkenyl radical having from 2, 3, 4, 5, 6, 7 or 8 atoms that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Examples include, but are not limited to vinyl, 2-propenyl i.e. –$CH=C(H)(CH_3)$, –$CH=C(CH_3)_2$, –$C(CH_3)=C(H)_2$, –$C(CH_3)=C(H)(CH_3)$, -$C(CH_2CH_3)=CH_2$, butadienyl e.g. 2-(butadienyl), pentadienyl e.g. 2,4-pentadienyl and 3-(1,4-pentadienyl), and hexadienyl, among others, and higher homologs and stereoisomers thereof. A "substituted" alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon. Each site of unsaturation may be either cis or trans configuration about the double bond(s).

[0058] The term "alkynyl", by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical, which may be mono- or polyunsaturated, having the number of carbon atoms designated. For example, "C_2–C_8 alkynyl" means an alkynyl radical having from 2 to 8 carbon atoms that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. "Unsubstituted alkynyl" refers to straight and branched chain groups such as those described with respect to unsubstituted alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Examples include, but are not limited to ethynyl e.g. -C≡C(H), 1- propynyl e.g. –$C{\equiv}C(CH_3)$, –$C{\equiv}C(CH_2CH_3)$, –$C(H_2)C{\equiv}C(H)$, –$C(H)_2C{\equiv}C(CH_3)$, and -$C(H)_2C{\equiv}C(CH_2CH_3)$ among others, and higher homologs and isomers thereof. A "substituted" alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

[0059] "Alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -$CH_2CH_2CH_2CH_2$-. Typically, an alkylene group will have from 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyl.

[0060] "Cycloalkyl" or "carbocycle", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl", "alkenyl" and "alkynyl" in which all ring atoms are carbon. "Cycloalkyl" or "carbocycle" refers to a mono- or polycyclic group. When used in connection with cycloalkyl substituents, the term "polycyclic" refers herein to fused and non-fused alkyl cyclic structures. "Cycloalkyl" or "carbocycle" may form a bridged ring or a spiro ring. The cycloalkyl group may have one or more double or triple bond(s). The term "cycloalkenyl" refers to a cycloalkyl group that has at least one site of alkenyl unsaturation between the ring vertices. The term "cycloalkynyl" refers to a cycloalkyl group that has at least one site of alkynyl unsaturation between the ring vertices. When "cycloalkyl" is used in combination with "alkyl", as in C_{3-8}cycloalkylC_{3-8}alkylene-, the cycloalkyl portion is meant to have the stated number of carbon atoms (e.g., from three to eight carbon atoms), while the alkylene portion has from one to eight carbon atoms. Typical cycloalkyl substituents have from 3 to 8 ring atoms. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like.

[0061] "Aryl" by itself or as part of another substituent refers to a polyunsaturated, aromatic, hydrocarbon group containing from 6 to 14 carbon atoms, which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Thus the phrase includes, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, naphthyl by way of example. Non-limiting examples of unsubstituted aryl groups include phenyl, 1-naphthyl, 2-naphthyl and 4-biphenyl. "Substituted aryl group" includes, for example, -CH_2OH (one carbon atom and one heteroatom replacing a carbon atom) and -CH_2SH. The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by -CH_2-CH_2-S-CH_2CH_2- - and -CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[0062] The terms "heterocycle", "heterocyclyl" or "heterocyclic" refer to a saturated or unsaturated non-aromatic cyclic group containing at least one heteroatom. As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si). Each heterocycle can be attached at any available ring carbon or heteroatom. Each heterocycle may have one or more rings. When multiple rings are present, they can be fused together or linked covalently. Each heterocycle typically contains 1, 2, 3, 4 or 5, independently selected heteroatoms. Preferably, these groups contain 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, 0, 1, 2, 3, 4 or 5 nitrogen atoms, 0, 1 or 2 sulfur atoms and 0, 1 or 2 oxygen atoms. More preferably, these groups contain 1, 2 or 3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Non-limiting examples of heterocycle groups include morpholin-3-one, piperazine-2-one, piperazin-1-oxide, pyridine-2-one, piperidine, morpholine, piperazine, isoxazoline, pyrazoline, imidazoline, pyrazol-5-one, pyrrolidine-2,5-dione, imidazolidine-2,4-dione, pyrrolidine, tetrahydroquinolinyl, decahydroquinolinyl, tetrahydrobenzooxazepinyl dihydrodibenzooxepin and the like.

[0063] "Heteroaryl" refers to a cyclic or polycyclic aromatic radical that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom or through a carbon atom and can contain 5 to 10 carbon atoms. Non-limiting examples of heteroaryl groups include 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl and 4-pyrimidyl. If not specifically stated, substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described herein. "Substituted heteroaryl" refers to a unsubstituted heteroaryl group as defined above in which one or more of the ring members is bonded to a non-hydrogen atom such as described above with respect to substituted alkyl groups and substituted aryl groups. Representative substituents include straight and branched chain alkyl groups–CH_3, –C_2H_5, -CH_2OH, –OH, –OCH_3, –OC_2H_5, –OCF_3, –$OC(=O)CH_3$, –$OC(=O)NH_2$, –$OC(=O)N(CH_3)_2$, -CN, –NO_2, –$C(=O)CH_3$, –CO_2H, –CO_2CH_3, –$CONH_2$, –NH_2,–$N(CH_3)_2$, –$NHSO_2CH_3$, -$NHCOCH_3$, –$NHC(=O)OCH_3$, –$NHSO_2CH_3$, –SO_2CH_3, –SO_2NH_2 and halo.

[0064] "Bicyclic heteroaryl" refers to bicyclic aromatic radical that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A bicyclic heteroaryl group can be attached to the remainder of the molecule through a heteroatom or through a carbon atom and can contain 5 to 10 carbon atoms. Non-limiting examples of bicyclic heteroaryl groups include 5-benzothiazolyl, purinyl, 2-benzimidazolyl, benzopyrazolyl, 5-indolyl, azaindole, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl and 6-quinolyl. If not specifically stated, substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described herein.

[0065] "Arylheteroaryl" or "aryleneheteroaryl" refers to a radical wherein a heteroaryl moiety is attached to an aryl moiety in a non-fused fashion. The aryl group is attached to the remainder of the molecule through a carbon atom and can contain 5 to 10 carbon atoms. Non-limiting examples of aryl and heteroaryl groups are described above. The term "phenylheteraryl" or "phenyleneheteroaryl" refers to a heteroaryl moiety attached to a phenyl moiety which is attached to the remainder of the molecule.

[0066] "Arylheterocyclyl" or "aryleneheterocyclyl" refers to a radical wherein a heterocyclyl moiety is attached to an aryl moiety in a non-fused fashion. The aryl group is attached to the remainder of the molecule through a carbon atom and can contain 5 to 10 carbon atoms. Non-limiting examples of aryl and heterocyclyl groups are described above. The term "phenylheterocyclyl" or "phenyleneheterocyclyl" refers to a heteroaryl moiety attached to a phenyl moiety which is attached to the remainder of the molecule.

[0067] In each of the above embodiments designating a number of atoms e.g. "C_{1-8}" is meant to include all possible embodiments that have one fewer atom. Non-limiting examples include C_{1-7}, C_{2-8}, C_{2-7}, C_{3-8}, C_{3-7} and the like.

[0068] Each of the terms herein (e.g., "alkyl," "heteroalkyl," "aryl" and "heteroaryl") is meant to include both "unsubstituted" and optionally "substituted" forms of the indicated radical, unless otherwise indicated. Typically each radical is substituted with 0, 1, 2 3 4 or 5 substituents, unless otherwise indicated. Examples of substituents for each type of radical are provided below.

[0069] "Substituted" refers to a group as defined herein in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atom

"substituents" such as, but not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy, and acyloxy groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amino, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, alkoxyamino, hydroxyamino, acylamino, sulfonylamino, N-oxides, imides, and enamines; and other heteroatoms in various other groups. "Substituents" also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, acyl, amido, alkoxycarbonyl, aminocarbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. "Substituents" further include groups in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to a cycloalkyl, heterocyclyl, aryl, and heteroaryl groups. Representative "substituents" include, among others, groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluoro, chloro, or bromo group. Another representative "substituent" is the trifluoromethyl group and other groups that contain the trifluoromethyl group. Other representative "substituents" include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, or aryloxy group. Other representative "substituents" include alkyl groups that have an amine, or a substituted or unsubstituted alkylamine, dialkylamine, arylamine, (alkyl)(aryl)amine, diarylamine, heterocyclylamine, diheterocyclylamine, (alkyl)(heterocyclyl)amine, or (aryl)(heterocyclyl)amine group. Still other representative "substituents" include those in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl group.

[**0070**] The herein-defined groups may include prefixes and/or suffixes that are commonly used in the art to create additional well-recognized substituent groups. As examples, "alkylamino" refers to a group of the formula $-NR^aR^b$. Unless stated otherwise, for the following groups containing R^a, R^b, R^c, R^d and R^e: R^a, and R^b are each independently selected from H, alkyl, alkoxy, thioalkoxy, cycloalkyl, aryl, heteroaryl, or heterocyclyl or are optionally joined together with the atom(s) to which they are attached to form a cyclic group. When R^a and R^b are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. For example, $-NR^aR^b$ is meant to include 1-pyrrolidinyl and 4-morpholinyl.

[0071] R^c, R^d, R^e and R^f are each independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl or alkylenearyl as defined herein.

[0072] Typically, a particular radical will have 0, 1, 2 or 3 substituents, with those groups having two or fewer substituents being preferred in the present invention. More preferably, a radical will be unsubstituted or monosubstituted. Most preferably, a radical will be unsubstituted.

[0073] "Substituents"for the alkyl and heteroalkyl radicals (as well as those groups referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocyclyl) can be a variety of groups selected from: $-OR^a$, =O, $=NR^a$, =N-OR^a, $-NR^aR^b$, $-SR^a$, halogen, $-SiR^aR^b R^c$, $-OC(O)R^a$, $-C(O)R^a$, $-CO_2R^a$, $-CONR^aR^b$, $-OC(O)NR^aR^b$, $-NR^bC(O)R^a$, $-NR^a$-$C(O)NR^bR^c$, $-NR^a$-$SO_2NR^bR^c$, $-NR^bCO_2 R^a$, -NH-$C(NH_2)$=NH, $-NR^aC(NH_2)$=NH, -NH-$C(NH_2)$=NR^a, -S(O) R^a, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^bSO_2R$, -CN and $-NO_2$, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred.

[0074] In some embodiments, "substituents"for the alkyl and heteroalkyl radicals are selected from: $-OR^a$, =O, - NR^aR^b, $-SR^a$, halogen, $-SiR^aR^bR^c$, $-OC(O)R^a$, $-C(O)R^a$, $-CO_2R^a$, $-CONR^aR^b$, $-OC(O)NR^aR^b$, $-NR^bC(O)R^a$, $-NR^bCO_2R^a$, $-NR^a$-$SO_2NR^bR^c$, -S(O) R^a, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^cSO_2R$, -CN and $-NO_2$, where R^a and R^b are as defined above. In some embodiments, substituents are selected from: $-OR^a$, =O, - NR^aR^b, halogen, $-OC(O)$ R^a, $-CO_2R^a$, $-CONR^aR^b$, $-OC(O)NR^aR^b$, $-NR^bC(O)R^a$, $-NR^bCO_2R^a$, $-NR^a$-$SO_2NR^bR^c$, $-SO_2R^a$, $-SO_2NR^aR^b$, -NR"SO_2R, -CN and $-NO_2$.

[0075] Examples of substituted alkyl are: $-(CH_2)_3NH_2$, $-(CH_2)_3NH(CH_3)$, $-(CH_2)_3NH(CH_3)_2$, $-CH_2C(=CH_2)CH_2NH_2$, $-CH_2C(=O)CH_2NH_2$, $-CH_2S(=O)_2CH_3$, $-CH_2OCH_2NH_2$, $-CO_2H$. Examples of substituents of substituted alkyl are: CH_2OH, –OH, $-OCH_3$, $-OC_2H_5$, $-OCF_3$, $-OC(=O)CH_3$, $-OC(=O)NH_2$, $-OC(=O)N(CH_3)_2$, –CN, $-NO_2$, $-C(=O)CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-NH_2$, $-N(CH_3)_2$, $-NHSO_2CH_3$, $-NHCOCH_3$, $-NHC(=O)OCH_3$, $-NHSO_2CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, and halo.

[0076] Similarly, "substituents" for the aryl and heteroaryl groups are varied and are selected from: -halogen, $-OR^a$, $-OC(O)$ R^a, $-NR^aR^b$, $-SR^a$, $-R^a$, -CN, $-NO_2$, $-CO_2R^a$, $-CONR^aR^b$, $-C(O)$ R^a, $-OC(O)NR^aR^b$, $-NR^bC(O)$ R^a, $-NR^bC(O)_2R^a$, $-NR^a$-$C(O)NR^bR^c$,

-NH-C(NH_2)=NH, -NR^aC(NH_2)=NH, -NH-C(NH_2)=NR^a, -S(O) R^a, -S(O) $_2$ R^a, -S(O) $_2$$NR^aR^b$, -$N_3$, -$CH(Ph)_2$, perfluoro$C_{1-8}$alkoxy, and perfluoro$C_{1-8}$alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R^a, R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-C_{1-8}alkyl, and (unsubstituted aryl)oxy-C_{1-8}alkyl.

[0077] Two of the "substituents"on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH_2)q-U-, wherein T and U are independently -NH-, -O-, -CH_2- or a single bond, and q is 0, 1 or 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -S(O) $_2$$NR^a$- or a single bond, and r is 1, 2 or 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$- -, where s and t are independently integers of 0 to 3, and X is -O-, -NR^a-, -S- , -S(O)-, -$S(O)_2$-, or -S(O) $_2$$NR^a$-. The substituent R^a in -NR^a- and -$S(O)_2NR^a$- is selected from hydrogen or unsubstituted C_{1-6}alkyl. Otherwise, R' is as defined above.

[0078] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "arylalkyloxycarbonyl" refers to the group (aryl)-(alkyl)-O-C(O)-.

[0079] The term "acyl" refers to the group –C(=O)R^c where R^c is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl. Acyl includes the "acetyl" group –C(=O)CH_3.

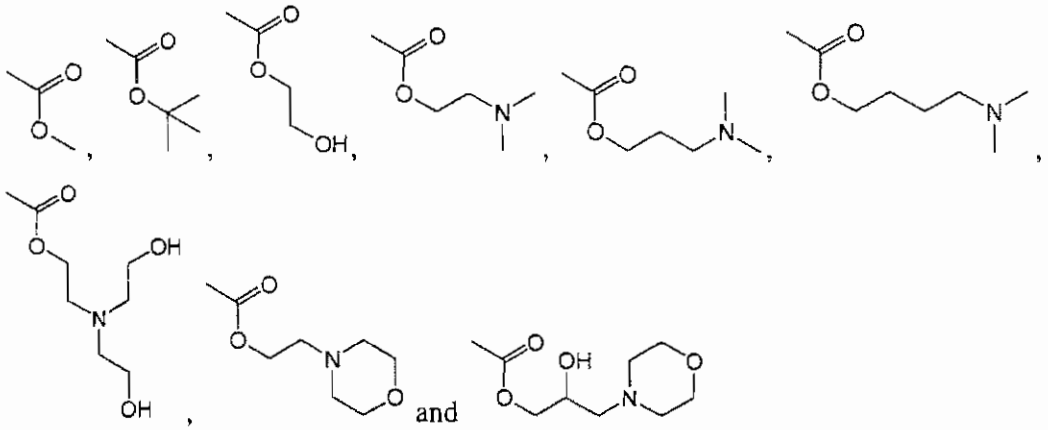
[0080] "Acylamino-" refers to the group -NR^aC(=O)R^c where R^c is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl.

[0081] "Acyloxy" refers to –OC(=O)–R^c where R^c is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl.

[0082] "Alkoxy" refers to $-OR^d$ wherein R^d is alkyl as defined herein. Representative examples of alkoxy groups include methoxy, ethoxy, *t*-butoxy, trifluoromethoxy, and the like.

[0083] "Alkoxyamino" refers to the group $-NHOR^d$ where R^d is alkyl.

[0084] "Alkoxycarbonyl" refers to $-C(=O)OR^d$ wherein R^d is alkyl. Representative alkoxycarbonyl groups include, for example, those shown below.



These alkoxycarbonyl groups can be further substituted as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.

[0085] "Alkoxycarbonylamino " refers to to $-NR^aC(=O)OR^d$ wherein R^d is alkyl.

[0086] "Alkoxysulfonylamino" refers to the group $-NR^aS(=O)_2-OR^d$ where R^d is alkyl.

[0087] "Alkylcarbonyl" refers to the group $-C(=O)R^c$ where R^c is alkyl.

[0088] "Alkylcarbonyloxy" refers to $-OC(=O)-R^c$ where R^c is alkyl.

[0089] "Alkylcarbonylamino" refers to $-NR^aC(=O)R^c$ wherein R^c is alkyl. Representative alkylcarbonylamino groups include, for example, $-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, $-NHC(=O)CH_2NH(CH_3)$, $-NHC(=O)CH_2N(CH_3)_2$, or $-NHC(=O)(CH_2)_3OH$.

[0090] "Alkylsulfanyl", "alkylthio", or "thioalkoxy" refers to the group $S-R^d$.where R^d is alkyl.

[0091] "Alkylsulfonyl" refers to $-S(=O)_2R^e$ where R^e is alkyl. Alkylsulfonyl groups employed in compounds of the present invention are typically C_{1-6}alkylsulfonyl groups.

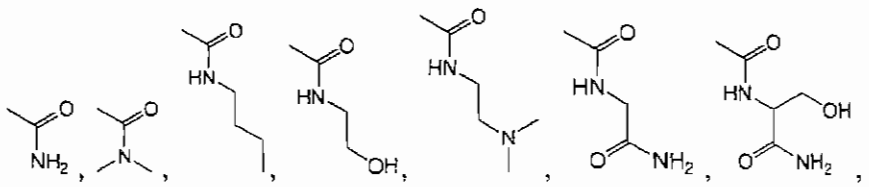
[0092] "Alkylsulfonylamino" refers to $-NR^aS(=O)_2-R^e$ wherein R^e is alkyl.

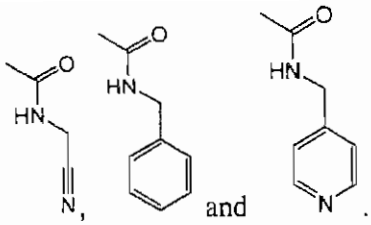
[0093] "Alkynyloxy" refers to the group -O-alkynyl, wherein alkynyl is as defined herein. Alkynyloxy includes, by way of example, ethynyloxy, propynyloxy, and the like.

[0094] "Amidino" refers to the group $-C(=NR^a)NR^bR^c$, wherein R^b and R^c independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic, and where R^b and R^c are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group. R^a is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkynyl, aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic, substituted heterocyclic, nitro, nitroso, hydroxy, alkoxy, cyano, -N=N-N-alkyl, $-N(alkyl)SO_2$-alkyl, - - N=N=N-alkyl, acyl and $-SO_2$-alkyl.

[0095] "Amino" refers to a monovalent radical $-NR^aR^b$ or divalent radical $-NR^a-$. The term "alkylamino" refers to the group $-NR^aR^b$ where R^a is alkyl and R^b is H or alkyl. The term "arylamino" refers to the group $-NR^aR^b$ where at least one R^a or R^b is aryl. The term "(alkyl)(aryl)amino" refers to the group $-NR^aR^b$ where R^a is alkyl and R^b is aryl. Additionally, for dialkylamino groups, the alkyl portions can be the same or different and can also be combined to form a 3-7 membered ring with the nitrogen atom to which each is attached. Accordingly, a group represented as $-NR^aR^b$ is meant to include piperidinyl, pyrrolidinyl, morpholinyl, azetidinyl and the like.

[0096] "Aminocarbonyl" or "aminoacyl" refers to the amide $-C(=O)-NR^aR^b$. The term "alkylaminocarbonyl" refers herein to the group $-C(=O)-NR^aR^b$ where R^a is alkyl and R^b is H or alkyl. The term "arylaminocarbonyl" refers herein to the group $-C(=O)-NR^aR^b$ where R^a or R^b is aryl. Representative aminocarbonyl groups include, for example, those shown below. These aminocarbonyl group can be further substituted as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.





[0097] "Aminocarbonylamino" refers to the group $-NR^aC(O)NR^aR^b$, wherein R^a is hydrogen or alkyl and R^a and R^b independently are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic, and where R^a and R^b are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group.

[0098] "Aminosulfonyl" refers to $-S(O)_2NR^aR^b$ where R is independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where R^a and R^b are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group and alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0099] "Aminosulfonyloxy" refers to the group $-O-SO_2NR^aR^b$, wherein R^a and R^b independently are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic; R^a and R^b are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group.

[0100] "Aminosulfonylamino" refers to the group $-NR^a-SO_2NR^bR^c$, wherein R^a is hydrogen or alkyl and R^b and R^c independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^b and R^c are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic

and substituted heterocyclic are as defined herein.

[0101] "Aminothiocarbonyl" refers to the group -C(S)NR^aR^b, wherein R^a and R^b independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^a and R^b are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0102] "Aminothiocarbonylamino" refers to the group --$NR^aC(S)NR^aR^b$, wherein R^a is hydrogen or alkyl and R^b and R^c are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group.

[0103] "Arylcarbonyl" refers to the group –$C(=O)R^c$ where R^c is aryl.

[0104] "Arylcarbonylamino" refers to –$NR^aC(=O)R^c$ wherein R^c is aryl.

[0105] "Arylcarbonyloxy" refers to –$OC(=O)–R^c$ where R^c is aryl.

[0106] "Aryloxy" refers to –OR^d where R^d is aryl. Representative examples of aryloxy groups include phenoxy, naphthoxy, and the like.

[0107] "Aryloxycarbonyl" refers to –$C(=O)OR^d$ wherein R^d is aryl.

[0108] "Aryloxycarbonylamino" refers to –$NR^aC(=O)OR^d$ wherein R^d is aryl.

[0109] "Arylsulfanyl", "arylthio", or "thioaryloxy" refers to the group S-R^d.where R^d is aryl.

[0110] "Arylsulfonyl" refers to –$S(=O)_2R^e$ where R^e is is aryl.

[0111] "Arylsulfonylamino" refers to –$NR^aS(=O)_2–R^e$ wherein R^e is aryl.

[0112] "Arylthio" refers to the group -S-aryl, wherein aryl is as defined herein. In other embodiments, sulfur may be oxidized to -S(O)- or -SO_2- moieties. The sulfoxide may exist as one or more stereoisomers.

[0113] "Azido" refers to –N_3.

[0114] "Bond" when used a element in a Markush group means that the corresponding group does not exist, and the groups of both sides are directly linked.

[0115] "Carbonyl" refers to the divalent group –C(=O)–.

[0116] "Carboxy" or "carboxyl" refers to the group $-CO_2H$.

[0117] "Carboxyl ester" or "carboxy ester" refers to the groups $-C(=O)OR^c$.

[0118] "(Carboxyl ester)amino" refers to the groups $-NR^a-C(O)OR^c$, where R^a is alkyl or hydrogen.

[0119] "(Carboxyl ester)oxy" or "Carbonate ester" refers to the groups $-O-C(=O)OR^c$.

[0120] "Cyano" refers to –CN.

[0121] "Cycloalkoxy" refers to $-OR^d$ where R^d is cycloalkyl.

[0122] "Cycloalkoxycarbonyl" refers to $-C(=O)OR^d$ wherein R^d is cycloalkyl.

[0123] "Cycloalkoxycarbonylamino " refers to to $-NR^aC(=O)OR^d$ wherein R^d is cycloalkyl.

[0124] "Cycloalkylalkylene" refers to a radical $-R^xR^y$ wherein R^x is an alkylene group and R^y is a cycloalkyl group as defined herein, *e.g.*, cyclopropylmethyl, cyclohexenylpropyl, 3-cyclohexyl-2-methylpropyl, and the like.

[0125] "Cycloalkylcarbonyl" refers to the group $-C(=O)R^c$ where R^c is cycloalkyl.

[0126] "Cycloalkylcarbonylamino" refers to $-NR^aC(=O)R^c$ wherein R^c is cycloalkyl.

[0127] "Cycloalkylcarbonyloxy" refers to $-OC(=O)-R^c$ where R^c is cycloalkyl.

[0128] "Cycloalkylsulfonylamino" refers to $-NR^aS(=O)_2-R^e$ wherein R^e is cycloalkyl.

[0129] "Cycloalkylthio" refers to -S-cycloalkyl. In other embodiments, sulfur may be oxidized to -S(O)- or $-SO_2-$ moieties. The sulfoxide may exist as one or more stereoisomers.

[0130] "Cycloalkenylox" refers to -O-cycloalkenyl.

[0131] "Cycloalkenylthio" refers to -S-cycloalkenyl. In other embodiments, sulfur may be oxidized to sulfinyl or sulfonyl moieties. The sulfoxide may exist as one or more stereoisomers.

[0132] "Ester" refers to $-C(=O)OR^d$ wherein R^d is alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl.

[0133] "Guanidino" refers to the group $-NHC(=NH)NH_2$.

[0134] "Halo" or "halogen" by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl", are meant to include alkyl in which one or more hydrogen is substituted with halogen atoms which can be the same or different, in a number ranging from one up to the maximum number of halogens permitted e.g. for alkyl, (2m'+1), where m' is the total number of carbon atoms in the alkyl group. For example, the term "haloC_{1-8}alkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. The term "perhaloalkyl" means, unless otherwise stated, alkyl substituted with (2m'+1) halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example, the term "perhaloC_{1-8}alkyl", is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like. Additionally, term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms.

[0135] "Heteroalkyl" means an alkyl radical as defined herein with one, two or three substituents independently selected from cyano, $-OR^W$, $-NR^XR^Y$, and $-S(O)_nR^Z$ (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom of the heteroalkyl radical. R^W is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, araalkyl, alkoxycarbonyl, aryloxycarbonyl, carboxamido, or mono- or di-alkylcarbamoyl. R^X is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl or araalkyl. Ry is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, araalkyl, alkoxycarbonyl, aryloxycarbonyl, carboxamido, mono- or di-alkylcarbamoyl or alkylsulfonyl. R^Z is hydrogen (provided that n is 0), alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, araalkyl, amino, mono-alkylamino, di-alkylamino, or hydroxyalkyl. Representative examples include, for example, 2-hydroxyethyl, 2,3-dihydroxypropyl, 2-methoxyethyl, benzyloxymethyl, 2-cyanoethyl, and 2-methylsulfonyl-ethyl. For each of the above, R^W, R^X ,R^Y, and R^Z can be further substituted by amino, fluorine, alkylamino, di-alkylamino, OH or alkoxy. Additionally, the prefix indicating the number of carbon atoms (*e.g.*, C_1-C_{10}) refers to the total number of carbon atoms in the portion of the heteroalkyl group exclusive of the cyano, $-OR^W$, $-NR^XR^Y$, or $-S(O)_nR^Z$ portions.

[0136] "Heteroarylcarbonyl" refers to the group $-C(=O)R^c$ where R^c is heteroaryl.

[0137] "Heteroarylcarbonylamino" refers to $-NR^aC(=O)R^c$ wherein R^c is heteroaryl.

[0138] "Heteroarylcarbonyloxy" refers to $-OC(=O)-R^c$ where R^c is heteroaryl.

[0139] "Heteroaryloxy" refers to $-OR^d$ where R^d is heteroaryl.

[0140] "Heteroaryloxycarbonyl" refers to $-C(=O)OR^d$ wherein R^d is heteroaryl.

[0141] "Heteroaryloxycarbonylamino " refers to to $-NR^aC(=O)OR^d$ wherein R^d is heteroaryl.

[0142] "Heteroarylsulfonyllamino" refers to $-NR^aS(=O)_2-R^e$ wherein R^e is heteroaryl.

[0143] "Heteroarylthio" refers to the group --S-heteroaryl. In other embodiments, sulfur may be oxidized to -S(O)- or $-SO_2-$ moieties. The sulfoxide may exist as one or more stereoisomers.

[0144] "Heterocyclylalkyl" or "Cycloheteroalkyl-alkyl" means a radical $-R^XR^Y$ where R^X is an alkylene group and R^Y is a heterocyclyl group as defined herein, *e.g.*, tetrahydropyran-2-ylmethyl, 4-(4-substituted-phenyl)piperazin-1-ylmethyl, 3-piperidinylethyl, and the like.

[0145] "Heterocycloxycarbonylamino " refers to to $-NR^aC(=O)OR^d$ wherein R^d is heterocyclyl.

[0146] "Heterocyclylcarbonyl" refers to the $-C(=O)R^c$ where R^c is heterocyclyl.

[0147] "Heterocyclylcarbonylamino" refers to $-NR^aC(=O)R^c$ wherein R^c is heterocyclyl.

[0148] "Heterocyclylcarbonyloxy" refers to $-OC(=O)-R^c$ where R^c s heterocyclyl.

[0149] "Heterocyclyloxy" refers to $-OR^d$ where R^d is heterocyclyl.

[0150] "Heterocyclyloxycarbonyl" refers to $-C(=O)OR^d$ wherein R^d is heterocyclyl.

[0151] "Heterocyclylsulfonyl" refers to $-S(=O)_2R^e$ where R^e is heterocyclyl.

[0152] "Heterocyclylsulfonyllamino" refers to $-NR^aS(=O)_2-R^e$ wherein R^e is heterocyclyl.

[0153] "Heterocyclylthio" refers to the group -S-heterocycyl. In other embodiments, sulfur may be oxidized to -S(O)- or $-SO_2-$ moieties. The sulfoxide may exist as one or more stereoisomers.

[0154] "Hydroxy" or "hydroxyl" refers to the group –OH.

[0155] "Hydroxyamino" refers to the group –NHOH.

[0156] "Nitro" refers to $-NO_2$.

[0157] "Nitroso" refers to the group --NO.

[0158] The terms "optional" or "optionally" as used throughout the specification means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclo group optionally mono- or di- substituted with an alkyl group means that the alkyl may but need not be present, and the description includes situations where the heterocyclo group is mono- or disubstituted with an alkyl group and situations where the heterocyclo group is not substituted with the alkyl group.

[0159] "Optionally substituted " means a ring which is optionally substituted independently with substituents. A site of a group that is unsubstituted may be substituted with hydrogen.

[0160] "Oxo" refers to the divalent group =O.

[0161] "Sulfanyl" refers to the group $-SR^f$ where R^f is as defined herein.

[0162] "Sulfinyl" refers to the group $-S(=O)-R^e$ where R^e is as defined herein.

[0163] "Sulfonic acid" refers to the group $-S(O)_2-OH$.

[0164] "Sulfonyl" refers to the group $-S(O)_2-R^e$ where R^e is as defined herein.

[0165] "Sulfonylamino" refers to $-NR^aS(=O)_2-R^e$ where R^a is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclyl and R^e is as defined herein.

[0166] "Sulfonyloxy" refers to the group $-OSO_2-R^e$.

[0167] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". "Stereoisomer" and "stereoisomers" refer to compounds that exist in different stereoisomeric forms if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Stereoisomers include enantiomers and diastereomers. Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a

compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture". Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (*see* discussion in Chapter 4 of ADVANCED ORGANIC CHEMISTRY, 4th edition J. March, John Wiley and Sons, New York, 1992) differ in the chirality of one or more stereocenters.

[0168] "Thioacyl" refers to the groups R^a-C(S)-.

[0169] "Thiol" refers to the group --SH.

[0170] "Tautomer" refers to alternate forms of a molecule that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a -N=C(H)-NH- ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles. A person of ordinary skill in the art would recognize that other tautomeric ring atom arrangements are possible.

[0171] It is understood that in all substituted groups defined above, polymers arrived at by defining substituents with further substituents to themselves (e.g., substituted aryl having a substituted aryl group as a substituent which is itself substituted with a substituted aryl group, which is further substituted by a substituted aryl group, etc.) are not intended for inclusion herein. In such cases, the maximum number of such substitutions is three. For example, serial substitutions of substituted aryl groups are limited to -substituted aryl-(substituted aryl)-substituted aryl.

[0172] "Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, Protective Groups in Organic Chemistry, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., Compendium of Synthetic Organic Methods, Vols. 1-8, 1971-1996, John Wiley & Sons, NY.

Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPPS groups) and allyl ethers.

[0173] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, *p*-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included

are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge, S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19, 1977). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0174] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0175] In addition to salt forms, the present invention provides compounds which are in a prodrug ester form. "Prodrug"s of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug. Prodrugs are typically obtained by masking a functional group in the drug believed to be in part required for activity with a progroup (defined below) to form a promoiety which undergoes a transformation, such as cleavage, under the specified conditions of use to release the functional group, and hence the active drug. The cleavage of the promoiety may proceed spontaneously, such as by way of a hydrolysis reaction, or it may be catalyzed or induced by another agent, such as by an enzyme, by light, by acid or base, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature. The agent may be endogenous to the conditions of use, such as an enzyme present in the cells to which the prodrug is administered or the acidic conditions of the stomach, or it may be supplied exogenously.

[0176] "Progroup" refers to a type of protecting group that, when used to mask a functional group within an active drug to form a promoiety, converts the drug into a prodrug. Progroups are typically attached to the functional group of the drug via bonds that are cleavable under specified conditions of use. Thus, a progroup is that portion of a promoiety that cleaves to

release the functional group under the specified conditions of use. As a specific example, an amide promoiety of the formula -NH-C(O)CH_3 comprises the progroup -C(O)CH_3.

[0177] A wide variety of progroups, as well as the resultant promoieties, suitable for masking functional groups in the active syk selective inhibitory compounds to yield prodrugs are well-known in the art. For example, a hydroxyl functional group may be masked as a sulfonate, ester (such as acetate or maleate) or carbonate promoiety, which may be hydrolyzed in vivo to provide the hydroxyl group. An amino functional group may be masked as an amide, carbamate, imine, urea, phosphenyl, phosphoryl or sulfenyl promoiety, which may be hydrolyzed in vivo to provide the amino group. A carboxyl group may be masked as an ester (including methyl, ethyl, pivaloyloxymethyl, silyl esters and thioesters), amide or hydrazide promoiety, which may be hydrolyzed in vivo to provide the carboxyl group. The invention includes those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations. Other specific examples of suitable progroups and their respective promoieties will be apparent to those of skill in the art.

[0178] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. "Solvate" refers to a complex formed by combination of solvent molecules with molecules or ions of the solute. The solvent can be an organic compound, an inorganic compound, or a mixture of both. Some examples of solvents include, but are not limited to, methanol, N,N-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, and water. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0179] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. These isomers can be resolved or asymmetrically synthesized using conventional methods to render the isomers "optically pure", i.e., substantially free of its other isomers. If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or

by derivation with a chrial auxilliary, where the resulting diastereomeric mixture is separated and the auxilliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diasteromers thus formed by fractional crystallization or chromatagraphic means well known in the art, and subsequent recovery of the pure enantiomers.

[0180] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0181] The term "administering" refers to oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intranasal or subcutaneous administration, or the implantation of a slow-release device *e.g.*, a mini-osmotic pump, to a subject. Adminsitration is by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.*

[0182] An "agonist" or "activator" refers to an agent or molecule that binds to a receptor of the invention, stimulates, increases, opens, activates, facilitates, enhances activation or enzymatic activity, sensitizes or up regulates the activity of a receptor of the invention.

[0183] An "antagonist" or "inhibitor" refers to an agent or molecule that inhibits or binds to, partially or totally blocks stimulation or activity, decreases, closes, prevents, delays activation or enzymatic activity, inactivates, desensitizes, or down regulates the activity of a receptor of the invention. As used herein, "antagonist" also includes a reverse or inverse agonist.

[0184] As used herein, the term "condition or disorder responsive to modulation of syk " and related terms and phrases refer to a condition or disorder associated with inappropriate,

e.g., less than or greater than normal, activity of syk and at least partially responsive to or affected by modulation of syk (e.g., syk antagonist or agonist results in some improvement in patient well-being in at least some patients). Inappropriate functional activity of syk might arise as the result of expression of syk in cells which normally do not express the receptor, greater than normal production of syk, or slower than normal metabolic inactivation or elimination of syk or its active metabolites, increased expression of syk or degree of intracellular activation (leading to, e.g., inflammatory and immune-related disorders and conditions) or decreased expression of syk . A condition or disorder associated with syk may include a " syk -mediated condition or disorder".

[0185] As used herein, the phrases "a condition or disorder mediated at least in part by syk kinase activity", and related phrases and terms refer to a condition or disorder characterized by inappropriate, e.g., greater than normal, syk activity. Inappropriate syk functional activity might arise as the result of syk expression in cells which normally do not express syk or increased syk expression or degree of intracellular activation (leading to, e.g., inflammatory and immune-related disorders and conditions). A condition or disorder mediated at least in part by syk kinase activity may be completely or partially mediated by inappropriate syk functional activity. However, a condition or disorder mediated at least in part by syk kinase activity is one in which modulation of syk results in some effect on the underlying condition or disorder (e.g., an syk antagonist results in some improvement in patient well-being in at least some patients).

[0186] The term "inflammation" as used herein refers to infiltration of white blood cells (*e.g.*, leukocytes, monocytes, *etc.*) into the area being treated for restenosis.

[0187] The term "intervention" refers to an action that produces an effect or that is intended to alter the course of a disease process. For example, "vascular intervention" refers to the use of an intravascular procedure such as angioplasty or a stent to open an obstructed blood vessel.

[0188] The term "intravascular device" refers to a device useful for a vascular recanalization procedure to restore blood flow through an obstructed blood vessel. Examples of intravascular devices include, without limitation, stents, balloon catheters, autologous venous/arterial grafts, prosthetic venous/arterial grafts, vascular catheters, and vascular shunts.

[0189] As used herein, the term "JAK" refers to a Janus kinase (RefSeq Accession No. P-43408) or a variant thereof that is capable of mediating gene expression *in vitro* or *in vivo*. JAK variants include proteins substantially homologous to native JAK, i.e., proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (e.g., JAK derivatives, homologs and fragments). The amino acid sequence of JAK variant preferably is at least about 80% identical to a native JAK, more preferably at least about 90% identical, and most preferably at least about 95% identical.

[0190] The term "leukocyte" refers to any of the various blood cells that have a nucleus and cytoplasm, separate into a thin white layer when whole blood is centrifuged, and help protect the body from infection and disease. Examples of leukocytes include, without limitation, neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

[0191] The term "mammal" includes, without limitation, humans, domestic animals (*e.g.*, dogs or cats), farm animals (cows, horses, or pigs), monkeys, rabbits, mice, and laboratory animals.

[0192] The terms "modulate", "modulation" and the like refer to the ability of a compound to increase or decrease the function and/or expression of syk , where such function may include transcription regulatory activity and/or protein-binding. Modulation may occur *in vitro* or *in vivo*. Modulation, as described herein, includes the inhibition, antagonism, partial antagonism, activation, agonism or partial agonism of a function or characteristic associated with syk , either directly or indirectly, and/or the upregulation or downregulation of the expression of syk , either directly or indirectly. In a preferred embodiment, the modulation is direct. Inhibitors or antagonists are compounds that, e.g., bind to, partially or totally block stimulation, decrease, prevent, inhibit, delay activation, inactivate, desensitize, or downregulate signal transduction. Activators or agonists are compounds that, e.g., bind to, stimulate, increase, open, activate, facilitate, enhance activation, activate, sensitize or upregulate signal transduction. The ability of a compound to inhibit the function of syk can be demonstrated in a biochemical assay, e.g., binding assay, or a cell-based assay, e.g., a transient transfection assay.

[0193] "Modulators" of activity are used to refer to "ligands", "antagonists" and "agonists" identified using *in vitro* and *in vivo* assays for activity and their homologs and mimetics. Modulators include naturally occurring and synthetic ligands, antagonists, agonists, molecules and the like. Assays to identify antagonists and agonists include, e.g., applying

putative modulator compounds to cells, in the presence or absence of a receptor of the invention and then determining the functional effects on a receptor of the invention activity. Samples or assays comprising a receptor of the invention that are treated with a potential activator, inhibitor, or modulator are compared to control samples without the inhibitor, activator, or modulator to examine the extent of effect. Control samples (untreated with modulators) are assigned a relative activity value of 100%. Inhibition is achieved when the activity value of a receptor of the invention relative to the control is about 80%, optionally 50% or 25-1%. Activation is achieved when the activity value of a receptor of the invention relative to the control is 110%, optionally 150%, optionally 200-500%, or 1000-3000% higher.

[0194] "Patient" refers to human and non-human animals, especially mammals. Examples of patients include, but are not limited to, humans, cows, dogs, cats, goats, sheep, pigs and rabbits.

[0195] Turning next to the compositions of the invention, the term "pharmaceutically acceptable carrier or excipient" means a carrier or excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable carrier or excipient" as used in the specification and claims includes both one and more than one such carrier or excipient.

[0196] The terms "pharmaceutically effective amount", "therapeutically effective amount" or "therapeutically effective dose" refers to the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The term "therapeutically effective amount" includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective amount will vary depending on the compound, the disorder or condition and its severity and the age, weight, etc., of the mammal to be treated.

[0197] The term "platelet" refers to a minute, nonnucleated, disklike cell found in the blood plasma of mammals that functions to promote blood clotting.

[0198] The terms "prevent", "preventing", "prevention" and grammatical variations thereof as used herein, refers to a method of partially or completely delaying or precluding the onset or recurrence of a disorder or condition and/or one or more of its attendant symptoms or barring a subject from acquiring or reacquiring a disorder or condition or reducing a subject's risk of acquiring or reaquiring a disorder or condition or one or more of its attendant symptoms.

[0199] The term "recanalization" refers to the process of restoring flow to or reuniting an interrupted channel of the body, such as a blood vessel.

[0200] The term "restenosis" refers to a re-narrowing or blockage of an artery at the same site where treatment, such as an angioplasty or a stent procedure, has been performed.

[0201] The phrase "selectively" or "specifically" when referring to binding to a receptor, refers to a binding reaction that is determinative of the presence of the receptor, often in a heterogeneous population of receptors and other biologics. Thus, under designated conditions, the compounds bind to a particular receptor at leást two times the background and more typically more than 10 to 100 times background. Specific binding of a compound under such conditions requires a compound that is selected for its specificity for a particular receptor. For example, small organic molecules can be screened to obtain only those compounds that specifically or selectively bind to a selected receptor and not with other receptors or proteins. A variety of assay formats may be used to select compounds that are selective for a particular receptor. For example, High-throughput screening assays are routinely used to select compounds that are selective for a particular a receptor.

[0202] As used herein, the term "Sickle cell anemia" refers to an inherited disorder of the red blood cells in which both hemoglobin alleles encode the sickle hemoglobin (S) protein, *i.e.*, the S/S genotype. The presence of abnormal hemoglobin results in the production of unusually shaped cells, which do not survive the usual length of time in the blood circulation. Thus, anemia results. "Anemia" refers to a decrease in the number of red blood cells and/or hemoglobin in the blood.

[0203] The term "Sickle cell disease" refers to an inherited disorder of the red blood cells in which one hemoglobin allele encodes the sickle hemoglobin (S) protein, and the other allele encodes another unusual hemoglobin protein, such as hemoglobin (S), (C), (D), (E), and (βThal). Examples of sickle cell disease genotypes include, without limitation, the S/S, S/C, S/D, S/E, and S/βThal genotypes. The most common types of sickle cell disease include

sickle cell anemia, sickle-hemoglobin C disease, sickle beta-plus thalassemia, and sickle beta-zero thalassemia.

[0204] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[0205] As used herein, the term "syk" refers to a spleen tyrosine kinase (RefSeq Accession No. P-043405) or a variant thereof that is capable of mediating a cellular response to T-cell receptors *in vitro* or *in vivo*. syk variants include proteins substantially homologous to native syk, i.e., proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (e.g., syk derivatives, homologs and fragments). The amino acid sequence of syk variant preferably is at least about 80% identical to a native syk, more preferably at least about 90% identical, and most preferably at least about 95% identical.

[0206] The term "syk inhibitor" refers to any agent that inhibits the catalytic activity of spleen tyrosine kinase.

[0207] The term "thrombosis" refers to the blockage or clotting of a blood vessel caused by a clumping of cells, resulting in the obstruction of blood flow. The term "thrombosis" refers to the clot that is formed within the blood vessel.

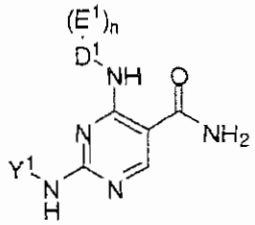
[0208] The terms "treat", "treating", "treatment" and grammatical variations thereof as used herein, includes partially or completely delaying, alleviating , mitigating or reducing the intensity of one or more attendant symptoms of a disorder or condition and/or alleviating, mitigating or impeding one or more causes of a disorder or condition. Treatments according to the invention may be applied preventively, prophylactically, pallatively or remedially.

[0209] The term "vessel" refers to any channel for carrying a fluid, such as an artery or vein. For example, a "blood vessel" refers to any of the vessels through which blood circulates in the body. The lumen of a blood vessel refers to the inner open space or cavity of the blood vessel.

2. Embodiments of the Invention

a. Compounds

[0210] The present invention provides in one group of embodiments, a compound having formula (I):

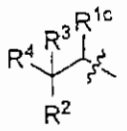


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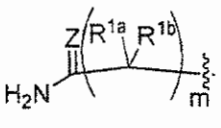
or a tautomer thereof or a pharmaceutically acceptable salt thereof,

wherein:

Y^1 is selected from the group consisting of:



and



;

Z is O or S;

D^1 is selected from the group consisting of:

(a) phenyl substituted with a group, R^5, wherein the phenyl is further optionally substituted with from 1 to 2 substituents, R^{7a}, independently selected from the group consisting of $C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkoxy, halo, $C_{1\text{-}8}$alkylsulfonyl and heterocyclyl;

R^5 is selected from the group consisting of:

(i) heteroaryl;

(ii) heterocyclyl;

(iii) $C_{1\text{-}8}$alkylheterocyclyl;

(iv) phenyleneheteroaryl

(v) phenyleneheterocyclyl

(vi) –L-phenyl;

(vii) –L-heterocyclyl; and

(viii) acyloxy;

L is selected from the group consisting of –CO-, -O-, -SO_2-, -CONH- and –$CONHCH_2$-;

each R^5 is optionally further substituted with from 1 to 2 substituents independently selected from the group consisting of C_{1-8}alkyl, hydroxyC_{1-8}alkyl-, aminoC_{1-8}alkyl, C_{1-8}alkylamino, C_{1-8}alkylcarbonyl, aminocarbonyl, cyano, hydroxy, oxo, halo, haloC_{1-8}alkyl, aminosulfonyl, C_{3-8}cycloalkyl and aryl;

(b) naphthyl substituted a substituent , R^{7b}, selected from the group consisting of halogen, C_{1-8}alkylcarbonyl, C_{1-8}alkylsulfonyl, aminosulfonyl, heterocyclylcarbonyl and aminocarbonyl;

(c) C_{3-8}cycloalkyl, optionally substituted with from 1 to 2 substituents, R^{7c}, independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, halo, C_{1-8}alkylsulfonyl and heterocyclyl;

(d) heteroaryl; optionally substituted with from 1 to 2 substituents, R^{7d}, independently selected from the group consisting of: C_{1-8} alkyl, amino, hydroxyl, oxo, halo, C_{1-8} alkoxy, hydroxyC_{1-8}alkyl-, aminoC_{1-8}alkyl, C_{1-8}alkylcarbonyl, haloC_{1-8}alkyl, C_{3-8}cycloalkyl, C_{1-8}aminocycloalkyl, aminoC_{1-8}alkylenecarbonyl, aminocarbonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenecarbonyl, C_{1-8}alkoxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkoxycarbonyl, C_{1-8} alkoxycarbonylamino, aryl, arylC_{1-8} alkoxycarbonylamino, C_{1-8}alkylsulfonyl, aminoC_{1-8}alkylenesulfonyl, aminosulfonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenesulfonyl, C_{1-8}alkoxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkoxysulfonyl, aminosulfonyl, and C_{1-8}alkylheterocyclyl; and

(e) heterocyclyl; with from 1 to 2 substituents, R^{7e}, independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, halo, C_{1-8}alkylsulfonyl and heterocyclyl;

each E^1 is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, C_{1-8}alkylthio, aminocarbonyl, C_{1-8}alkoxycarbonylC_{1-8}alkylene, C_{1-8}alkoxycarbonyl$C_{1-8}C_{1-8}$alkoxy, C_{1-8}alkoxycarbonylamino, oxo, halo, cyano, haloC_{1-8}alkyl, haloC_{1-8}alkoxy, aminosulfonyl, heteroarylsulfinyl; amino, hydroxyl, C_{1-8}arylalkylene, phenyl, aminoC_{1-8}alkyl, aminoC_{3-8}cycloalkyl, heterocyclyl, heteroaryl and heterocyclylC_{1-8}alkylene;

each R^{1a}, R^{1b} and R^{1c} is independently selected from the group consisting of: H, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, C_{1-8}haloalkyl, amino, C_{1-8}alkylamino, C_{1-8} alkoxycarbonylaminoC_{1-8} alkylene, C_{3-8}cycloalkyl, heteroaryl, C_{1-8} alkylC_{3-8}cycloalkyl, C_{1-8}alkylthioC_{1-8} alkyl, C_{1-8}alkylsulfonylC_{1-8} alkylene, aminocarbonyl, C_{1-8}alkoxyC_{1-8}alkyl, haloC_{1-8}alkyl, aryl and heterocyclyl; wherein the aryl is optionally substituted by hydroxyl, C_{1-8}alkoxy, halo or haloC_{1-8}alkyl; or taken together with R^3 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or hetercycloalkyl ring;

R^2 is selected from the group consisting of H, amino, C_{1-8}alkylamino, hydroxycarbonylamino C_{1-8}alkoxycarbonylamino ,arylC_{1-8}alkoxycarbonylamino and hydroxyl;

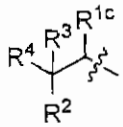
R^3 is selected from the group consisting of H, C_{1-8}alkyl, C_{1-8}alkylamino, amino aminoC$_{1-8}$alkyl, carboxy, C_{1-8}alkylaminoC$_{1-8}$alkyl, C_{1-8}alkoxyC$_{1-8}$alkyl, hydroxyC$_{1-8}$alkyl; carboxyC$_{1-8}$alkyl, C_{3-8}cycloalkylC$_{1-8}$alkyl, aryloxyC$_{1-8}$alkyl, arylC$_{1-8}$alkyl, heteroarylC$_{1-8}$alkyl, and hydroxyC$_{1-8}$alkoxy and hydroxyC$_{1-8}$alkoxy; or may be combined with R^{1c} or R^4 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring;

R^4 is H or alkyl or may be combined with R^3 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring;

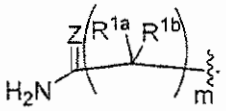
the subscript n is 0, 1, 2, 3 or 4; and

the subscript m is an integer of 1, 2 or 3; and the wavy line indicates the point of attachment to the rest of the molecule.

[0211] In one group of embodiments,Y^1 is:



[0212] In one group of embodiments,Y^1 is:



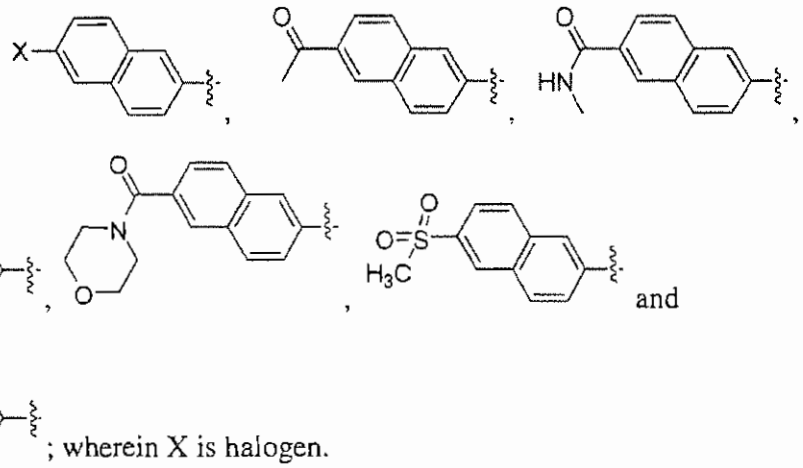
[0213] In one group of embodiments, Z is O. In another group of embodiments, Z is S.

[0214] In one group of embodiments, D^1 is phenyl.

[0215] In one group of embodiments, R^5 is heteroaryl. In another group of embodiments, R^5 is heterocyclyl. In another group of embodiments, R^5 is C_{1-8}alkylheterocyclyl. In another group of embodiments, R^5 is phenyleneheteroaryl. In another group of embodiments, R^5 is phenyleneheterocyclyl. In another group of embodiments, R^5 is –L-phenyl. In another group of embodiments, R^5 is –L-heterocyclyl. In another group of embodiments, R^5 is acyloxy.

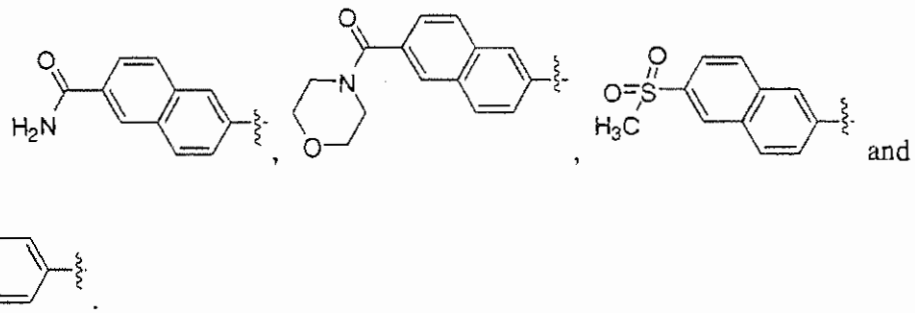
[0216] In another group of embodiments, D^1 is naphthyl.

[0217] The present invention provides in another embodiment, a compound wherein D^1- is selected from the group consisting of:



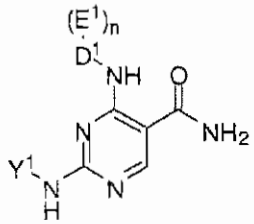
; wherein X is halogen.

[0218] The present invention provides in another embodiment, a compound wherein D^1- is selected from the group consisting of:



In another group of embodiments, D^1 is C_{3-8}cycloalkyl. In another group of embodiments, D^1 is heteroaryl. In another group of embodiments, D^1 is heterocyclyl.

[0219] The present invention provides in another embodiment, a compound having formula (I):

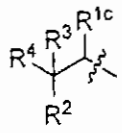


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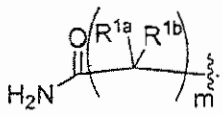
or a pharmaceutically acceptable salt thereof,

wherein:

Y^1 is selected from the group consisting of:



and



;

D^1 is selected from the group consisting of:

(a) phenyl substituted with a heteroaryl group R^5, wherein the phenyl is further optionally substituted with from 1 to 2 substituents, R^{7a}, independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, halo, C_{1-8}alkylsulfonyl and heterocyclyl; and the heteroaryl is optionally further substituted with from 1 to 2 substituents independently selected from the group consisting of C_{1-8}alkyl, hydroxyC_{1-8}alkyl-, aminoC_{1-8}alkyl, C_{1-8}alkylcarbonyl, aminocarbonyl, hydroxy, oxo, halo, haloC_{1-8}alkyl, aminosulfonyl and C_{3-8}cycloalkyl;

(b) naphthyl substituted a substituent , R^{7b}, selected from the group consisting of C_{1-8}alkylsulfonyl, aminosulfonyl, heterocyclylcarbonyl and aminocarbonyl;

(c) C_{3-8}cycloalkyl, optionally substituted with from 1 to 2 substituents, R^{7c}, independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, halo, C_{1-8}alkylsulfonyl and heterocyclyl;

(d) bicyclic heteroaryl; optionally substituted with from 1 to 2 substituents, R^{7d}, independently selected from the group consisting of: C_{1-8} alkyl, C_{1-8}alkylcarbonyl, aminoC_{1-8}alkylenecarbonyl, aminocarbonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenecarbonyl, C_{1-8}alkoxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkoxycarbonyl, aminocarbonyl, amino, C_{1-8} alkoxycarbonylamino, arylC_{1-8} alkoxycarbonylamino, hydroxyl, C_{1-8} alkoxy, C_{1-8}alkylsulfonyl, aminoC_{1-8}alkylenesulfonyl, aminosulfonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenesulfonyl, C_{1-8}alkoxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkoxysulfonyl, aminosulfonyl, oxo, halo, phenyl heterocyclyl and C_{1-8}alkylheterocyclyl; and

(e) heterocyclyl; with from 1 to 2 substituents, R^{7e}, independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, halo, C_{1-8}alkylsulfonyl and heterocyclyl;

each E^1 is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, C_{1-8}alkylthio, aminocarbonyl, C_{1-8}alkoxycarbonylC_{1-8}alkylene, C_{1-8}alkoxycarbonyl$C_{1-8}C_{1-8}$alkoxy, C_{1-8}alkoxycarbonylamino, oxo, halo, cyano, haloC_{1-8}alkyl,

haloC_{1-8}alkoxy, aminosulfonyl, heteroarylsulfinyl; amino, hydroxyl, C_{1-8}arylalkylene, phenyl, aminoC_{1-8}alkyl, aminoC_{3-8}cycloalkyl, heterocyclyl, heteraryl and heterocyclylC_{1-8}alkylene;

each R^{1a}, R^{1b} and R^{1c} is independently selected from the group consisting of: H, C_{1-8}alkyl, hydroxyC_{1-8} alkyl, amino, C_{1-8}alkylamino, C_{1-8} alkoxycarbonylaminoC_{1-8} alkylene, C_{3-8}cycloalkyl, heteroaryl, C_{1-8} alkylC_{3-8}cycloalkyl, C_{1-8}alkylthioC_{1-8} alkyl, C_{1-8}alkylsulfonylC_{1-8} alkylene, aminocarbonyl, aryl, and heterocyclyl; wherein the aryl is optionally substituted by hydroxyl, C_{1-8}alkoxy, halo or haloC_{1-8}alkyl; or taken together with R^3 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or hetercycloalkyl ring;

R^2 is selected from the group consisting of H, amino, arylC_{1-8}alkoxycarbonylamino and hydroxyl;

R^3 is selected from the group consisting of H, C_{1-8}alkyl, C_{1-8}alkylamino, amino C_{1-8}alkylaminoC_{1-8}alkyl, C_{1-8}alkoxyC_{1-8}alkylene, hydroxyC_{1-8}alkyl and hydroxyC_{1-8}alkoxy; or may be combined with R^{1c} or R^4 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring;

R^4 is H or alkyl or may be combined with R^3 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring;

the subscript n is 0, 1, 2, 3 or 4; and

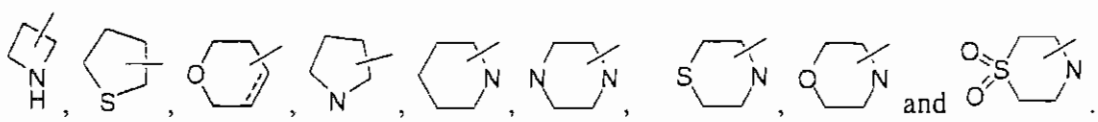
the subscript m is an integer of 1, 2 or 3; and the wavy line indicates the point of attachment to the rest of the molecule.

[0220] The present invention provides in another embodiment, a compound wherein D^1 is C_{3-8}cycloalkyl.

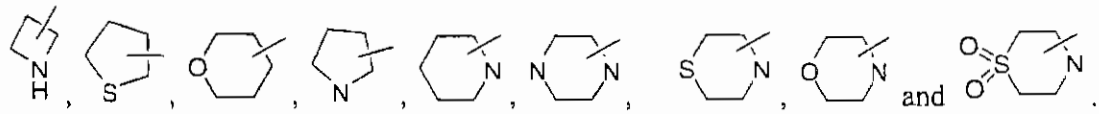
[0221] The present invention provides in another embodiment, a compound wherein D^1 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0222] The present invention provides in another embodiment, a compound wherein D^1 is heterocyclyl.

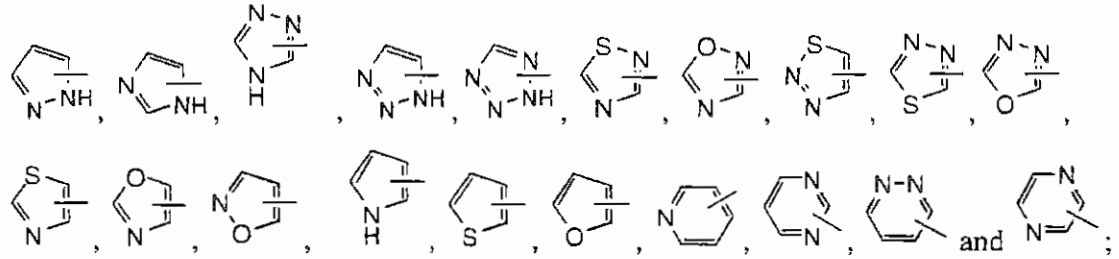
[0223] The present invention provides in another group of embodiments, a compound wherein any of the heterocyclyl groups of formula I is selected from the group consisting of:



[0224] The present invention provides in another embodiment, a compound wherein the heterocyclyl is selected from the group consisting of:

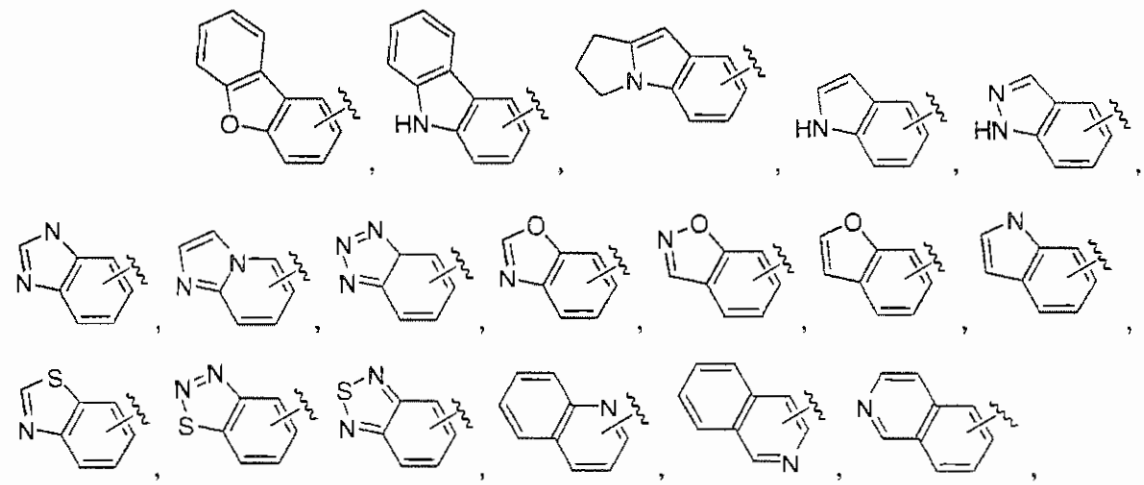


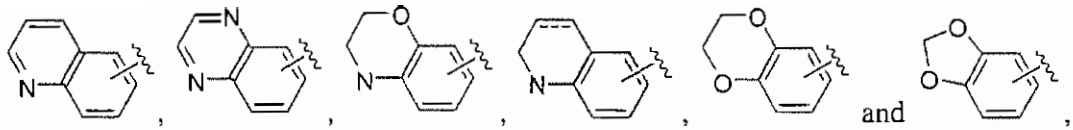
[0225] The present invention provides in another group of embodiments, a compound wherein a heteroaryl group of the compound of formula I is selected from the group consisting of:



each of which is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of: $C_{1\text{-}8}$ alkyl, amino, hydroxyl, oxo, halo, $C_{1\text{-}8}$ alkoxy, hydroxy$C_{1\text{-}8}$alkyl-, amino$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkylcarbonyl, halo$C_{1\text{-}8}$alkyl, $C_{3\text{-}8}$cycloalkyl, $C_{1\text{-}8}$aminocycloalkyl, amino$C_{1\text{-}8}$alkylenecarbonyl, aminocarbonyl, $C_{1\text{-}8}$alkyleneamino$C_{1\text{-}8}$alkylenecarbonyl, $C_{1\text{-}8}$alkoxy$C_{1\text{-}8}$alkylenecarbonyl, hydroxy$C_{1\text{-}8}$alkylenecarbonyl, hydroxy$C_{1\text{-}8}$alkoxycarbonyl, $C_{1\text{-}8}$ alkoxycarbonylamino, aryl, aryl$C_{1\text{-}8}$ alkoxycarbonylamino, $C_{1\text{-}8}$alkylsulfonyl, amino$C_{1\text{-}8}$alkylenesulfonyl, aminosulfonyl, $C_{1\text{-}8}$alkyleneamino$C_{1\text{-}8}$alkylenesulfonyl, $C_{1\text{-}8}$alkoxy$C_{1\text{-}8}$alkylenesulfonyl, hydroxy$C_{1\text{-}8}$alkylenesulfonyl, hydroxy$C_{1\text{-}8}$alkoxysulfonyl, aminosulfonyl, and $C_{1\text{-}8}$alkylheterocyclyl.

[0226] The present invention provides in another group of embodiments, a compound wherein a heteroaryl group of the compound of formula I is a polycyclic heteroaryl group selected from the group consisting of:

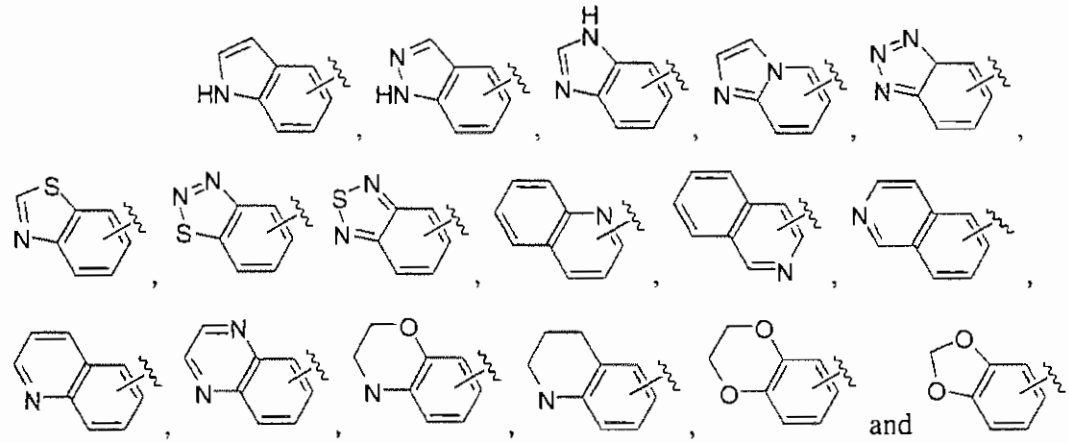




optionally substituted with from 1 to 3 R^{7d} substituents independently selected from the group consisting of: C_{1-8} alkyl, C_{1-8}alkylcarbonyl, C_{1-8}aminocycloalkyl, aminoC_{1-8}alkylenecarbonyl, aminocarbonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenecarbonyl, C_{1-8}alkoxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkoxycarbonyl, aminocarbonyl, amino, C_{1-8} alkoxycarbonylamino, aryl, arylC_{1-8} alkoxycarbonylamino, hydroxyl, C_{1-8} alkoxy, C_{1-8}alkylsulfonyl, aminoC_{1-8}alkylenesulfonyl, aminosulfonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenesulfonyl, C_{1-8}alkoxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkoxysulfonyl, aminosulfonyl, oxo, halo, phenyl and C_{1-8}alkylheterocyclyl; and the wavy line indicates the point of attachment to the rest of the molecule.

[0227] The present invention provides in another embodiment, a compound wherein: D^1 is bicyclic heteroaryl.

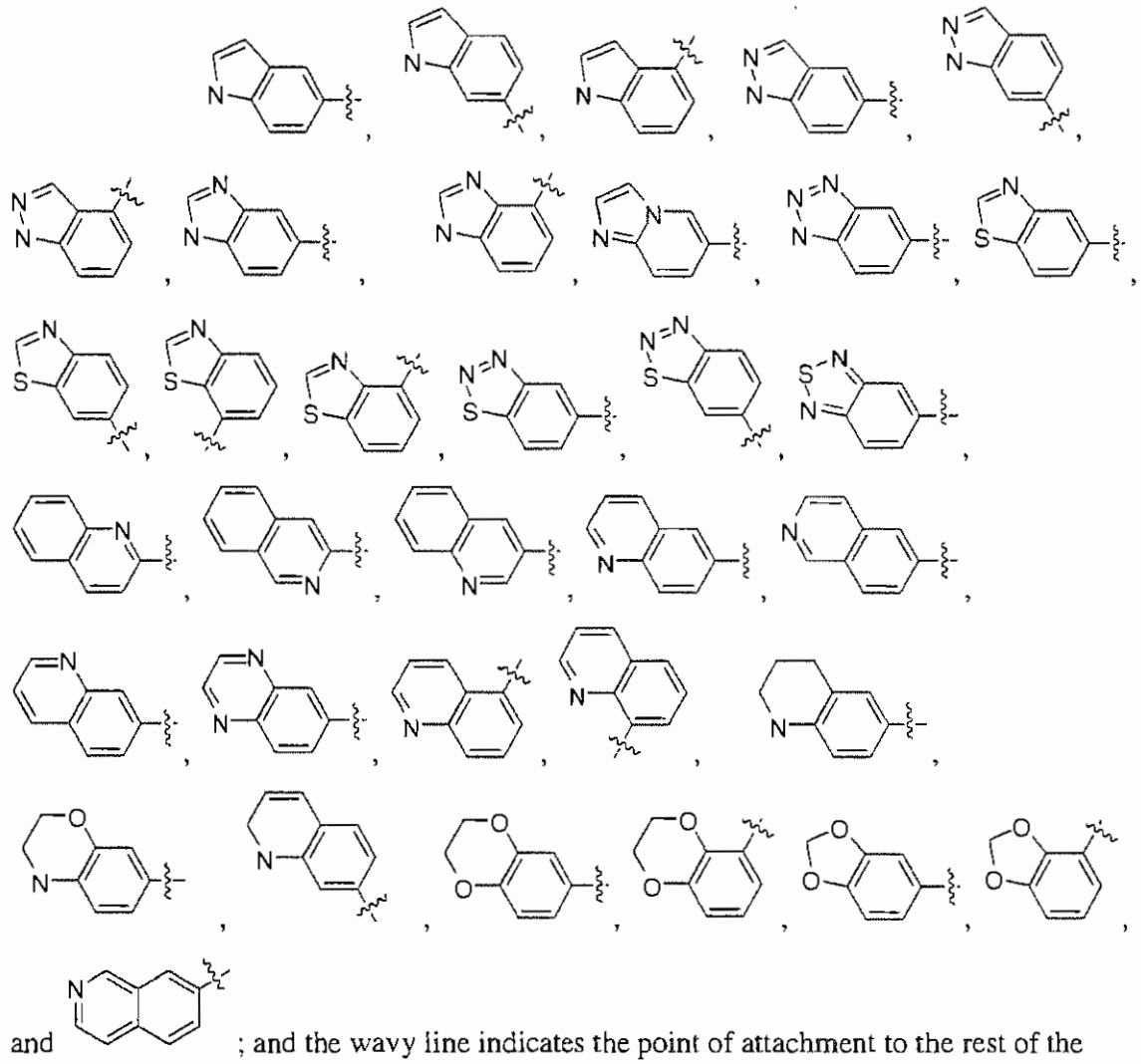
[0228] The present invention provides in another embodiment, a compound wherein D^1 is selected from the group consisting of:



optionally substituted with from 1 to 3 R^{7d} substituents independently selected from the group consisting of: C_{1-8} alkyl, C_{1-8}alkylcarbonyl, aminoC_{1-8}alkylenecarbonyl, aminocarbonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenecarbonyl, C_{1-8}alkoxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkoxycarbonyl, aminocarbonyl, amino, C_{1-8} alkoxycarbonylamino, arylC_{1-8} alkoxycarbonylamino, hydroxyl, C_{1-8} alkoxy, C_{1-8}alkylsulfonyl, aminoC_{1-8}alkylenesulfonyl, aminosulfonyl,

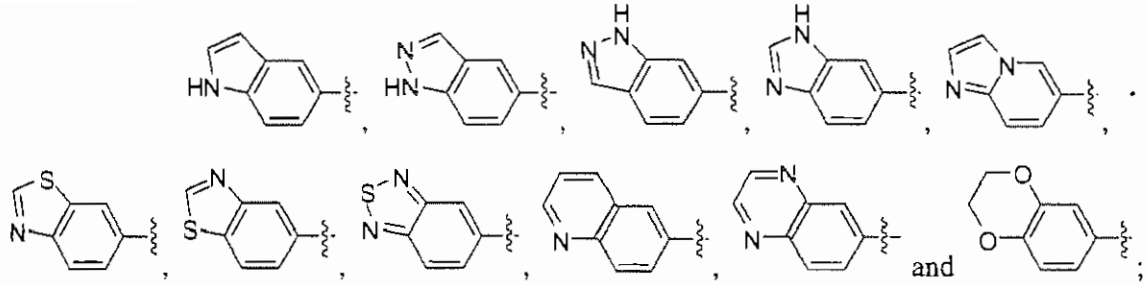
C_{1-8}alkyleneaminoC_{1-8}alkylenesulfonyl, C_{1-8}alkoxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkoxysulfonyl, aminosulfonyl, oxo, halo, phenyl and C_{1-8}alkylheterocyclyl; and the wavy line indicates the point of attachment to the rest of the molecule.

[0229] The present invention provides in another embodiment, a compound wherein D^1 is selected from the group consisting of:



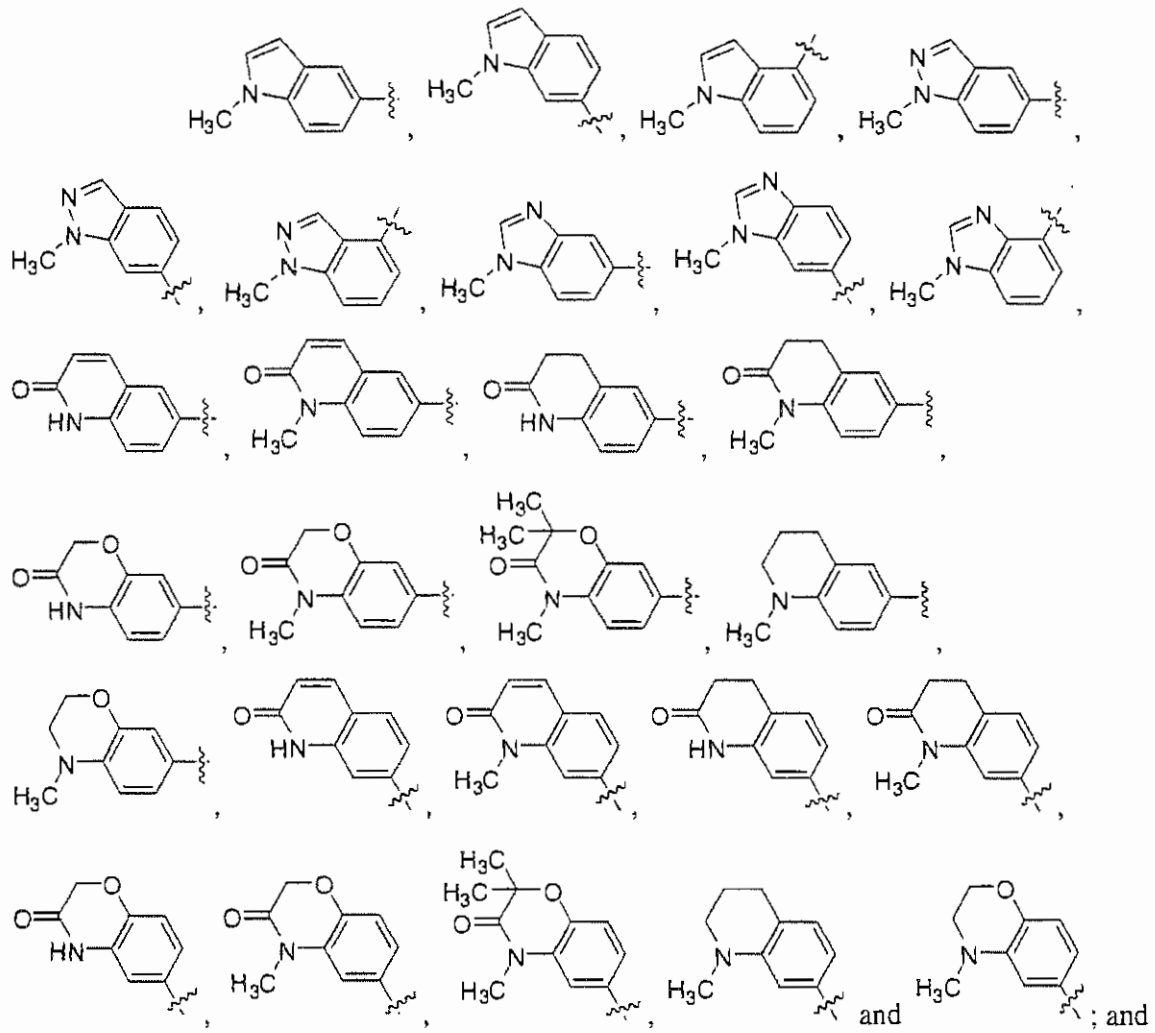
and ; and the wavy line indicates the point of attachment to the rest of the molecule.

[0230] The present invention provides in another embodiment, a compound wherein D^1 is selected from the group consisting of:



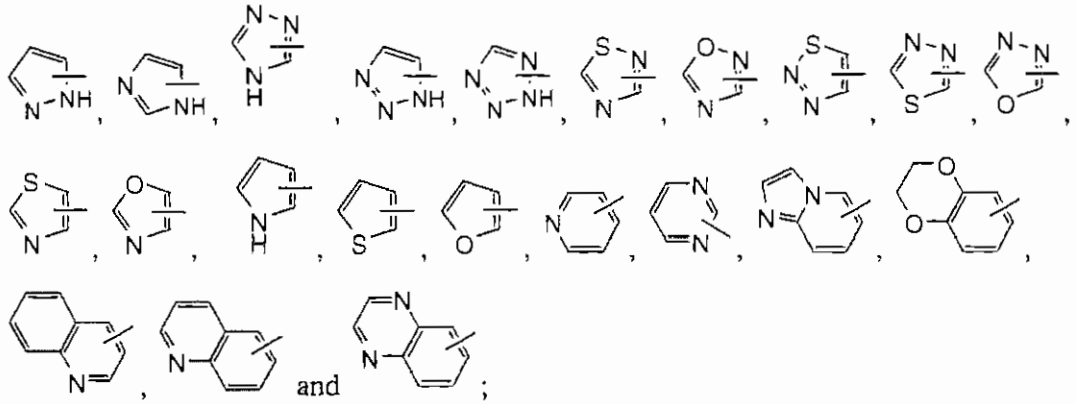
and the wavy line indicates the point of attachment to the rest of the molecule.

[0231] The present invention provides in another embodiment, a compound wherein D^1 is selected from the group consisting of:



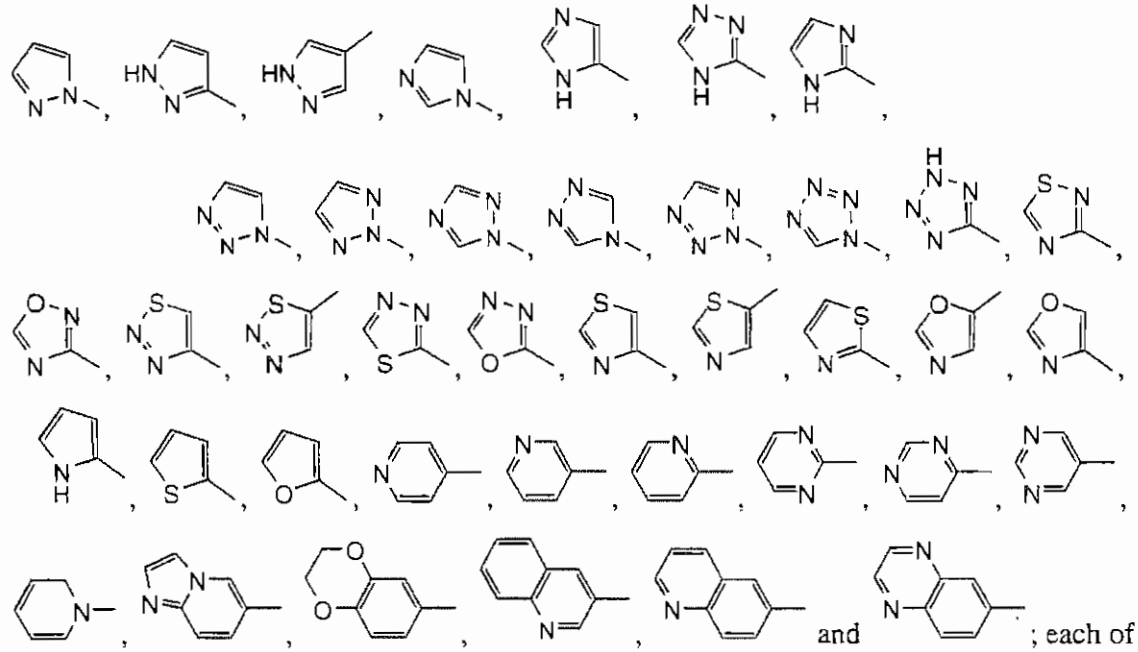
the wavy line indicates the point of attachment to the rest of the molecule.

[0232] The present invention provides in another embodiment, a compound wherein R^5 is selected from the group consisting of



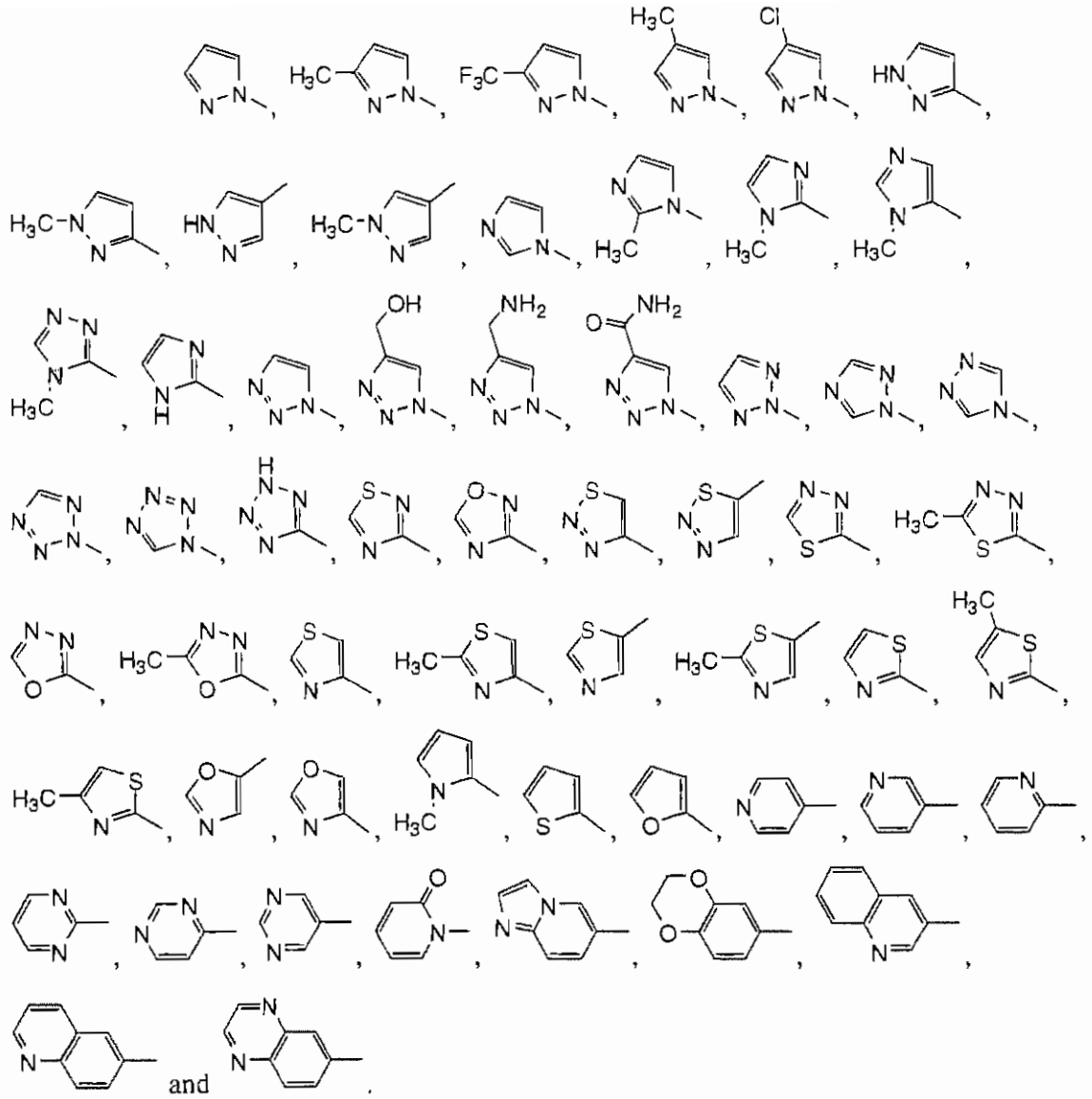
each of which is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of $C_{1\text{-}8}$alkyl, hydroxy$C_{1\text{-}8}$alkyl-, amino$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkylcarbonyl, aminocarbonyl, hydroxy, oxo, halo, halo$C_{1\text{-}8}$alkyl, aminosulfonyl and $C_{3\text{-}8}$cycloalkyl.

[0233] The present invention provides in another embodiment, a compound wherein R^5 is selected from the group consisting of



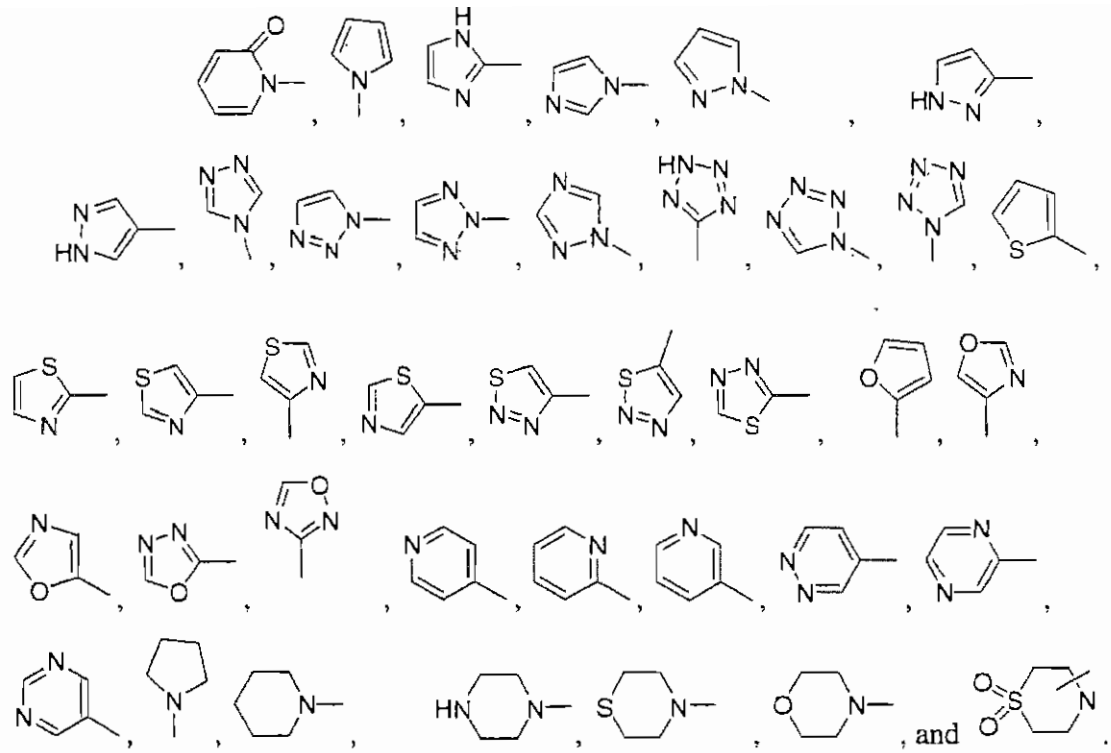
each of which is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of $C_{1\text{-}8}$alkyl, hydroxy$C_{1\text{-}8}$alkyl-, amino$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkylcarbonyl, aminocarbonyl, hydroxy, oxo, halo, halo$C_{1\text{-}8}$alkyl, aminosulfonyl and $C_{3\text{-}8}$cycloalkyl.

[0234] The present invention provides in another embodiment, a compound wherein R^5 is selected from the group consisting of

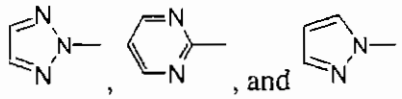


[0235] The present invention provides in another embodiment, a compound wherein each E^1 is independently selected from the group consisting of $C_{1\text{-}8}$alkyl, heteroaryl, heterocyclyl, halo, $C_{1\text{-}8}$haloalkyl, $C_{1\text{-}8}$alkoxy, $C_{1\text{-}8}$acyl, amino$C_{1\text{-}8}$alkyl, aminosulfonyl, $C_{1\text{-}8}$alkylsulfonyl and acylamino.

[0236] The present invention provides in another embodiment, a compound wherein each E^1 is independently selected from the group consisting of

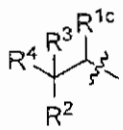


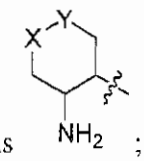
[0237] The present invention provides in another embodiment, a compound wherein each E^1 is independently selected from the group consisting of



[0238] The present invention provides in another embodiment, a compound wherein R^2 is amino.

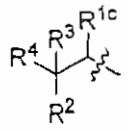
[0239] The present invention provides in another embodiment, a compound wherein the moiety:



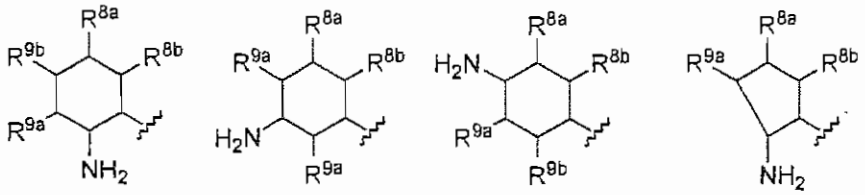
is ;

wherein X and Y is each independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

[0240] The present invention provides in another embodiment, a compound wherein the moiety:



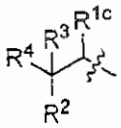
is selected from the group consisting of:



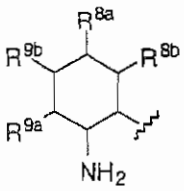
; wherein each R^{8a} and R^{8b} is independently H, hydroxyl, halo or if on adjacent carbon atoms, may be combined with the atoms to which they are attached to form a fused benzene ring; and

each R^{9a} and R^{9b} is independently H, hydroxyl, halo or, if on adjacent carbon atoms, may be combined with the atoms to which they are attached to form a fused benzene ring; and the wavy line indicates the point of attachment to the rest of the molecule.

[0241] The present invention provides in another embodiment, a compound wherein the moiety:

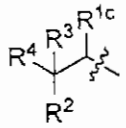


is

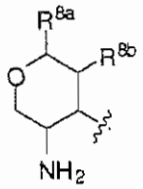


; wherein each R^{8a} and R^{8b} is independently H or may be combined with the atoms to which they are attached to form a fused benzene ring; and each R^{9a} and R^{9b} is independently H or may be combined with the atoms to which they are attached to form a fused benzene ring; and the wavy line indicates the point of attachment to the rest of the molecule.

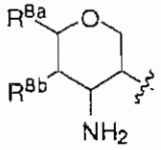
[0242] The present invention provides in another embodiment, a compound wherein: the moiety:



is



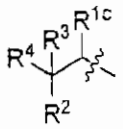
or



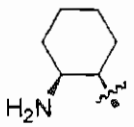
;

wherein each R^{8a} and R^{8b} is independently H or may be combined with the atoms to which they are attached to form a fused benzene ring; and the wavy line indicates the point of attachment to the rest of the molecule.

[0243] The present invention provides in another group of embodiments, a compound wherein the moiety:

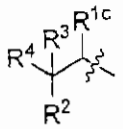


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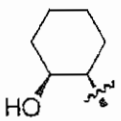


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[0244] The present invention provides in another group of embodiments, a compound wherein the moiety:



is



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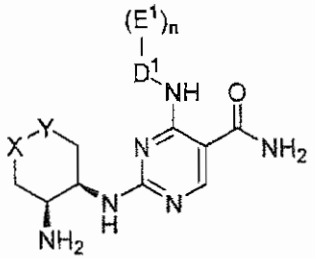
[0245] The present invention provides in another group of embodiments, a compound wherein R^{1c} is selected from the group consisting of: C_{1-8}alkyl, hydroxyC_{1-8} alkyl, C_{1-8}alkoxyC_{1-8}alkyl and haloC_{1-8}alkyl;

R^2 is selected from the group consisting of H, amino and C_{1-8}alkylamino;

R^3 is selected from the group consisting of H, C_{1-8}alkyl, C_{1-8}alkylamino, aminoC_{1-8}alkyl, carboxy, aminoC_{1-8}alkylaminoC_{1-8}alkyl, C_{1-8}alkoxyC_{1-8}alkyl, hydroxyC_{1-8}alkyl, carboxyC_{1-8}alkyl, C_{3-8}cycloalkylC_{1-8}alkyl, aryloxyC_{1-8}alkyl, arylC_{1-8}alkyl, heteroarylC_{1-8}alkyl, and hydroxyC_{1-8}alkoxy; or may be combined with R^{1c} or R^4 and the atoms to which they are attached to form a C_{3-8}cycloalkyl or heterocyclyl ring;

R^4 is H or alkyl or may be combined with R^3 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring.

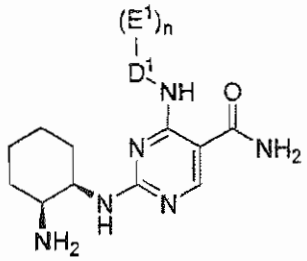
[0246] The present invention provides in another group of embodiments, a compound having the formula:



;

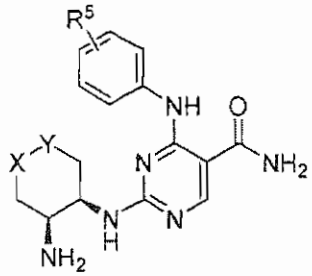
wherein each X and Y is independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

[0247] The present invention provides in another group of embodiments, a compound having the formula:



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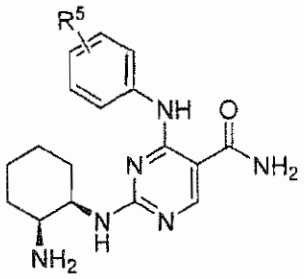
[0248] The present invention provides in another group of embodiments, a compound having the formula:



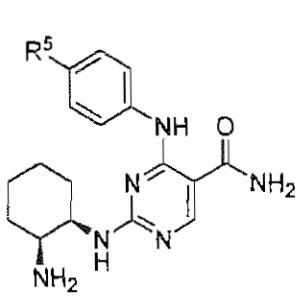
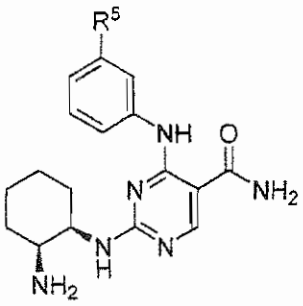
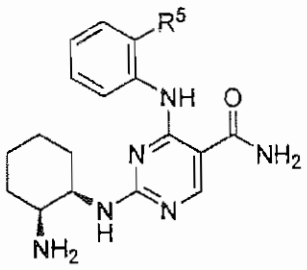
;

wherein each X and Y is independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

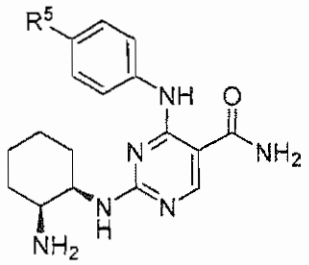
[0249] The present invention provides in another group of embodiments, a compound having the formula:



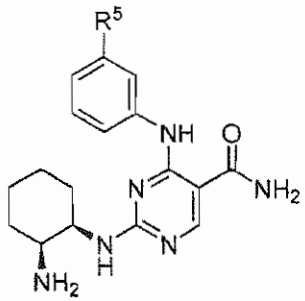
[0250] The present invention provides in another group of embodiments, a compound having a formula selected from the group consisting of:


,

and

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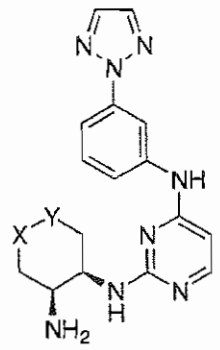
[0251] The present invention provides in another group of embodiments, a compound having the formula:



[0252] The present invention provides in another group of embodiments, a compound having the formula:

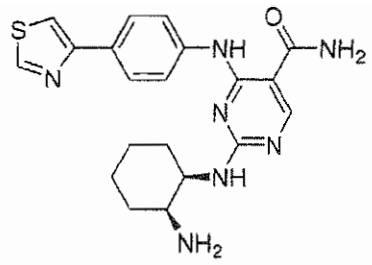
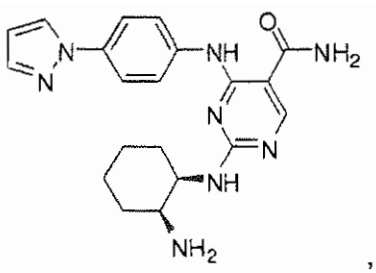
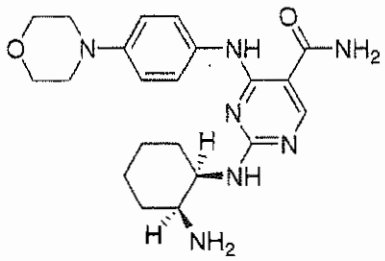
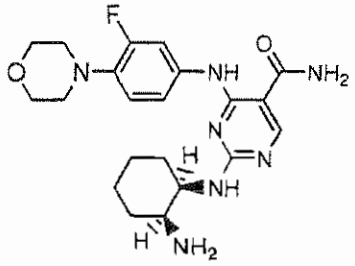
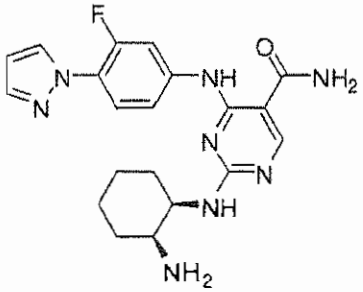
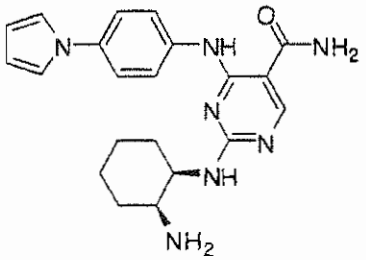
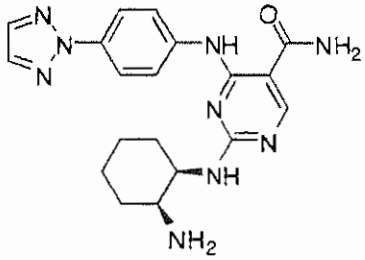


[0253] The present invention provides in another group of embodiments, a compound having the formula:

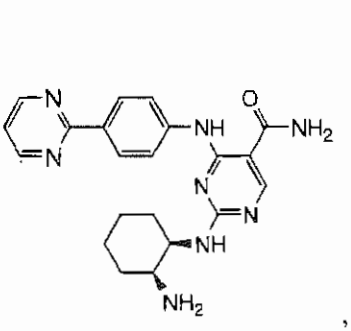
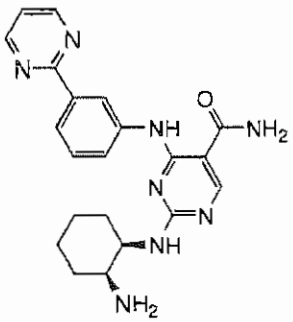
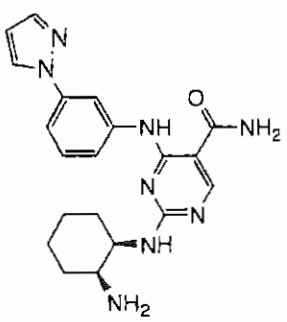
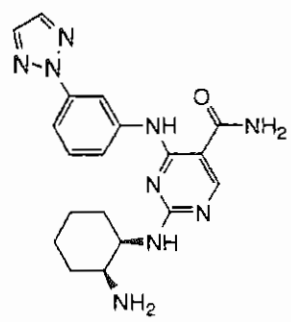
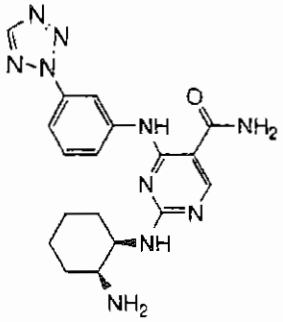
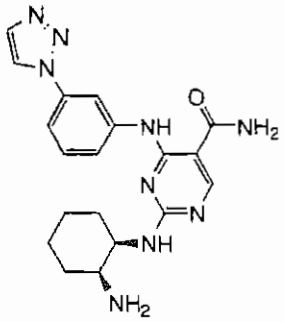

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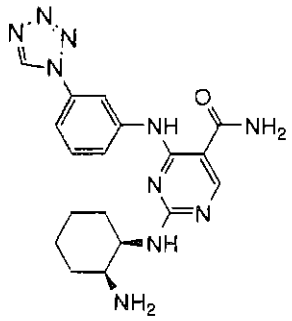
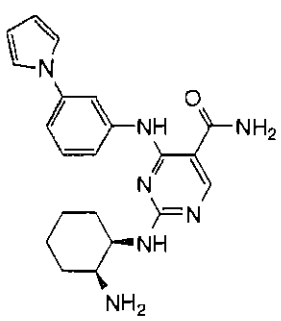
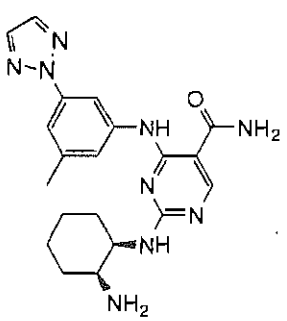
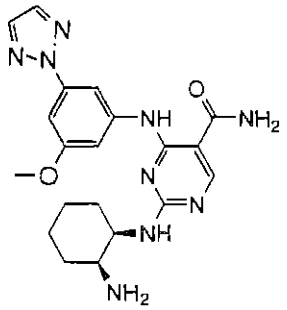
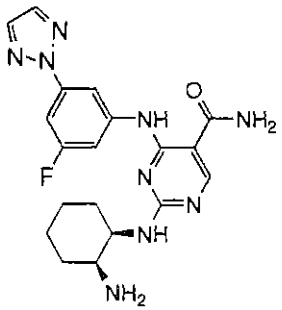
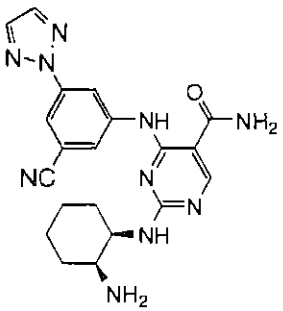
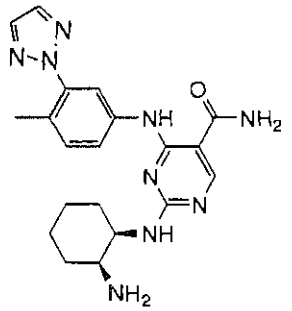
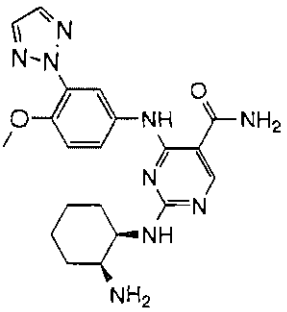
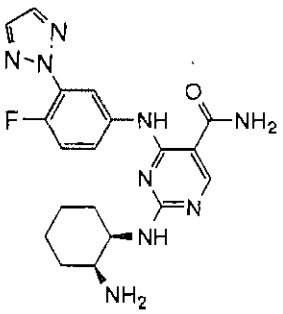
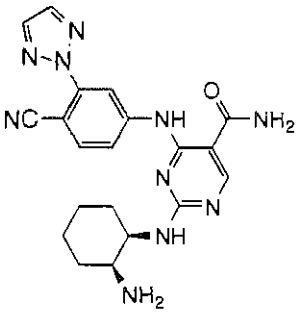
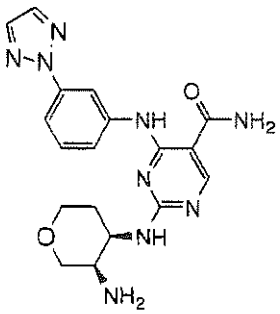
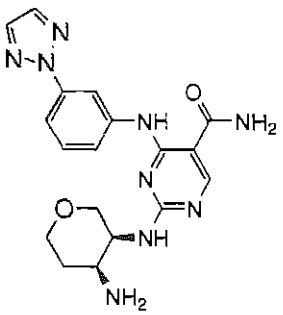
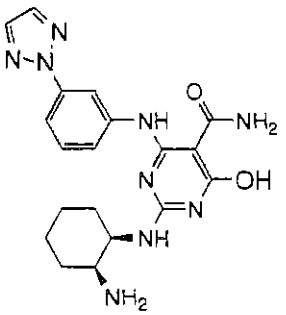
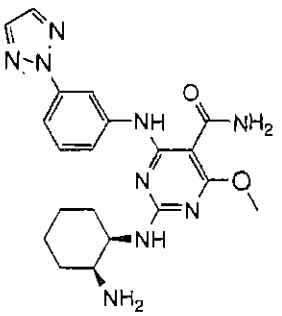
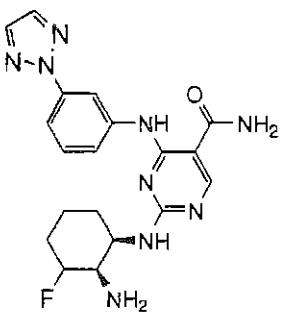
wherein each X and Y is independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

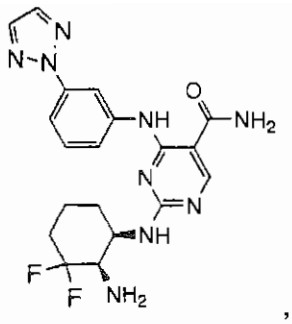
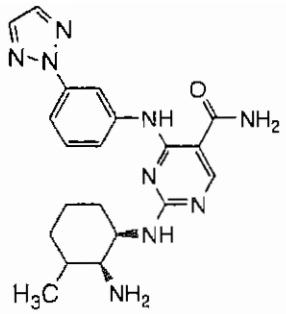
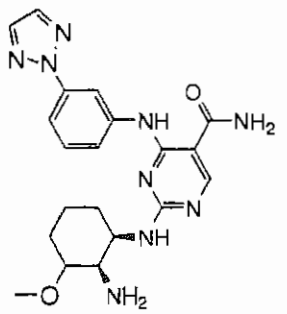
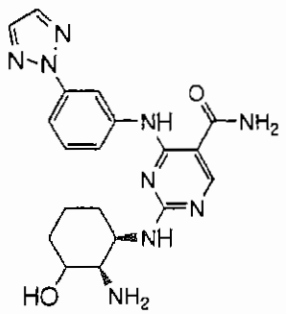
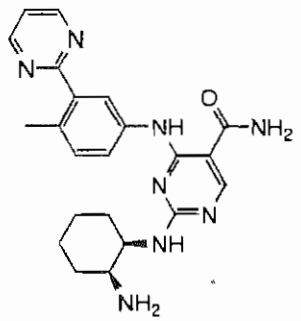
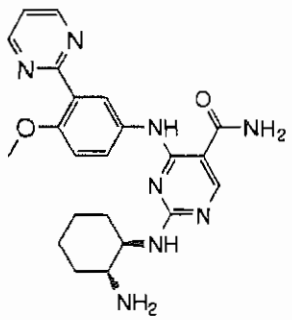
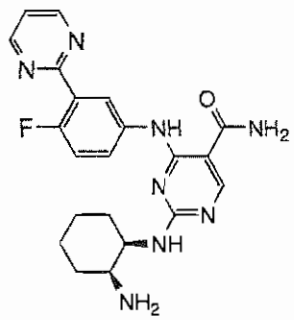
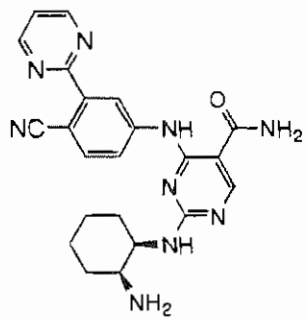
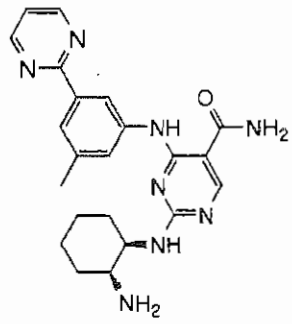
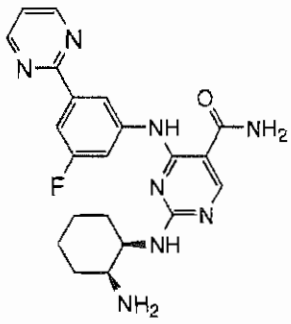
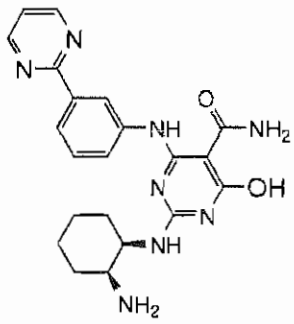
[0254] The present invention provides in another embodiment, a compound selected from the group consisting of:


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and .

[0255] The present invention provides in another embodiment, a compound selected from the group consisting of:

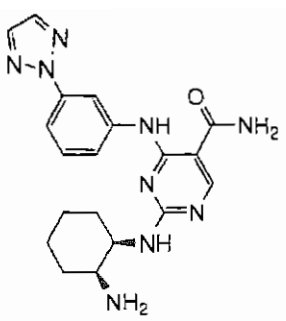
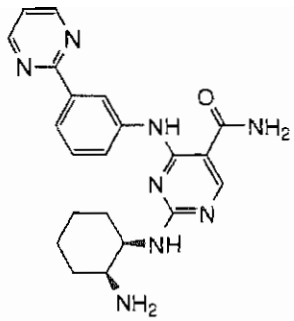

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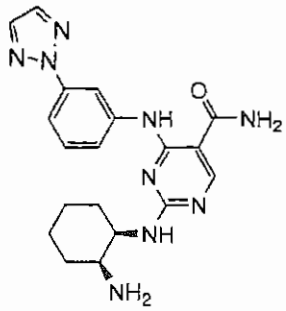












and

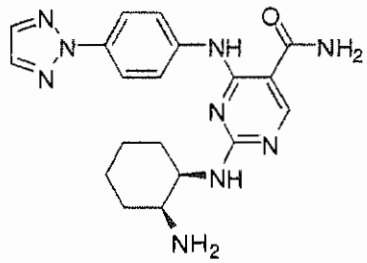
5 **[0256]** The present invention provides in another embodiment, a compound, having the fomula:


and


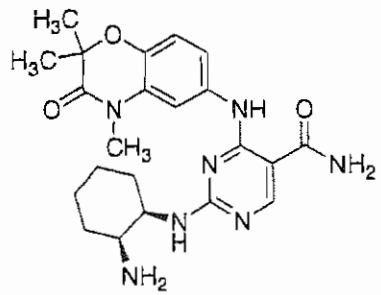
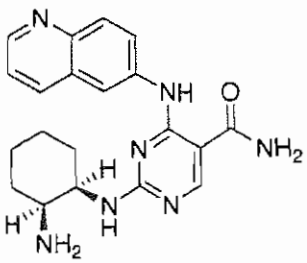
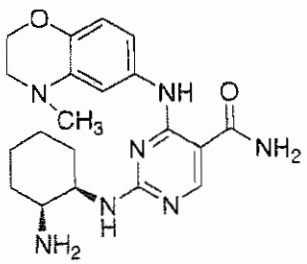
[0257] The present invention provides in another embodiment, a compound, having the fomula:



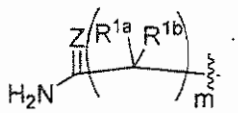
[0258] The present invention provides in another embodiment, a compound, having the fomula:



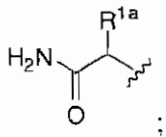
[0259] The present invention provides in another embodiment, a compound selected from the group consisting of:


,

and


[0260] The present invention provides in another embodiment, a compound wherein the moiety:



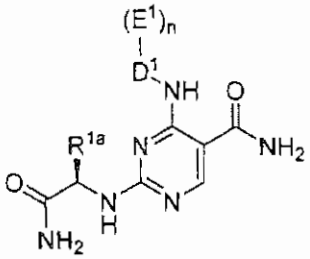
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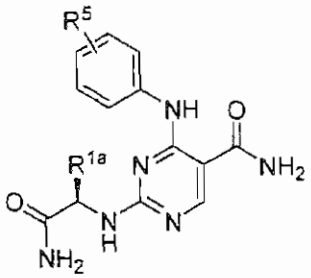
;

and the wavy line indicates the point of attachment to the rest of the molecule.

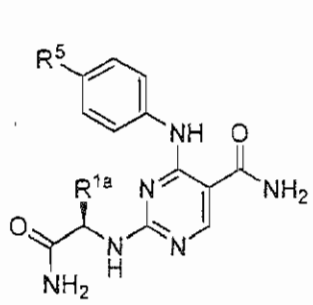
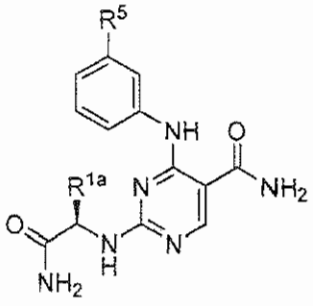
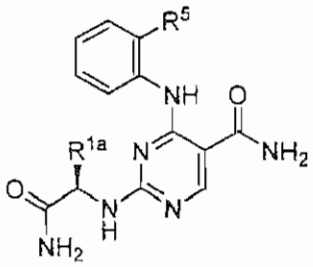
[0261] The present invention provides in another group of embodiments, a compound having the formula:



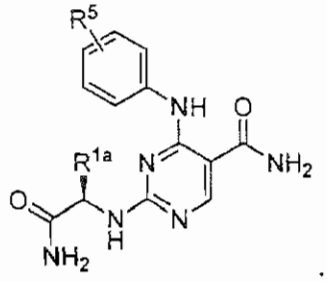
[0262] The present invention provides in another group of embodiments, a compound having the formula:



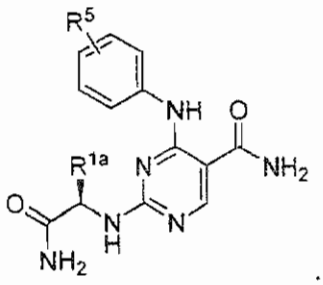
[0263] The present invention provides in another group of embodiments, a compound having a formula selected from the group consisting of:



and


[0264] The present invention provides in another group of embodiments, a compound having the formula:



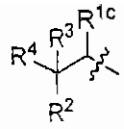
[0265] The present invention provides in another group of embodiments, a compound having the formula:



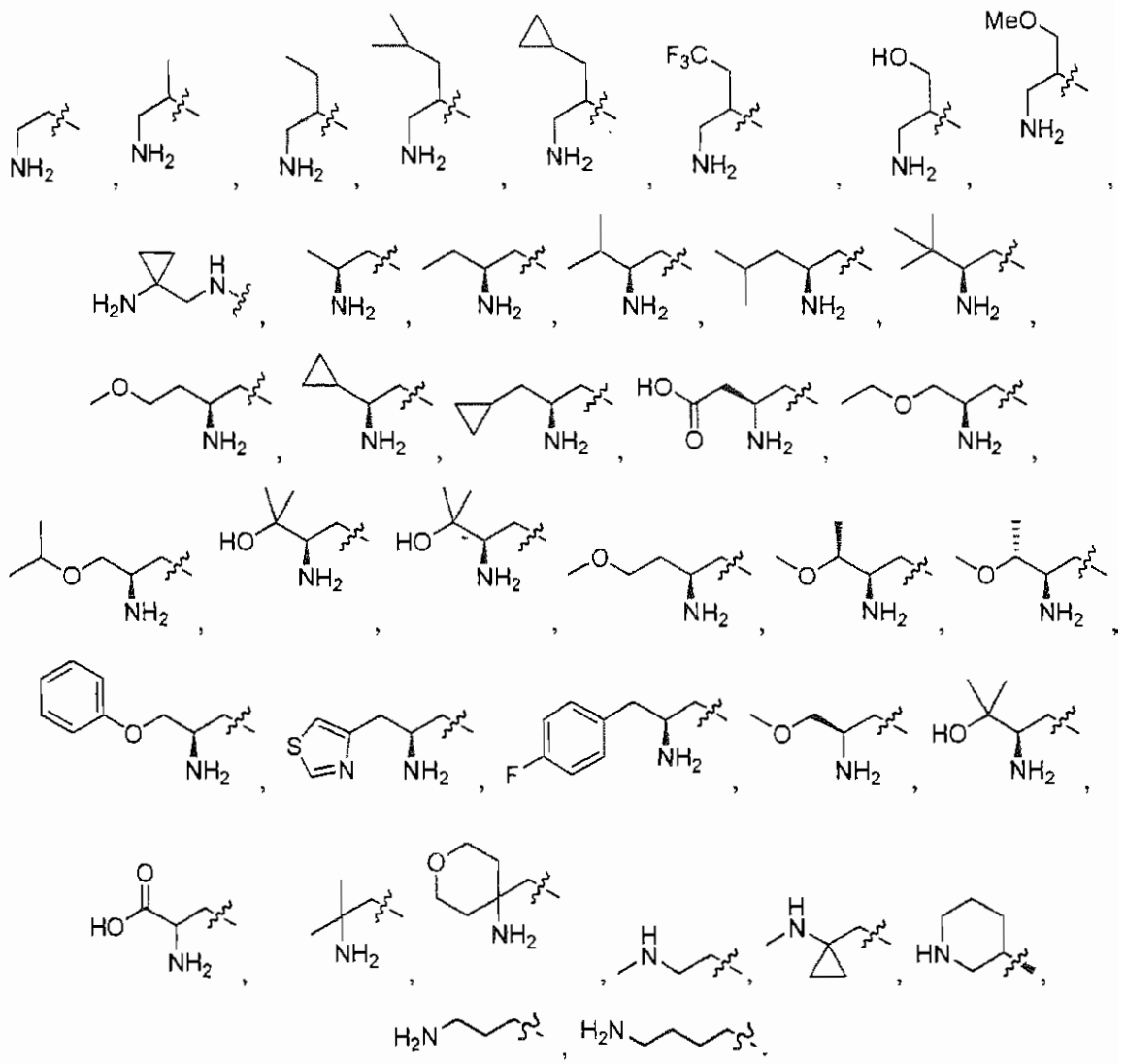
[0266] The present invention provides in another embodiment, a compound wherein R^{1a} is selected from the group consisting of C_{1-8}alkyl, hydroxylC_{1-8}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl and heterocyclyl.

[0267] The present invention provides in another embodiment, a compound wherein R^{1a} is selected from the group consisting of C_{1-8}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl and heterocyclyl.

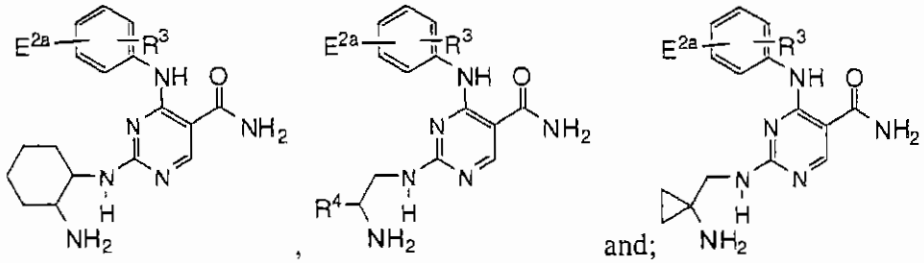
[0268] The present invention provides in another group of embodiments, a compound wherein the moiety:



is selected from the group consisting of:



[0269] The present invention provides in another embodiment, a compound having the structure selected from the group consisting of formula IIa-c:



and;

IIa IIb IIc

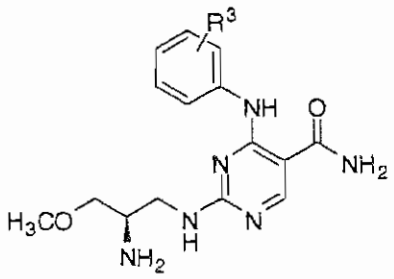
or a pharmaceutically acceptable salt thereof, wherein:

E^{2a} is selected from the group consisting of C_{1-8} alkoxy, C_{1-8}alkylC_{3-8}cycloalkylcarbonylamino, C_{1-8}alkoxyC_{1-8}alkylenecarbonylamino-, C_{1-8}alkoxycarbonylamino and C_{1-8}alkylcarbonylamino;

R^3 is selected from the group consisting of H, halo, C_{1-8}alkyl and C_{1-8}alkoxy; and

R^4 is selected from the group consisting of H, C_{1-8}alkyl and C_{1-8}alkoxy C_{1-8}alkylene.

[0270] The present invention provides in another embodiment, a compound having formula (IId):

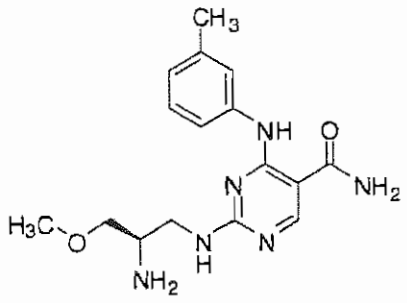


(IId)

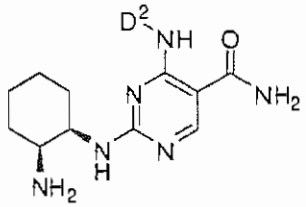
or a pharmaceutically acceptable salt thereof,

wherein R^3 is H or C_{1-8}alkyl.

[0271] The present invention provides in another embodiment, a compound having formula:



[0272] The present invention provides in another embodiment, a compound having formula (IIe):

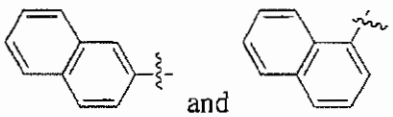


(IIe)

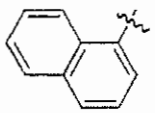
wherein: D^2 is a bicyclic aryl group.

[0273] The present invention provides in another embodiment, a compound wherein: D^2 is naphthyl, optionally substituted with from 1 to 2 substituents, E^{2b}, independently selected from the group consisting of halo, $C_{1\text{-}8}$alkoxy and $C_{1\text{-}8}$alkylaminocarbonyl.

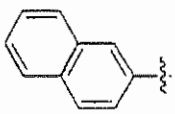
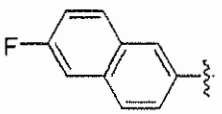
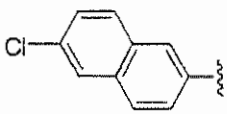
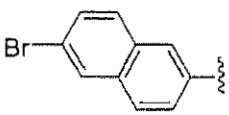
[0274] The present invention provides in another embodiment, a compound wherein D^2 is

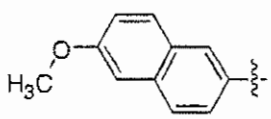
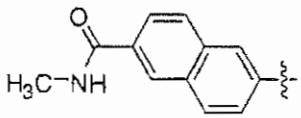
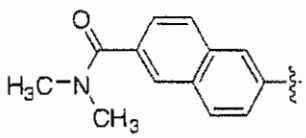
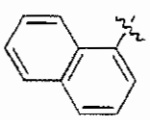
 and .

[0275] The present invention provides in another embodiment, a compound wherein D^2 is

.

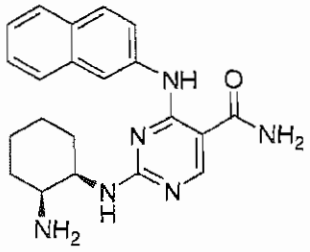
[0276] The present invention provides in another embodiment, a compound wherein D^2 is selected from the group consisting of:

, , , ,

, ,  and ;

and the wavy line indicates the point of attachment to the rest of the molecule.

[0277] The present invention provides in another embodiment, a compound, having the formula



[0278] The present invention provides in another embodiment, a compound having the structure found in the Examples.

[0279] The present invention provides in another embodiment, a compound having the structure found in the tables.

[0280] It is understood that in another group of embodiments, any of the above embodiments may also be combined with other embodiments listed herein, to form other embodiments of the invention.

b. Methods of Synthesis

[0281] The compounds of the present invention may be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples. In general, the compounds of structure (I) above may be made by the following **Figure 3**, wherein all substituents are as defined above unless indicated otherwise.

[0282] Compounds having formula I may be prepared according to **Figure 3**. Carboxylic acid 1.1 is converted to acid chloride 1.2 via a one-step procedure by treatment with a chlorination agent, such as thionyl chloride, and esterification with an alcohol, such as ethanol, to form compound 1.3 using conditions similar to that described below. Ester 1.3 is dichlorinated with a chlorinating agent, such as phosphorous oxychloride. Selective displacement of the 4-chloro group of the 2,4-dichloropyrimidine by an appropriate amine, such as E^1-D^1-NH_2 (available commercially or synthesized using methods known to those skilled in the art), under basic conditions, such as with diisopropylamine (DIA), provides compounds of formula 1.5. Subsequent hydrolysis of the ester, displacement of the second chloro group with EDC and treatment with ammonia gives compound 1.7. Benzotriazolyl ether compound 1.7 may also be prepared through a linear route. Displacement of the benzotriazolyl ether group with an appropriate amine, such as Y^1-NH_2 (available commercially or synthesized using methods known to those skilled in the art), gives the desired product I, wherein E^1-D^1 and Y^1 are as previously defined.

[0283] One skilled in the art will recognize that in certain embodiments of structure (I) when E^1-D^1 or Y^1 comprises a terminal heteroatom, it may be advantageous to use a protecting group strategy. The protecting group can be removed using methods known to those skilled in the art to yield compounds of structure (1).

[0284] The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form of acid addition salts as described below.

c. Inhibition of syk Kinase

[0285] The activity of a specified compound as an inhibitor of a syk kinase may be assessed in vitro or in vivo. In some embodiments, the activity of a specified compound can be tested in a cellular assay. Selectivity could also be ascertained in biochemical assays with isolated kinases.

[0286] Similar types of assays can be used to assess JAK kinase inhibitory activity and to determine the degree of selectivity of the particular compound as compared to syk kinase. One means of assaying for such inhibition is detection of the effect of the compounds of the present invention on the upregulation of downstream gene products. In the Ramos/IL4 assay, B-cells are stimulated with the cytokine Interleukin-4 (IL-4) leading to the activation of the JAK/Stat pathway through phosphorylation of the JAK family kinases, JAK1 and JAK3, which in tum phosphorylate and activate the transcription factor Stat-6. One of the genes upregulated by activated Stat-6 is the low affinity IgE receptor, CD23. To study the effect of inhibitors (e.g., the 2,4-substituted pyrimindinediamine compounds described herein) on the JAK1 and JAK3 kinases, human Ramos B-cells are stimulated with human IL-4. 10' post-stimulation, cells are subjected to intracellular flow cytometry to measure the extent of STAT-6 phosphorylation. 20 to 24 hours post-stimulation, cells are stained for upregulation of CD23 and analyzed using flow cytometry. A reduction of the amount of phospohorylated STAT-6 and/or cell surface CD23 present compared to control conditions indicates that the test compound actively inhibits the JAK kinase pathway.

[0287] Additionally, IL-6 stimulation of Ramos B-cells induces JAKs 1, 2, and Tyk2, leading to Stat-3 and Erk phosphorylation. 10' post-stimulation, cells are subjected to intracellular flow cytometry to measure the ability of compound to inhibit these

phosphorylation events. To specifically measure the activity of JAK2, the CellSensor irf1-bla HEL cell line expressing the beta-lactamase reporter gene controlled by Stat5 will be used (Invitrogen, Carlsbad, CA). These cells express a constituitively active JAK2 mutant (JAK2V617F), found naturally in myeloproliferative neoplasms (Constantinescu, S., *et.al, Trends Biochem. Sci.*, 2008; 33:122-31). A reduction in the amount of beta-lactamase reporter gene expression is used a measure of the JAK2 inhibitory activity of compounds.

[0288] The activity of the compounds of the invention may additionally be characterized by assaying the effect of the compounds of the present invention described herein on A549 lung epithelial cells and U937 cells. A549 lung epithelial cells and U937 cells up-regulate ICAM-1 (CD54) surface expression in response to a variety of different stimuli. Therefore, using ICAM-1 expression as readout, test compound effects on different signaling pathways can be assessed in the same cell type. Stimulation with IL-1β through the IL-1 β receptor activates the TRAF6/NFκB pathway resulting in up-regulation of ICAM-1. IFN.gamma. induces ICAM-1 up-regulation through activation of the JAK1/JAK2 pathway. The up-regulation of ICAM-1 can be quantified by flow cytometry across a compound dose curve and EC_{50} values are calculated.

[0289] The activity of the compounds of the invention may additionally be characterized by assaying the effect of the compounds of the present invention described herein on A549 lung epithelial cells and U937 cells. A549 lung epithelial cells and U937 cells up-regulate ICAM-1 (CD54) surface expression in response to a variety of different stimuli. Therefore, using ICAM-1 expression as readout, test compound effects on different signaling pathways can be assessed in the same cell type. Stimulation with IL-1β through the IL-1 β receptor activates the TRAF6/NFκB pathway resulting in up-regulation of ICAM-1. IFN.gamma. induces ICAM-1 up-regulation through activation of the JAK1/JAK2 pathway. The up-regulation of ICAM-1 can be quantified by flow cytometry across a compound dose curve and EC_{50} values are calculated. Exemplary assays of this type are described in greater detail in the Examples.

[0290] Active compounds as described herein generally inhibit the JAK kinase pathway with an IC_{50} in the range of about 1 mM or less, as measured in the assays described herein. Of course, skilled artisans will appreciate that compounds which exhibit lower IC_{50}s, (on the order, for example, of 100 μM, 75 μM, 50 μM, 40 μM, 30 μM, 20 μM, 15 μM, 10 μM, 5 μM, 1 μM, 500 nM, 100 nM, 10 nM, 1 nM, or even lower) can be particularly useful in therapeutic applications. In instances where activity specific to a particular cell type is

desired, the compound can be assayed for activity with the desired cell type and counter-screened for a lack of activity against other cell types. The desired degree of "inactivity" in such counter screens, or the desired ratio of activity vs. inactivity, may vary for different situations and can be selected by the user.

[0291] The active compounds also typically inhibit IL-4 stimulated expression of CD23 in B-cells with an IC_{50} in the range of about 20 μM or less, typically in the range of about 10 μM, 1 μM, 500 nM, 100 nM, 10 nM, 1 nM, or even lower. A suitable assay that can be used is the assay described in the Examples, "Assay for Ramos B-cell Line Stimulated with IL-4." In certain embodiments, the active compounds of the present invention have an IC_{50} of less than or equal to 5 μM, greater than 5 μM but less than 20 μM, greater than 20 μM, or greater than 20 μM but less than 50 μM in the assay described in the Examples.

[0292] The active compounds also typically inhibit expression of ICAM1 (CD54) induced by IFN.gamma. exposure in U937 or A549 cells with an IC_{50} in the range of about 20 μM or less, typically in the range of about 10 μM, 1 μM, 500 nM, 100 nM, 10 nM, 1 nM, or even lower. The IC_{50} against expression of ICAM (CD54) in IFN.gamma. stimulated cells can be determined in a functional cellular assay with an isolated A549 or U937 cell line. Suitable assays that can be used are the assays described in the Examples, "A549 Epithelial Line Stimulated with IFNγ" and "U937 IFN.gamma. ICAM1 FACS Assay," respectively. In certain embodiments, the active compounds of the present invention have an IC_{50} of less than or equal to 20 μM, greater than 20 μM, or greater than 20μM but less than 50 μM in the assays described in the Examples.

d. Compositions and Methods of Administration

[0293] The present invention further provides compositions comprising one or more compounds of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, and a pharmaceutically acceptable carrier or diluent. It will be appreciated that the compounds of formula (I)) in this invention may be derivatized at functional groups to provide prodrug derivatives which are capable of conversion back to the parent compounds *in vivo*. Examples of such prodrugs include the physiologically acceptable and metabolically labile ester derivatives, such as methoxymethyl esters, methylthiomethyl esters, or pivaloyloxymethyl esters derived from a hydroxyl group of the compound or a carbamoyl moiety derived from

an amino group of the compound. Additionally, any physiologically acceptable equivalents of the compounds of formula (I), similar to metabolically labile esters or carbamates, which are capable of producing the parent compounds of formula (I) *in vivo*, are within the scope of this invention.

[0294] As used herein, the term "pharmaceutically acceptable salts" refers to any acid or base addition salt whose counter-ions are non-toxic to the patient in pharmaceutical doses of the salts. A host of pharmaceutically acceptable salts are well known in the pharmaceutical field. If pharmaceutically acceptable salts of the compounds of this invention are utilized in these compositions, those salts are preferably derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, lucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, hydrohalides (*e.g.*, hydrochlorides and hydrobromides), sulphates, phosphates, nitrates, sulphamates, malonates, salicylates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, ethanesulphonates, cyclohexylsulphamates, quinates, and the like. Pharmaceutically acceptable base addition salts include, without limitation, those derived from alkali or alkaline earth metal bases or conventional organic bases, such as triethylamine, pyridine, piperidine, morpholine, N-methylmorpholine, ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

[0295] Furthermore, the basic nitrogen-containing groups may be quaternized with agents like lower alkyl halides, such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides, such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

[0296] The compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (*e.g.*, blood, lymphatic system, central nervous system, etc.), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

[0297] The pharmaceutical compositions of the invention can be manufactured by methods well known in the art such as conventional granulating, mixing, dissolving, encapsulating, lyophilizing, or emulsifying processes, among others. Compositions may be produced in various forms, including granules, precipitates, or particulates, powders, including freeze dried, rotary dried or spray dried powders, amorphous powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. Formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these.

[0298] The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of drug calculated to produce the desired onset, tolerability, and/or therapeutic effects, in association with a suitable pharmaceutical excipient (*e.g.*, an ampoule). In addition, more concentrated compositions may be prepared, from which the more dilute unit dosage compositions may then be produced. The more concentrated compositions thus will contain substantially more than, *e.g.*, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more times the amount of one or more syk inhibitors.

[0299] Methods for preparing such dosage forms are known to those skilled in the art (*see*, for example, *REMINGTON'S PHARMACEUTICAL SCIENCES*, 18TH ED., Mack Publishing Co., Easton, PA (1990)). In addition, pharmaceutically acceptable salts of the syk inhibitors of the present invention (*e.g.*, acid addition salts) may be prepared and included in the compositions using standard procedures known to those skilled in the art of synthetic organic chemistry and described, *e.g.*, by J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th Ed. (New York: Wiley-Interscience, 1992).

[0300] The compositions typically include a conventional pharmaceutical carrier or excipient and may additionally include other medicinal agents, carriers, adjuvants, diluents, tissue permeation enhancers, solubilizers, and the like. Preferably, the composition will

contain about 0.01% to about 90%, preferably about 0.1% to about 75%, more preferably about 0.1% to 50%, still more preferably about 0.1% to 10% by weight of one or more syk inhibitors, with the remainder consisting of suitable pharmaceutical carrier and/or excipients. Appropriate excipients can be tailored to the particular composition and route of administration by methods well known in the art, *e.g.*, *REMINGTON'S PHARMACEUTICAL SCIENCES*, *supra*.

[0301] Pharmaceutically acceptable carriers that may be used in these compositions include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances, such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0302] Examples of suitable excipients include, but are not limited to, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, saline, syrup, methylcellulose, ethylcellulose, hydroxypropylmethylcellulose, and polyacrylic acids such as Carbopols. The compositions can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying agents; suspending agents; preserving agents such as methyl-, ethyl-, and propyl-hydroxy-benzoates; pH adjusting agents such as inorganic and organic acids and bases; sweetening agents; and flavoring agents.

[0303] Administration of a composition comprising one or more syk inhibitors with one or more suitable pharmaceutical excipients as advantageous can be carried out via any of the accepted modes of administration. Thus, administration can be, for example, oral, topical, intravenous, subcutaneous, transcutaneous, transdermal, intramuscular, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, by inhalation or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally or intravenously.

The formulations of the invention may be designed as short-acting, fast-releasing, or long-acting. Still further, compounds can be administered in a local rather than systemic means, such as administration (*e.g.*, injection) as a sustained release formulation. According to a representative embodiment, the compositions of this invention are formulated for pharmaceutical administration to a mammal, preferably a human being.

[0304] The compositions of the present invention containing one or more syk inhibitors can be administered repeatedly, *e.g.*, at least 2, 3, 4, 5, 6, 7, 8, or more times, or the composition may be administered by continuous infusion. Suitable sites of administration include, but are not limited to, skin, bronchial, gastrointestinal, anal, vaginal, eye, and ear. The formulations may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, pills, capsules, powders, solutions, suspensions, emulsions, suppositories, retention enemas, creams, ointments, lotions, gels, aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0305] The pharmaceutical compositions of this invention may be in any orally acceptable dosage form, including tablets, capsules, cachets, emulsions, suspensions, solutions, syrups, elixirs, sprays, boluses, lozenges, powders, granules, and sustained-release formulations. Suitable excipients for oral administration include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0306] In some embodiments, the compositions take the form of a pill, tablet, or capsule, and thus, the composition can contain, along with one or more syk inhibitors, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and/or a binder such a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof. A tablet can be made by any compression or molding process known to those of skill in the art. Compressed tablets may be prepared by compressing in a suitable machine the syk inhibitors in a free-flowing form, *e.g.*, a powder or granules, optionally mixed with accessory

ingredients, *e.g.,* binders, lubricants, diluents, disintegrants, or dispersing agents. Molded tablets can be made by molding in a suitable machine a mixture of the powdered syk inhibitors with any suitable carrier.

[0307] Alternatively, the pharmaceutical compositions of this invention may be in the form of suppositories for rectal administration. These may be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax, polyethylene glycol (PEG), hard fat, and/or hydrogenated cocoglyceride. Compositions suitable for rectal administration may also comprise a rectal enema unit containing one or more syk inhibitors and pharmaceutically-acceptable vehicles (*e.g.,* 50% aqueous ethanol or an aqueous salt solution) that are physiologically compatible with the rectum and/or colon. The rectal enema unit contains an applicator tip protected by an inert cover, preferably comprised of polyethylene, lubricated with a lubricant such as white petrolatum, and preferably protected by a one-way valve to prevent back-flow of the dispensed formula. The rectal enema unit is also of sufficient length, preferably two inches, to be inserted into the colon via the anus.

[0308] Liquid compositions can be prepared by dissolving or dispersing one or more syk inhibitors and optionally one or more pharmaceutically acceptable adjuvants in a carrier such as, for example, aqueous saline, aqueous dextrose, glycerol, ethanol, and the like, to form a solution or suspension, *e.g.,* for oral, topical, or intravenous administration. Pharmaceutical formulations may be prepared as liquid suspensions or solutions using a sterile liquid, such as oil, water, alcohol, and combinations thereof. Pharmaceutically suitable surfactants, suspending agents or emulsifying agents, may be added for oral or parenteral administration. Suspensions may include oils, such as peanut oil, sesame oil, cottonseed oil, corn oil and olive oil. Suspension preparation may also contain esters of fatty acids, such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. Suspension formulations may include alcohols, such as ethanol, isopropyl alcohol, hexadecyl alcohol, glycerol and propylene glycol. Ethers, such as poly(ethyleneglycol), petroleum hydrocarbons, such as mineral oil and petrolatum, and water may also be used in suspension formulations.

[0309] The pharmaceutical compositions of this invention may also be in a topical form, especially when the target of treatment includes areas or organs readily accessible by topical

application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. For topical administration, the composition containing one or more syk inhibitors can be in the form of emulsions, lotions, gels, foams, creams, jellies, solutions, suspensions, ointments, and transdermal patches.

[0310] Topical application for the lower intestinal tract may be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used. For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions may be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters, wax, cetyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0311] The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. For delivery by inhalation, the compositions can be delivered as a dry powder or in liquid form via a nebulizer. Such compositions are prepared according to techniques known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons and/or other conventional solubilizing or dispersing agents.

[0312] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative, such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment, such as petrolatum.

[0313] For parenteral administration, the compositions can be in the form of sterile injectable solutions and sterile packaged powders. Preferably, injectable solutions are formulated at a pH of about 4.5 to about 7.5.

[0314] Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation. Compounds may be formulated for parenteral administration by injection such as by bolus injection or continuous infusion. A unit dosage form for injection may be in ampoules or in multi- dose containers.

[0315] The compositions of the present invention can also be provided in a lyophilized form. Such compositions may include a buffer, *e.g.*, bicarbonate, for reconstitution prior to administration, or the buffer may be included in the lyophilized composition for reconstitution with, *e.g.*, water. The lyophilized composition may further comprise a suitable vasoconstrictor, *e.g.*, epinephrine. The lyophilized composition can be provided in a syringe, optionally packaged in combination with the buffer for reconstitution, such that the reconstituted composition can be immediately administered to a patient.

[0316] Any of the above dosage forms containing effective amounts are within the bounds of routine experimentation and within the scope of the invention. A therapeutically effective dose may vary depending upon the route of administration and dosage form. The representative compound or compounds of the invention is a formulation that exhibits a high therapeutic index. The therapeutic index is the dose ratio between toxic and therapeutic effects which can be expressed as the ratio between LD_{50} and ED_{50}. The LD_{50} is the dose

lethal to 50% of the population and the ED_{50} is the dose therapeutically effective in 50% of the population. The LD_{50} and ED_{50} are determined by standard pharmaceutical procedures in animal cell cultures or experimental animals.

[0317] Besides those representative dosage forms described above, pharmaceutically acceptable excipients and carriers and dosage forms are generally known to those skilled in the art and are included in the invention. It should be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex and diet of the patient, and the time of administration, rate of excretion, drug combination, judgment of the treating physician and severity of the particular disease being treated. The amount of active ingredient(s) will also depend upon the particular compound and other therapeutic agent, if present, in the composition.

e. Methods of Use

[0318] The invention provides methods of inhibiting or decreasing syk activity as well as treating or ameliorating a syk associated state, symptom, condition, disorder or disease in a patient in need thereof (*e.g.*, human or non-human). In one embodiment, the syk associated state, symptom, condition, disorder or disease is mediated, at least in part by syk kinase activity. In more specific embodiments, the present invention provides a method for treating a condition or disorder mediated at least in part by syk kinase activity is cardiovascular disease, inflammatory disease or autoimmune disease.

[0319] In one embodiment, the invention provides methods for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising the step of administering to the mammal a therapeutically effective amount of a compound of the present invention. Such conditions include, but are not limited, to restenosis, acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombosis occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolism, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with

heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, conditions requiring the fitting of prosthetic devices, and the like.

[0320] In a further embodiment, the present invention provides a method for treating thrombosis, immune thrombocytic purura, heparin induced thrombocytopenia, dilated cardiomypathy, sickle cell disease, atherosclerosis, myocardial infarction, vacular inflammation, unstable angina or acute coronary syndromes.

[0321] In another embodiment, the present invention also provides a method for treating allergy, asthma, theumatoid arthritis, B Cell mediated disease such as Non-Hodgkin's Lymphoma, anti phospholipids syndrome, lupus, psoriasis, multiple sclerosis, end stage renal disease or chronic lymphocytic leukemia.

[0322] In another embodiment, the present invention provides a method for treating hemolytic anemia or immune thrombocytopenic purpura.

[0323] The compounds described herein are also potent and/or selective inhibitors of JAK kinases. As a consequence of this activity, the compounds can be used in a variety of in vitro, in vivo, and ex vivo contexts to regulate or inhibit JAK kinase activity, signaling cascades in which JAK kinases play a role, and the biological responses effected by such signaling cascades. For example, in one embodiment, the compounds can be used to inhibit JAK kinase, either in vitro or in vivo, in virtually any cell type expressing the JAK kinase, such as in hematopoietic cells in which, for example, JAK3 is predominantly expressed. They may also be used to regulate signal transduction cascades in which JAK kinases, particularly JAK3, play a role. Such JAK-dependent signal transduction cascades include, but are not limited to, the signaling cascades of cytokine receptors that involve the common gamma chain, such as, for example, the IL-4, IL-7, IL-5, IL-9, IL-15 and IL-21, or IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptor signaling cascades. The compounds may also be used in vitro or in vivo to regulate, and in particular to inhibit, cellular or biological responses affected by such JAK-dependent signal transduction cascades. Such cellular or biological responses include, but are not limited to, IL-4/ramos CD23 upregulation and IL-2 mediated T-cell proliferation. Importantly, the compounds can be used to inhibit JAK kinases in vivo as a therapeutic approach towards the treatment or prevention of diseases mediated, either wholly or in part, by a JAK kinase activity (referred to herein as "JAK kinase mediated diseases").

Non-limiting examples of JAK kinase mediated diseases that can be treated or prevented with the compounds include, but are not limited to, the following: allergies; asthma; autoimmune diseases such as transplant rejection (e.g., kidney, heart, lung, liver, pancreas, skin, small intestine, large intestine, host versus graft reaction (HVGR), and graft versus host reaction (GVHR)), rheumatoid arthritis, and amyotrophic lateral sclerosis; T-cell mediated autoimmune diseases such as multiple sclerosis, psoraiasis, and Sjogren's syndrome; Type II inflammatory diseases such as vascular inflammation (including vasculitis, arteritis, atherosclerosis, and coronary artery disease); diseases of the central nervous system such as stroke; pulmonary diseases such as bronchitis obliteraus and primary pulmonary hypertension; solid, delayed Type IV hypersensitivity reactions; and hematologic malignancies such as leukemia and lymphomas.

[0324] Examples of diseases that are mediated, at least in part, by JAK kinases that can be treated or prevented according to the methods include, but are not limited to, allergies, asthma, autoimmune diseases such as transplant rejection (e.g., kidney, heart, lung, liver, pancreas, skin, host versus graft reaction (HVGR), etc.), rheumatoid arthritis, and amyotrophic lateral sclerosis, multiple sclerosis, psoraiasis and Sjogren's syndrome, Type II inflammatory disease such as vascular inflammation (including vasculitis, ateritis, atherosclerosis and coronary artery disease) or other inflammatory diseases such as osteoarthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, idiopathic inflammatory bowel disease, irritable bowel syndrome, spastic colon, low grade scarring (e.g., scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction), and sicca complex or syndrome, diseases of the central nervous system such as stroke, pulmonary diseases such as bronchitis obliterous and primary and primary pulmonary hypertension, delayed or cell-mediated, Type IV hypersensitivity and solid and hematologic malignancies such as leukemias and lyphomas.

[0325] In another embodiment, this invention provides a method of inhibiting an activity of a JAK kinase, comprising contacting the JAK kinase with an amount of a compound effective to inhibit an activity of the JAK kinase, wherein the compound is selected from the compounds of this invention. In certain embodiments of the methods described herein, the method is carried out in vivo.

[0326] In another embodiment, this invention provides a method of inhibiting an activity of a JAK kinase, comprising contacting in vitro a JAK3 kinase with an amount of a compound effective to inhibit an activity of the JAK kinase, wherein the compound is selected from the compounds of this invention.

[0327] In a specific embodiment, the compounds can be used to treat and/or prevent rejection in organ and/or tissue transplant recipients (i.e., treat and/or prevent allorgraft rejection). Allografts can be rejected through either a cell-mediated or humoral immune reaction of the recipient against transplant (histocompability) antigens present on the membranes of the donor's cells. The strongest antigens are governed by a complex of genetic loci termed human leukocyte group A (HLA) antigens. Together with the ABO blood groups antigens, they are the chief transplantation antigens detectable in humans.

[0328] Rejection following transplantation can generally be broken into three categories: hyperacute, occurring hours to days following transplantation; acute, occurring days to months following transplantation; and chronic, occurring months to years following transplantation.

[0329] Hyperacute rejection is caused mainly by the production of host antibodies that attack the graft tissue. In a hyperacute rejection reaction, antibodies are observed in the transplant vascular very soon after transplantation. Shortly thereafter, vascular clotting occurs, leading to ischemia, eventual necrosis and death. The graft infarction is unresponsive to known immunosuppressive therapies. Because HLA antigens can be identified in vitro, pre-transplant screening is used to significantly reduce hyperacute rejection. As a consequence of this screening, hyperacute rejection is relatively uncommon today.

[0330] Acute rejection is thought to be mediated by the accumulation of antigen specific cells in the graft tissue. The T-cell-mediated immune reaction against these antigens (i.e., HVGR or GVHR) is the principle mechanism of acute rejection. Accumulation of these cells leads to damage of the graft tissue. It is believed that both CD4+ helper T-cells and CD8+ cytotoxic T-cells are involved in the process and that the antigen is presented by donor and host dendritic cells. The CD4+ helper T-cells help recruit other effector cells, such as macrophapges and eosinophils, to the graft. Accessing T-cell activation signal transduction cascades (for example, CD28, CD40L, and CD2 cascades) are also involved.

[0331] The cell-mediated acute rejection can be reversed in many cases by intensifying immunotherapy. After successful reversal, severely damaged elements of the graft heal by

fibrosis and the remainder of the graft appears normal. After resolution of acute rejection, dosages of immunosuppressive drugs can be reduced to very low levels.

[0332] Chronic rejection, which is a particular problem in renal transplants, often progresses insidiously despite increased immunosuppressive therapy. It is thought to be due, in large part, to cell-mediated Type IV hypersensitivity. The pathologic profile differs from that of acute rejection. The arterial endothelium is primarily involved with extensive proliferation that may gradually occlude the vessel lumen, leading to ischemia, fibrosis, a thickened intima, and atherosclerotic changes. Chronic rejection is mainly due to a progressive obliteration of graft vasculature and resembles a slow, vasculitic process.

[0333] In Type IV hypersensitivity, CD8 cytotoxic T-cells and CD4 helper T cells recognize either intracellular or extracellular synthesized antigen when it is complexed, respectively, with either Class I or Class II MHC molecules. Macrophages function as antigen-presenting cells and release IL-1, which promotes proliferation of helper T-cells. Helper T-cells release interferon gamma and IL-2, which together regulate delayed hyperactivity reactions mediated by macrophage activation and immunity mediated by T cells. In the case of organ transplant, the cytotoxic T-cells destroy the graft cells on contact.

[0334] Since JAK kinases play a critical role in the activation of T-cells, the compounds described herein can be used to treat and/or prevent many aspects of transplant rejection, and are particularly useful in the treatment and/or prevention of rejection reactions that are mediated, at least in part, by T-cells, such as HVGR or GVHR. The compounds can also be used to treat and/or prevent chronic rejection in transplant recipients and, in particular, in renal transplant recipients. The compound can also be administered to a tissue or an organ prior to transplanting the tissue or organ in the transplant recipient.

[0335] In another embodiment, this invention provides a method of treating a T-cell mediated autoimmune disease, comprising administering to a patient suffering from such an autoimmune disease an amount of a compound effective to treat the autoimmune disease wherein the compound is selected from the compounds of the invention. In certain embodiments of the methods the autoimmune disease is multiple sclerosis (MS), psoraisis, or Sjogran's syndrome. Such autoimmune disease include, but are not limited to, those autoimmune diseases that are frequently designated as single organ or single cell-type autoimmune disorders and those autoimmune disease that are frequently designated as involving systemic autoimmune disorder. Non-limiting examples of diseases frequently

designated as single organ or single cell-type autoimmune disorders include: Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, ulcerative colitis and membranous glomerulopathy. Non-limiting examples of diseases often designated as involving systemic autoimmune disorder include: systemic lupus erythematosis, rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, multiple sclerosis and bullous pemphigoid. Additional autoimmune diseases, which can be .beta.-cell (humoral) based or T-cell based, include Cogan's syndrome, ankylosing spondylitis, Wegener's granulomatosis, autoimmune alopecia, Type I or juvenile onset diabetes, and thyroiditis.

[0336] The types of autoimmune diseases that may be treated or prevented with such prodrugs generally include those disorders involving tissue injury that occurs as a result of a humoral and/or cell-mediated response to immunogens or antigens of endogenous and/or exogenous origin. Such diseases are frequently referred to as diseases involving the nonanaphylactic (i.e., Type II, Type III and/or Type IV) hypersensitivity reactions.

[0337] Type I hypersensitivity reactions generally result from the release of pharmacologically active substances, such as histamine, from mast and/or basophil cells following contact with a specific exogenous antigen. As mentioned above, such Type I reactions play a role in numerous diseases, including allergic asthma, allergic rhinitis, etc.

[0338] Type II hypersensitivity reactions (also referred to as cytotoxic, cytolytic complement-dependent or cell-stimulating hypersensitivity reactions) result when immunoglobulins react with antigenic components of cells or tissue, or with an antigen or hapten that has become intimately coupled to cells or tissue. Diseases that are commonly associated with Type II hypersensitivity reactions include, but are not limited, to autoimmune hemolytic anemia, erythroblastosis fetalis and Goodpasture's disease.

[0339] Type III hypersensitivity reactions, (also referred to as toxic complex, soluble complex, or immune complex hypersensitivity reactions) result from the deposition of soluble circulating antigen-immunoglobulin complexes in vessels or in tissues, with accompanying acute inflammatory reactions at the site of immune complex deposition. Non-limiting examples of prototypical Type III reaction diseases include the Arthus reaction, rheumatoid

arthritis, serum sickness, systemic lupus erythematosis, certain types of glomerulonephritis, multiple sclerosis and bullous pemphingoid.

[0340] Type IV hypersensitivity reactions (frequently called cellular, cell-mediated, delayed, or tuberculin-type hypersensitivity reactions) are caused by sensitized T-lymphocytes which result from contact with a specific antigen. Non-limiting examples of diseases cited as involving Type IV reactions are contact dermatitis and allograft rejection.

[0341] Autoimmune diseases associated with any of the above nonanaphylactic hypersensitivity reactions may be treated or prevented with the prodrugs according to structural formulae (I) and (Ia). In particular, the methods may be used to treat or prevent those autoimmune diseases frequently characterized as single organ or single cell-type autoimmune disorders including, but not limited to: Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, ulcerative colitis and membranous glomerulopathy, as well as those autoimmune diseases frequently characterized as involving systemic autoimmune disorder, which include but are not limited to: systemic lupus erythematosis (SLE), rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, multiple sclerosis and bullous pemphigoid.

[0342] It will be appreciated by skilled artisans that many of the above-listed autoimmune diseases are associated with severe symptoms, the amelioration of which provides significant therapeutic benefit even in instances where the underlying autoimmune disease may not be ameliorated.

[0343] Therapy using the compounds described herein can be applied alone, or it can be applied in combination with or adjunctive to other common immunosuppressive therapies, such as, for example, the following: mercaptopurine; corticosteroids such as prednisone; methylprednisolone and prednisolone; alkylating agents such as cyclophosphamide; calcineurin inhibitors such as cyclosporine, sirolimus, and tacrolimus; inhibitors of inosine monophosphate dehydrogenase (IMPDH) such as mycophenolate, mycophenolate mofetil, and azathioprine; and agents designed to suppress cellular immunity while leaving the recipient's humoral immunologic response intact, including various antibodies (for example,

antilymphocyte globulin (ALG), antithymocyte globulin (ATG), monoclonal anti-T-cell antibodies (OKT3)) and irradiation. These various agents can be used in accordance with their standard or common dosages, as specified in the prescribing information accompanying commercially available forms of the drugs (see also: the prescribing information in the 2006 Edition of The Physician's Desk Reference), the disclosures of which are incorporated herein by reference. Azathioprine is currently available from Salix Pharmaceuticals, Inc., under the brand name AZASAN; mercaptopurine is currently available from Gate Pharmaceuticals, Inc., under the brand name PURINETHOL; prednisone and prednisolone are currently available from Roxane Laboratories, Inc.; Methyl prednisolone is currently available from Pfizer; sirolimus (rapamycin) is currently available from Wyeth-Ayerst under the brand name RAPAMUNE; tacrolimus is currently available from Fujisawa under the brand name PROGRAF; cyclosporine is current available from Novartis under the brand dame SANDIMMUNE and from Abbott under the brand name GENGRAF; IMPDH inhibitors such as mycophenolate mofetil and mycophenolic acid are currently available from Roche under the brand name CELLCEPT and from Novartis under the brand name MYFORTIC; azathioprine is currently available from Glaxo Smith Kline under the brand name IMURAN; and antibodies are currently available from Ortho Biotech under the brand name ORTHOCLONE, from Novartis under the brand name SIMULECT (basiliximab), and from Roche under the brand name ZENAPAX (daclizumab).

[0344] In another embodiment, the compounds could be administered either in combination or adjunctively with an inhibitor of a syk kinase. syk kinase is a tyrosine kinase known to play a critical role in Fcy receptor signaling, as well as in other signaling cascades, such as those involving B-cell receptor signaling (Turner et al., (2000), Immunology Today 21:148-154) and integrins beta(1), beta (2), and beta (3) in neutrophils (Mocsai et al., (2002), Immunity 16:547-558). For example, syk kinase plays a pivotal role in high affinity IgE receptor signaling in mast cells that leads to activation and subsequent release of multiple chemical mediators that trigger allergic attacks. However, unlike the JAK kinases, which help regulate the pathways involved in delayed or cell-mediated Type IV hypersensitivity reactions, syk kinase helps regulate the pathways involved in immediate IgE-mediated, Type I hypersensitivity reactions. Certain compounds that affect the syk pathway may or may not also affect the JAK pathways.

[0345] Suitable syk inhibitory compounds are described, for example, in Ser. No. 10/355,543 filed Jan. 31, 2003 (publication no. 2004/0029902); WO 03/063794; Ser. No.

10/631,029 filed Jul. 29, 2003; WO 2004/014382; Ser. No. 10/903,263 filed Jul. 30, 2004; PCT/US2004/24716 filed Jul. 30, 2004 (WO005/016893); Ser. No. 10/903,870 filed Jul. 30, 2004; PCT/US2004/24920 filed Jul. 30, 2004; Ser. No. 60/630,808 filed Nov. 24, 2004; Ser. No. 60/645,424 filed Jan. 19, 2005; and Ser. No. 60/654,620, filed Feb. 18, 2005, the disclosures of which are incorporated herein by reference. The described herein and syk inhibitory compounds could be used alone or in combination with one or more conventional transplant rejection treatments, as described above.

[0346] In a specific embodiment, the compounds can be used to treat or prevent these diseases in patients that are either initially non-responsive (resistant) to or that become non-responsive to treatment with a syk inhibitory compound or one of the other current treatments for the particular disease. The compounds could also be used in combination with syk inhibitory compounds in patients that are syk-compound resistant or non-responsive. Suitable syk-inhibitory compounds with which the compounds can be administered are provided infra.

[0347] In another embodiment, this invention provides a method of treating a T-cell mediated autoimmune disease, comprising administering to a patient suffering from such an autoimmune disease an amount of a compound effective to treat the autoimmune disease wherein the compound is selected from the compounds of the invention, as described herein, and the compound is administered in combination with or adjunctively to a compound that inhibits syk kinase with an IC_{50} in the range of at least 10 μM.

[0348] In another embodiment, this invention provides a method of treating or preventing allograft transplant rejection in a transplant recipient, comprising administering to the transplant recipient an amount of a compound effective to treat or prevent the rejection wherein the compound is selected from the compounds of the invention, as described herein. In a further embodiment, the compound is administered to a tissue or an organ prior to transplanting the tissue or organ in the transplant recipient.

[0349] In another embodiment, this invention provides a method of treating or preventing allograft transplant rejection in a transplant recipient, in which the rejection is acute rejection, comprising administering to the transplant recipient an amount of a compound effective to treat or prevent the rejection, wherein the compound is selected from the compounds of the invention.

[0350] In another embodiment, this invention provides a method of treating or preventing allograft transplant rejection in a transplant recipient, in which the rejection is chronic

rejection, comprising administering to the transplant recipient an amount of a compound effective to treat or prevent the rejection, wherein the compound is selected from the compounds of the invention.

[0351] In another embodiment, this invention provides a method of treating or preventing allograft transplant rejection in a transplant recipient, in which the rejection is mediated by HVGR or GVHR, comprising administering to the transplant recipient an amount of a compound effective to treat or prevent the rejection, wherein the compound is selected from the compounds of this invention, as described herein.

[0352] In another embodiment, this invention provides a method of treating or preventing allograft transplant rejection in a transplant recipient, in which the allograft transplant is selected from a kidney, a heart, a liver, and a lung, comprising administering to the transplant recipient an amount of a compound effective to treat or prevent the rejection, wherein the compound is selected from the compounds of this invention, as described herein.

[0353] In another embodiment, this invention provides a method of treating or preventing allograft transplant rejection in a transplant recipient, in which the allograft transplant is selected from a kidney, a heart, a liver, and a lung, comprising administering to the transplant recipient an amount of a compound effective to treat or prevent the rejection wherein the compound is selected from the compounds of the invention, as described herein, in which the compound is administered in combination with or adjunctively to another immunosuppressant.

[0354] In another embodiment, this invention provides a method of treating or preventing allograft transplant rejection in a transplant recipient, in which the allograft transplant is selected from a kidney, a heart, a liver, and a lung, comprising administering to the transplant recipient an amount of a compound effective to treat or prevent the rejection, wherein the compound is selected from the compounds of the invention, as described herein, in which the compound is administered in combination with or adjunctively to another immunosuppressant, in which the immunosuppressant is selected from cyclosporine, tacrolimus, sirolimus, an inhibitor of IMPDH, mycophenolate, mycophanolate mofetil, an anti-T-Cell antibody, and OKT3.

[0355] The compounds described herein are cytokine moderators of IL-4 signaling. As a consequence, the compounds could slow the response of Type I hypersensitivity reactions. Thus, in a specific embodiment, the compounds could be used to treat such reactions and,

therefore, the diseases associated with, mediated by, or caused by such hypersensitivity reactions (for example, allergies), prophylactically. For example, an allergy sufferer could take one or more of the JAK selective compounds described herein prior to expected exposure to allergens to delay the onset or progress of, or eliminate altogether, an allergic response.

[0356] When used to treat or prevent such diseases, the compounds can be administered singly, as mixtures of one or more compounds, or in mixture or combination with other agents useful for treating such diseases and/or the symptoms associated with such diseases. The compounds may also be administered in mixture or in combination with agents useful to treat other disorders or maladies, such as steroids, membrane stabilizers, 5-lipoxygenase (5LO) inhibitors, leukotriene synthesis and receptor inhibitors, inhibitors of IgE isotype switching or IgE synthesis, IgG isotype switching or IgG synthesis, beta.-agonists, tryptase inhibitors, aspirin, cyclooxygenase (COX) inhibitors, methotrexate, anti-TNF drugs, anti CD20 antibody, PD4 inhibitors, p38 inhibitors, PDE4 inhibitors, and antihistamines, to name a few. The compounds can be administered per se in the form of prodrugs or as pharmaceutical compositions, comprising an active compound or prodrug.

[0357] In another embodiment, this invention provides a method of treating or preventing a Type IV hypersensitivity reaction, comprising administering to a subject an amount of a compound effective to treat or prevent the hypersensitivity reaction, wherein the compound is selected from the compounds of this invention, as described herein.

[0358] In another embodiment, this invention provides a method of treating or preventing a Type IV hypersensitivity reaction, which is practical prophylactically, comprising administering to a subject an amount of a compound effective to treat or prevent the hypersensitivity reaction, wherein the compound is selected from the compounds of this invention, as described herein, and is administered prior to exposure to an allergen.

[0359] In another embodiment, this invention provides a method of inhibiting a signal transduction cascade in which JAK3 kinase plays a role, comprising contacting a cell expressing a receptor involved in such a signaling cascade with a compound wherein the compound is selected from the compounds of this invention, as described herein.

[0360] In another embodiment, this invention provides a method of treating or preventing a JAK kinase-mediated disease, comprising administering to a subject an amount of compound

effective to treat or prevent the JAK kinase-mediated disease, wherein the compound is selected from the compounds of this invention, as described herein.

[0361] In another embodiment, this invention provides a method of treating or preventing a JAK kinase-mediated disease, in which the JAK-mediated disease is HVGR or GVHR, comprising administering to a subject an amount of compound effective to treat or prevent the JAK kinase-mediated disease, wherein the compound is selected from the compounds of the invention, as described herein.

[0362] In another embodiment, this invention provides a method of treating or preventing a JAK kinase-mediated disease, in which the JAK-mediated disease is acute allograft rejection, comprising administering to a subject an amount of compound effective to treat or prevent the JAK kinase-mediated disease, wherein the compound is selected from the compounds of the invention, as described herein.

[0363] In another embodiment, this invention provides a method of treating or preventing a syk kinase-mediated disease, in which the JAK-mediated disease is chronic allograft rejection, comprising administering to a subject an amount of compound effective to treat or prevent the JAK kinase-mediated disease, wherein the compound is selected from the compounds of the invention, as described herein.

[0364] Active compounds of the invention typically inhibit the syk pathway. The activity of a specified compound as an inhibitor of a syk kinase can be assessed in vitro or in vivo. In some embodiments, the activity of a specified compound can be tested in a cellular assay.

[0365] "Cell proliferative disorder" refers to a disorder characterized by abnormal proliferation of cells. A proliferative disorder does not imply any limitation with respect to the rate of cell growth, but merely indicates loss of normal controls that affect growth and cell division. Thus, in some embodiments, cells of a proliferative disorder can have the same cell division rates as normal cells but do not respond to signals that limit such growth. Within the ambit of "cell proliferative disorder" is neoplasm or tumor, which is an abnormal growth of tissue. Cancer refers to any of various malignant neoplasms characterized by the proliferation of cells that have the capability to invade surrounding tissue and/or metastasize to new colonization sites.

[0366] Generally, cell proliferative disorders treatable with the compounds disclosed herein relate to any disorder characterized by aberrant cell proliferation. These include various

tumors and cancers, benign or malignant, metastatic or non-metastatic. Specific properties of cancers, such as tissue invasiveness or metastasis, can be targeted using the methods described herein. Cell proliferative disorders include a variety of cancers, including, among others, ovarian cancer, renal cancer, gastrointestinal cancer, kidney cancer, bladder cancer, pancreatic cancer, lung squamous carcinoma, and adenocarcinoma.

[0367] In some embodiments, the cell proliferative disorder treated is a hematopoietic neoplasm, which is aberrant growth of cells of the hematopoietic system. Hematopoietic malignancies can have its origins in pluripotent stem cells, multipotent progenitor cells, oligopotent committed progenitor cells, precursor cells, and terminally differentiated cells involved in hematopoiesis. Some hematological malignancies are believed to arise from hematopoietic stem cells, which have the ability for self renewal. For instance, cells capable of developing specific subtypes of acute myeloid leukemia (AML) (Cynthia K. Hahn, Kenneth N. Ross, Rose M. Kakoza, Steven Karr, Jinyan Du, Shao-E Ong, Todd R. Golub, Kimberly Stegmaier, Syk is a new target for AML differentiation, Blood, 2007, 110, Abstract 209) upon transplantation display the cell surface markers of hematopoietic stem cells, implicating hematopoietic stem cells as the source of leukemic cells. Blast cells that do not have a cell marker characteristic of hematopoietic stem cells appear to be incapable of establishing tumors upon transplantation (Blaire et al., 1997, Blood 89:3104-3112). The stem cell origin of certain hematological malignancies also finds support in the observation that specific chromosomal abnormalities associated with particular types of leukemia can be found in normal cells of hematopoietic lineage as well as leukemic blast cells. For instance, the reciprocal translocation t(9q34;22q11) associated with approximately 95% of chronic myelogenous leukemia appears to be present in cells of the myeloid, erythroid, and lymphoid lineage, suggesting that the chromosomal aberration originates in hematopoietic stem cells. A subgroup of cells in certain types of CML displays the cell marker phenotype of hematopoietic stem cells.

[0368] Although hematopoietic neoplasms often originate from stem cells, committed progenitor cells or more terminally differentiated cells of a developmental lineage can also be the source of some leukemias. For example, forced expression of the fusion protein Bcr/Abl (associated with chronic myelogenous leukemia) in common myeloid progenitor or granulocyte/macrophage progenitor cells produces a leukemic-like condition. Moreover, some chromosomal aberrations associated with subtypes of leukemia are not found in the cell population with a marker phenotype of hematopoietic stem cells, but are found in a cell

population displaying markers of a more differentiated state of the hematopoietic pathway (Turhan et al., 1995, Blood 85:2154-2161). Thus, while committed progenitor cells and other differentiated cells may have only a limited potential for cell division, leukemic cells may have acquired the ability to grow unregulated, in some instances mimicking the self-renewal characteristics of hematopoietic stem cells (Passegue et al., Proc. Natl. Acad. Sci. USA, 2003, 100:11842-9).

[0369] In some embodiments, the hematopoietic neoplasm treated is a lymphoid neoplasm, where the abnormal cells are derived from and/or display the characteristic phenotype of cells of the lymphoid lineage. Lymphoid neoplasms can be subdivided into B-cell neoplasms, T and NK-cell neoplasms, and Hodgkin's lymphoma. B-cell neoplasms can be further subdivided into precursor B-cell neoplasm and mature/peripheral B-cell neoplasm. Exemplary B-cell neoplasms are precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia) while exemplary mature/peripheral B-cell neoplasms are B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone B-cell lymphoma, hairy cell leukemia, plasma cell myeloma/plasmacytoma, extranodal marginal zone B-cell lymphoma of MALT type, nodal marginal zone B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, primary effusion lymphoma, and Burkitt's lymphoma/Burkitt cell leukemia. T-cell and Nk-cell neoplasms are further subdivided into precursor T-cell neoplasm and mature (peripheral) T-cell neoplasms. Exemplary precursor T-cell neoplasm is precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia) while exemplary mature (peripheral) T-cell neoplasms are T-cell prolymphocytic leukemia T-cell granular lymphocytic leukemia, aggressive NK-cell leukemia, adult T-cell lymphoma/leukemia (HTLV-1), extranodal NK/T-cell lymphoma, nasal type, enteropathy-type T-cell lymphoma, hepatosplenic gamma-delta T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, Mycosis fungoides/Sezary syndrome, Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type, Peripheral T-cell lymphoma, not otherwise characterized, Angioimmunoblastic T-cell lymphoma, Anaplastic large-cell lymphoma, T/null cell, primary systemic type. The third member of lymphoid neoplasms is Hodgkin's lymphoma, also referred to as Hodgkin's disease. Exemplary diagnosis of this class that can be treated with the compounds include, among others, nodular lymphocyte-predominant Hodgkin's lymphoma, and various classical forms of Hodgkin's disease,

exemplary members of which are Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2), Lymphocyte-rich classical Hodgkin's lymphoma, Mixed cellularity Hodgkin's lymphoma, and Lymphocyte depletion Hodgkin's lymphoma. In various embodiments, any of the lymphoid neoplasms that are associated with aberrant JAK activity can be treated with the syk inhibitory compounds.

[0370] In some embodiments, the hematopoietic neoplasm treated is a myeloid neoplasm. This group comprises a large class of cell proliferative disorders involving or displaying the characteristic phenotype of the cells of the myeloid lineage. Myeloid neoplasms can be subdivided into myeloproliferative diseases, myelodysplastic/myeloproliferative diseases, myelodysplastic syndromes, and acute myeloid leukemias. Exemplary myeloproliferative diseases are chronic myelogenous leukemia (e.g., Philadelphia chromosome positive (t(9;22)(qq34;q11)), chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, chronic idiopathic myelofibrosis, polycythemia vera, and essential thrombocythemia. Exemplary myelodysplastic/myeloproliferative diseases are chronic myelomonocytic leukemia, atypical chronic myelogenous leukemia, and juvenile myelomonocytic leukemia. Exemplary myelodysplastic syndromes are refractory anemia, with ringed sideroblasts and without ringed sideroblasts, refractory cytopenia (myelodysplastic syndrome) with multilineage dysplasia, refractory anemia (myelodysplastic syndrome) with excess blasts, 5q-syndrome, and myelodysplastic syndrome. In various embodiments, any of the myeloid neoplasms that are associated with aberrant syk activity can be treated with the syk inhibitory compounds.

[0371] In some embodiments, the compounds can be used to treat Acute myeloid leukemias (AML), which represent a large class of myeloid neoplasms having its own subdivision of disorders. These subdivisions include, among others, AMLs with recurrent cytogenetic translocations, AML with multilineage dysplasia, and other AML not otherwise categorized. Exemplary AMLs with recurrent cytogenetic translocations include, among others, AML with t(8;21)(q22;q22), AML1(CBF-alpha)/ETO, Acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RAR-alpha), AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q11), CBFb/MYH11X), and AML with 11q23 (MLL) abnormalities. Exemplary AML with multilineage dysplasia are those that are associated with or without prior myelodysplastic syndrome. Other acute myeloid leukemias not classified within any definable group include, AML minimally differentiated, AML without maturation, AML with maturation, Acute myelomonocytic leukemia, Acute

monocytic leukemia, Acute erythroid leukemia, Acute megakaryocytic leukemia, Acute basophilic leukemia, and Acute panmyelosis with myelofibrosis.

[0372] "Treating" within the context of the invention means an alleviation of symptoms associated with a disorder or disease, or halt of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder.

[0373] The term "mammal" includes organisms which express syk. Examples of mammals include mice, rats, cows, sheep, pigs, goats, horses, bears, monkeys, dogs, cats and, preferably, humans. Transgenic organisms which express syk are also included in this definition.

[0374] The inventive methods comprise administering an effective amount of a compound or composition described herein to a mammal or non-human animal. As used herein, "effective amount" of a compound or composition of the invention includes those amounts that antagonize or inhibit syk. An amount which antagonizes or inhibits syk is detectable, for example, by any assay capable of determining syk activity, including the one described below as an illustrative testing method. Effective amounts may also include those amounts which alleviate symptoms of a syk associated disorder treatable by inhibiting syk. Accordingly, "antagonists of syk" include compounds which interact with the syk, and modulate, *e.g.*, inhibit or decrease, the ability of a second compound, *e.g.*, another syk ligand, to interact with the syk. The syk binding compounds are preferably antagonists of syk. The language "syk binding compound" (*e.g.*, exhibits binding affinity to the receptor) includes those compounds which interact with syk resulting in modulation of the activity of syk. Syk binding compounds may be identified using an *in vitro* (e.g., cell and non-cell based) or *in vivo* method. A description of *in vitro* methods are provided below.

[0375] The amount of compound present in the methods and compositions described herein should be sufficient to cause a detectable decrease in the severity of the disorder, as measured by any of the assays described in the examples. The amount of syk modulator needed will depend on the effectiveness of the modulator for the given cell type and the length of time required to treat the disorder. In certain embodiments, the compositions of this invention may further comprise another therapeutic agent. When a second agent is used, the second agent may be administered either as a separate dosage form or as part of a single dosage form with the compounds or compositions of this invention. While one or more of the inventive compounds can be used in an application of monotherapy to treat a disorder, disease or

symptom, they also may be used in combination therapy, in which the use of an inventive compound or composition (therapeutic agent) is combined with the use of one or more other therapeutic agents for treating the same and/or other types of disorders, symptoms and diseases. Combination therapy includes administration of the two or more therapeutic agents concurrently or sequentially. The agents may be administered in any order. Alternatively, the multiple therapeutic agents can be combined into a single composition that can be administered to the patient. For instance, a single pharmaceutical composition could comprise the compound or pharmaceutically acceptable salt, ester or prodrug thereof according to the formula I, another therapeutic agent (*e.g.*, methotrexate) or a tautomer thereof or a pharmaceutically acceptable salt, ester or prodrug thereof, and a pharmaceutically acceptable excipient or carrier.

[0376] The invention comprises a compound having the formula **I**, a method for making an inventive compound, a method for making a pharmaceutical composition from at least one inventive compound and at least one pharmaceutically acceptable carrier or excipient, and a method of using one or more inventive compounds to treat a variety of disorders, symptoms and diseases (*e.g.*, inflammatory, autoimmune, neurological, neurodegenerative, oncology and cardiovascular), such as RA, osteoarthritis, irritable bowel disease IBD, asthma, chronic obstructive pulmonary disease COPD and MS. The inventive compounds and their pharmaceutically acceptable salts and/or neutral compositions may be formulated together with a pharmaceutically acceptable excipient or carrier and the resulting composition may be administered *in vivo* to mammals, such as men, women and animals, to treat a variety of disorders, symptoms and diseases. Furthermore, the inventive compounds can be used to prepare a medicament that is useful for treating a variety of disorders, symptoms and diseases.

[0377] All of the compounds of the present invention are either potent inhibitors of syk kinases, exhibiting IC_{50}s in the respective assay in the range of less than 5 μM, with most being in the nanomolar, and several in the sub-nanomolar, range. In some embodiments, the compounds of the present invention may be "dual" syk/JAK inhibitors in that they inhibit both syk and JAK kinase to some degree. In other embodiments, the compounds of the present invention may selectively inhibit syk kinase, but not appreciably inhibit one or more JAK kinases. In other embodiments, the compounds of the present invention may selectively inhibit JAK kinase, but not appreciably inhibit one or more syk kinases.

f. Kits

[0378] Still another aspect of this invention is to provide a kit comprising separate containers in a single package, wherein the inventive pharmaceutical compounds, compositions and/or salts thereof are used in combination with pharmaceutically acceptable carriers to treat states, disorders, symptoms and diseases where syk plays a role.

I. EXAMPLES

[0379] The following examples are offered to illustrate, but not to limit, the claimed invention.

[0380] The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis;* Wiley & Sons: New York, 1967-2004, Volumes 1-22; *Rodd's Chemistry of Carbon Compounds,* Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and Organic Reactions, Wiley & Sons: New York, 2005, Volumes 1-65.

[0381] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0382] Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range from about -78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C, and most preferably and conveniently at about room (or ambient) temperature, *e.g.*, about 20 °C to about 75 °C.

[0383] Referring to the examples that follow, compounds of the present invention were synthesized using the methods described herein, or other methods, which are well known in the art.

[0384] The compounds and/or intermediates may be characterized by high performance liquid chromatography (HPLC) using a Waters Alliance chromatography system with a 2695 Separation Module (Milford, Mass.). The analytical columns may be C-18 SpeedROD RP-18E Columns from Merck KGaA (Darmstadt, Germany). Alternately, characterization may be performed using a Waters Unity (UPLC) system with Waters Acquity UPLC BEH C-18 2.1 mm x 15 mm columns. A gradient elution may be used, typically starting with 5 % acetonitrile/95 % water and progressing to 95 % acetonitrile over a period of 5 minutes for the Alliance system and 1 minute for the Acquity system. All solvents may contain 0.1 % trifluoroacetic acid (TFA). Compounds may be detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents may be from EMD Chemicals, Inc. (Gibbstown, NJ). In some instances, purity may be assessed by thin layer chromatography (TLC) using glass backed silica gel plates, such as, for example, EMD Silica Gel 60 2.5 cm x 7.5 cm plates. TLC results may be readily detected visually under ultraviolet light, or by employing well known iodine vapor and other various staining techniques.

[0385] Mass spectrometric analysis may be performed on one of two Agilent 1100 series LCMS instruments and the Acquity system with acetonitrile / water as the mobile phase. One system may use TFA as the modifier and measure in positive ion mode [reported as MH+, (M+1) or (M+H)+] and the other may use either formic acid or ammonium acetate and measure in both positive [reported as MH^+, (M+1) or $(M+H)^+$] and negative [reported as M-, (M-1) or $(M-H)^-$] ion modes.

[0386] Nuclear magnetic resonance (NMR) analysis may be performed on some of the compounds with a Varian 400 MHz NMR (Palo Alto, Calif.). The spectral reference may be either TMS or the known chemical shift of the solvent.

[0387] The purity of some of the invention compounds may be assessed by elemental analysis (Robertson Microlit, Madison NJ.).

[0388] Melting points may be determined on a Laboratory Devices Mel-Temp apparatus (Holliston, Mass.).

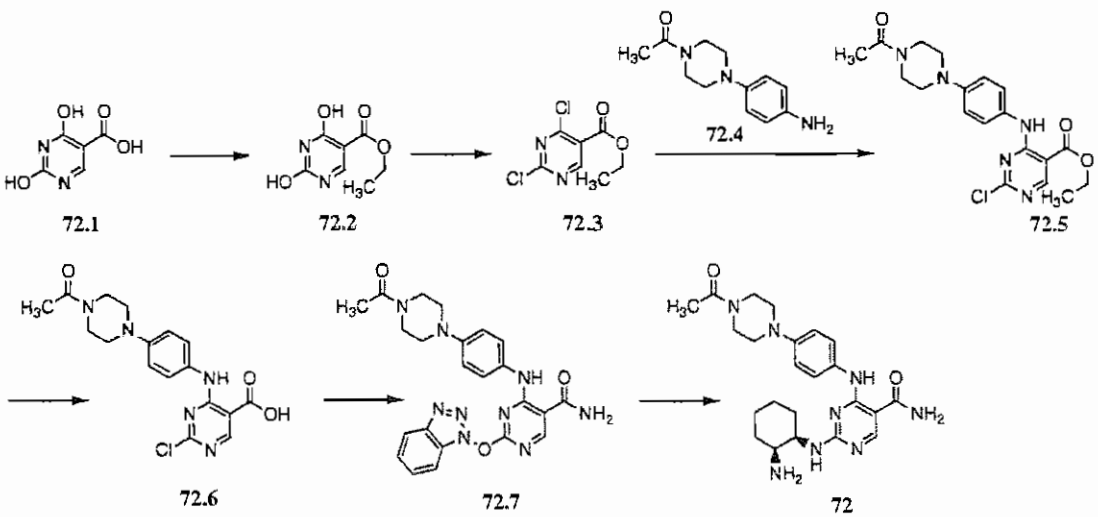
[0389] Preparative separations may be carried out as needed, using either an Sq16x or an Sg100c chromatography system and prepackaged silica gel columns all purchased from Teledyne Isco, (Lincoln, NE). Alternately, compounds and intermediates may be purified by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a C-18 reversed phase column. Typical solvents employed for the Isco systems and

flash column chromatography may be dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous hydroxyamine and triethyl amine. Typical solvents employed for the reverse phase HPLC may be varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

General methods

[0390] The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this application.

Example 1. 4-(4-(4-acetylpiperazin-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0391] Step 1: To a stirring solution of carboxylic acid **72.1** (85g, 540 mmol) in thionyl chloride (425 mL) was added pyridine (8.5 mL, 0.11 mmol), slowly. The reaction was stirred at 75°C overnight at which time it was concentrated and dried under vacuum to a light yellow powder. This yellow solid was slowly diluted with 750 mL of ethanol and refluxed overnight. The next day the reaction was determined to be complete by HPLC and then cooled in an ice bath and the solid filtered and washed with diethyl ether affording ethyl ester **72.2**an off-white powder (91 g, 87% for two steps). MS found for $C_7H_8N_2O_4$ as $(M+H)^+$ 185.0.

[0392] Step 2: Ester **72.2** (22 g, 120 mmol) was dissolved in phosphorous oxychloride (60 mL, 600 mmol) and the mixture treated with N,N-diethylaniline (27 mL, 167 mmol) and the mixture heated to 105°C until the reaction was determined to be complete by HPLC. It was

then cooled to RT and slowly added to 1 L of crushed ice resulting in the formation of a beige precipitate which was collected by filtration and dried under vacuum affording dichloride **72.3**a light yellow powder (22.5 g, 85%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.13 (s, 1H), 4.37 (q, 2H), 1.32 (t, 3H).

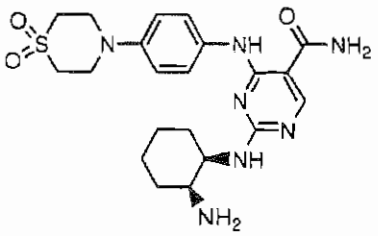
[0393] Step 3: Dichloropyrimidine **72.3** (500 mg, 2.3 mmol) was dissolved in NMP (10 mL) and stirred in ice bath. To it was added a soluntion of aniline **72.4** (540 mg, 2.5 mmol) and ethyldiisopropylamine (DIEA, 0.82 mL, 4.6 mmol) in 10 mL NMP dropwise using an additional funnel. The mixture was stirred for 1 hour, diluted with ethyl acetate, washed with brine, concentrated and subjected to flash column to isolate compound **72.5** a white solid (905 mg, 97%). MS found for $C_{19}H_{22}ClN_5O_3$ as $(M+H)^+$ 404.1.

[0394] Step 4: Ethyl ester **72.5** (5 mg, 2.2 mmol) was dissolved in 100 mL THF. To it were added lithium hydroxide hydrate (190 mg, 4.4 mmol) and 10 mL water. The mixture was stirred for 1 hour and to it was carefully added 1N HCl solution till pH reaching 3. The mixture was concentrated in vacuo to remove THF. White solid crashed out and was isolated using a Büchner funnel. It was washed with water and dried in vacuum oven to give compound **72.6** (900 mg, 99%) as a white solid. MS found for $C_{17}H_{18}ClN_5O_3$ as $(M+H)^+$ 376.1.

[0395] Step 5: Carboxylic acid **72.6** (900 mg, 2.2 mmol) was dissolved in 30 mL NMP. To it were added EDC hydrochloride (690 mg, 3.6 mmol) and HOBt hydrate (490 mg, 3.6 mmol). The mixture was stirred at RT for 90 minutes. To it was then added ammonia (commercial 0.5N solution in dioxane, 24 mL, 12 mmol). The mixture was stirred for overnight. It was then concentrated in vacuo and taken into water and chloroform. The chloroform phase was separated and washed with brine four times. The chloroform phase was then dried over $MgSO_4$ and concentrated in vacuo to afford compound **72.7** as a light yellow solid (720 mg, 63%). MS found for $C_{23}H_{23}N_9O_3$ as $(M+H)^+$ 474.2.

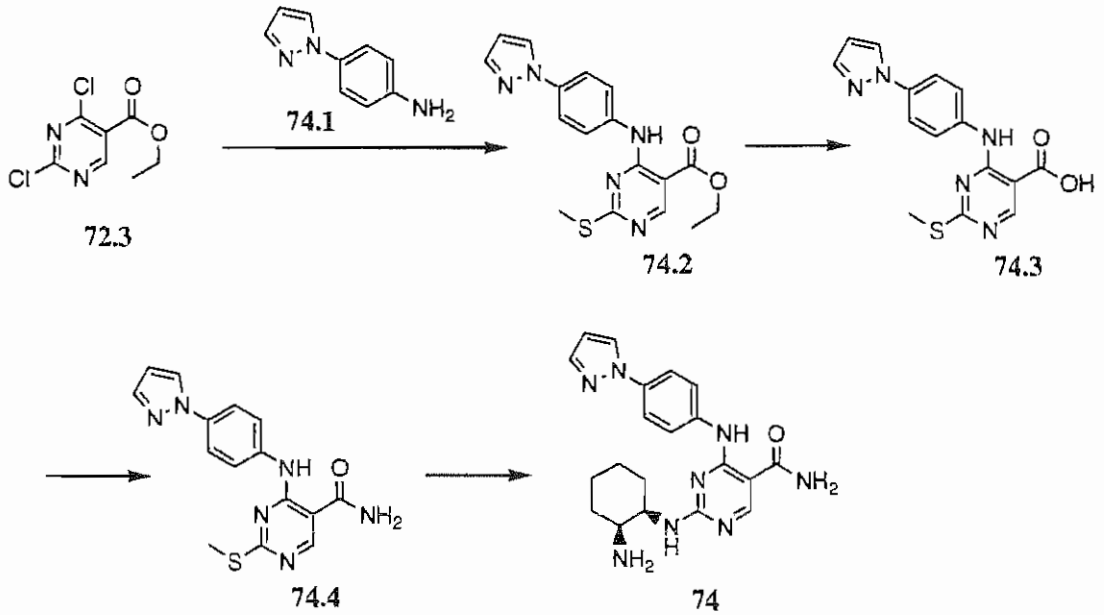
[0396] Step 6: Benzotriazolyl ether **72.7** (100 mg, 0.21 mmol) was dissolved in 3 mL DMSO. To it was added cis-1,2-diaminocyclohexane (124 μL, 1.05 mmol). The mixture was stirred for 1 hour at 120°C bath in a sealed flask. This mixture was then subjected to preparative HPLC to isolate the racemic title compound **72**. MS found for $C_{23}H_{32}N_8O_2$ as $(M+H)^+$ 453.2. UV λ=240, 297 nm.

Example 2. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(1,1-dioxo)thiomorpholinophenylamino)pyrimidine-5-carboxamide



[0397] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 1 with 4-(1,1-dioxo)thiomorpholinoaniline to replace aniline **72.4**. MS found for $C_{21}H_{29}N_7O_3S$ as $(M+H)^+$ 460.2. UV λ=236, 312 nm.

Example 3. 4-(4-(1H-pyrazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0398] Step 1: Dichloropyrimidine **72.3** (1.12 g, 5.05 mmol) was dissolved in 60 mL DMF and stirred at RT. To it were added 4-(1H-pyrazol-1-yl)aniline **74.1** (0.96 g, 6.1 mmol) in one portion and ethyldiisopropylamine (DIEA, 1.58 mL, 9.1 mmol) dropwise using a syringe. The mixture was stirred for 1 hour at RT. To it was then added sodium thiomethxoide (885 mg, 12.6 mmol). The mixture was stirred at RT for overnight, diluted with ethyl acetate, washed with brine three times, dried over $MgSO_4$, concentrated in vacuo and subjected to flash column to afford compound **50.2** was a white solid. MS found for $C_{17}H_{17}N_5O_2S$ as $(M+H)^+$ 356.1.

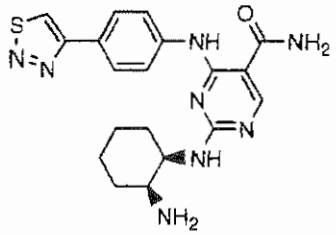
[0399] Step 2: Ethyl ester **74.2** from Step 1 was dissolved in 200 mL THF. To it were added lithium hydroxide hydrate (424 mg, 10.1 mmol) and 20 mL water. The mixture was

stirred for 2 days at RT. It was concentrated in vacuo to remove THF and carefully treated with 1N HCl till pH reaching 3. A white solid crashed out from the solution. It was isolated using a Büchner funnel, washed with cold water, dried in vacuum oven to give compound **74.3** (1.12 g, 68% for 2 step2). MS found for $C_{15}H_{13}N_5O_2S$ as $(M+H)^+$ 328.1.

[0400] Step 3: Carboxylic acid **74.3** (1.12 g, 3.4 mmol) was dissolved in 60 mL DMF. To it were added EDC hydrochloride (0.98 g, 5.1 mmol) and HOBt hydrate (0.69 g, 5.1 mmol). The mixture was stirred at RT for 2 hours. To it was then added ammonia (commercial 0.5N solution in dioxane, 34 mL, 17 mmol). The mixture was stirred for 2 hours. It was then concentrated in vacuo to remove dioxane. To it was added 300 mL water. A light yellow solid crashed out. It was isolated using a Büchner funnel, washed with cold water, dried in vacuum oven to give compound **74.4** (1.12 g, 99%). MS found for $C_{15}H_{14}N_6OS$ as $(M+H)^+$ 327.1.

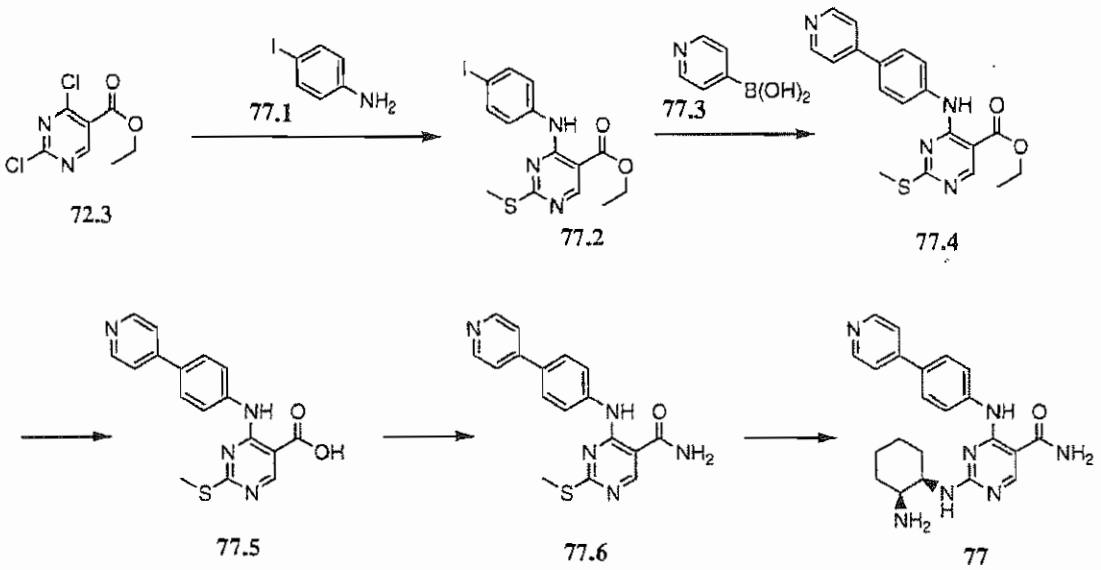
[0401] Step 4: Compound **74.4** (50 mg, 0.15 mmol) was dissolved in 4 mL NMP. To it was added MCPBA (65% pure, 45 mg, 0.17 mmol). It was stirred at RT for 30 minutes. To it then were added cis-1,2-diaminocyclohexane (53 µL, 0.45 mmol) and DIEA (78 µL, 0.45 mmol). The mixture was stirred for 50 minutes at 90°C bath. This mixture was then subjected to preparative HPLC to isolate the racemic title compound **74**. MS found for $C_{20}H_{24}N_8O$ as $(M+H)^+$ 393.2. UV λ=239, 304 nm. NMR (CD_3OD): δ 8.41 (s, 1H), 8.12 (m, 1H), 7.70 (d, J=8.4 Hz, 2H), 7.63 (d, J=7.2 Hz, 2H), 7.62 (s, 1H), 6.43 (dd, J=2.4, 2.0 Hz, 1H), 4.27 (m, 1H), 3.60 (m, 1H), 1.83-1.45 (m, 8H) ppm.

Example 4. 4-(4-(1,2,3-thiadiazol-4-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0402] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 3 with 4-(1,2,3-thiadiazol-4-yl)aniline to replace aniline **74.1**. MS found for $C_{19}H_{22}N_8OS$ as $(M+H)^+$ 411.2. UV λ=231, 311 nm. NMR (CD_3OD): δ 9.24 (s, 1H), 8.56 (s, 1H), 8.15 (d, J=5.6 Hz, 2H), 7.84 (m, 2H), 4.43 (m, 1H), 3.76 (m, 1H), 1.91-1.60 (m, 8H) ppm.

Example 5. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyridin-4-yl)phenylamino)pyrimidine-5-carboxamide



[0403] Step 1: Dichloropyrimidine **72.3** (3.02 g, 13.6 mmol) was dissolved in 100 mL DMF and stirred at RT. To it were added 4-iodoaniline **77.1** (3.59 g, 16.3 mmol) in one portion and ethyldiisopropylamine (DIEA, 4.25 mL, 24.4 mmol) dropwise using a syringe. The mixture was stirred for 2.5 hours at RT. To it was then added sodium thiomethxoide (2.38 g, 34 mmol). The mixture was stirred at RT for 1.5 hr, diluted with ethyl acetate, washed with brine three times, dried over $MgSO_4$, treated with activated carbon, concentrated in vacuo to afford crude compound **77.2** was a light brown solid (4.50 g, 79%). MS found for $C_{14}H_{14}IN_3O_2S$ as $(M+H)^+$ 416.1.

[0404] Step 2: Iodobenzene **77.2** (620 mg, 1.5 mmol) was dissolved in 20 mL dioxane and 10 mL water. To it were added boronic acid **77.3** (406 mg, 3.3 mmol), Na_2CO_3 (480 mg, 4.5 mmol) and $Pd(PPh_3)_2Cl_2$ (211 mg, 0.3 mmol). The mixture was degassed using argon stream for 3 minutes and stirred in 85°C bath under argon for 1 hour. The mixture was concentrated and diluted with chloroform. It was washed with brine, dried over $MgSO_4$, concentrated and subjected to flash column to isolate compound **77.4** (300 mg, 55%). MS found for $C_{19}H_{18}N_4O_2S$ as $(M+H)^+$ 367.1.

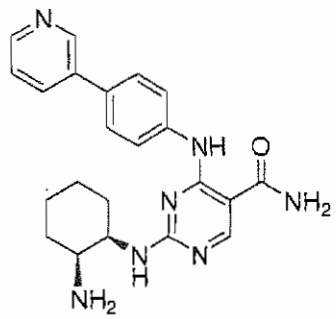
[0405] Step 3: Ethyl ester **77.4** (300 mg, 0.82 mmol) was dissolved in 30 mL THF. To it were added lithium hydroxide hydrate (104 mg, 2.46 mmol) and 10 mL water. The mixture was stirred for 2 hours at RT. It was concentrated in vacuo to remove THF and carefully treated with 1N HCl till pH reaching 3. A light yellow solid crashed out from the solution. It

was isolated using a Büchner funnel, washed with cold water, dried in vacuum oven to give compound **77.5** (250 mg, 90%). MS found for $C_{17}H_{14}N_4O_2S$ as $(M+H)^+$ 339.1.

[0406] Step 4: Carboxylic acid **77.5** (250 mg, 0.74 mmol) was dissolved in 10 mL DMF. To it were added EDC hydrochloride (213 mg, 1.1 mmol) and HOBt hydrate (150 mg, 1.1 mmol). The mixture was stirred at RT for 90 minutes. To it was then added ammonia (commercial 0.5N solution in dioxane, 7.4 mL, 3.7 mmol). The mixture was stirred for overnight. It was then concentrated in vacuo to remove dioxane. To it was added water 100 mL. A light yellow solid crashed out. It was isolated using a Büchner funnel, washed with cold water, dried in vacuum oven to give compound **77.6** (230 mg, 92%). MS found for $C_{17}H_{15}N_5OS$ as $(M+H)^+$ 338.1.

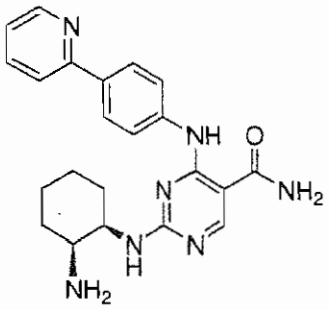
[0407] Step 5: Compound **77.6** (25 mg, 0.074 mmol) was dissolved in 3 mL NMP. To it was added MCPBA (65% pure, 22 mg, 0.081 mmol). It was stirred at RT for 30 minutes. To it was then added cis-1,2-diaminocyclohexane (70 μL, 0.60 mmol). The mixture was stirred for 30 minutes at 90°C bath. This mixture was then subjected to preparative HPLC to isolate the racemic title compound **77**. MS found for $C_{22}H_{25}N_7O$ as $(M+H)^+$ 404.2. UV λ=238, 337 nm.

Example 6. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyridin-3-yl)phenylamino)pyrimidine-5-carboxamide



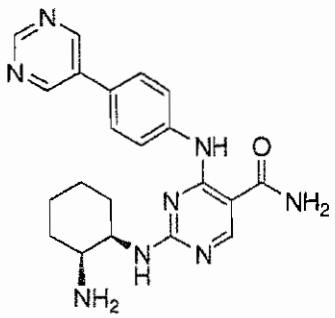
[0408] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 5 with pyridine-3-boronic acid to replace pyridine-4-boronic acid **77.3**. MS found for $C_{22}H_{25}N_7O$ as $(M+H)^+$ 404.2. UV λ=239, 311 nm.

Example 7. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyridin-2-yl)phenylamino)pyrimidine-5-carboxamide



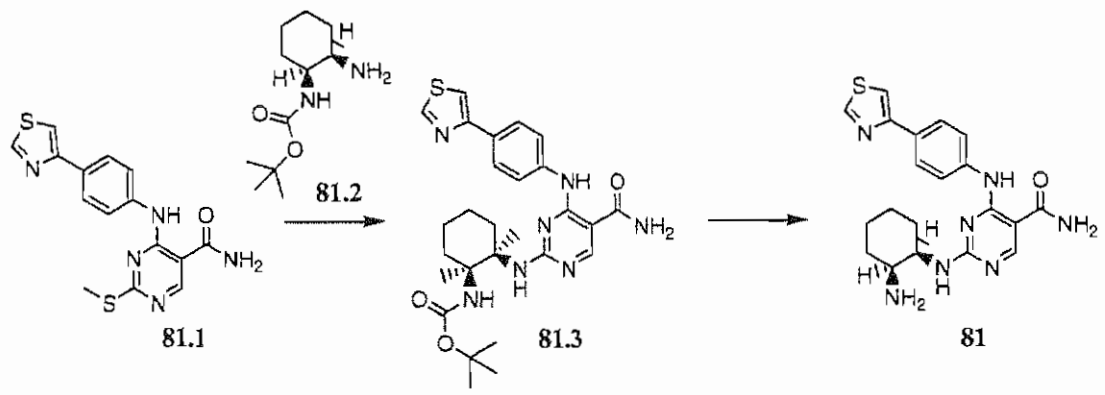
[0409] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 1 with 4-(pyridin-2-yl)aniline to replace aniline **72.4**. MS found for $C_{22}H_{25}N_7O$ as $(M+H)^+$ 404.2. UV λ=241, 330 nm.

Example 8. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyrimidin-5-yl)phenylamino)pyrimidine-5-carboxamide



[0410] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 5 with pyrimidine-5-boronic acid to replace pyridine-4-boronic acid **77.3**. MS found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.2. UV λ=243, 308 nm. NMR (CD_3OD): δ 9.13 (s, 1H), 9.08 (s, 2H), 8.55 (s, 1H), 7.82 (m, 4H), 4.44 (m, 1H), 3.74 (m, 1H), 1.94-1.60 (m, 8H) ppm.

Example 9. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxamide

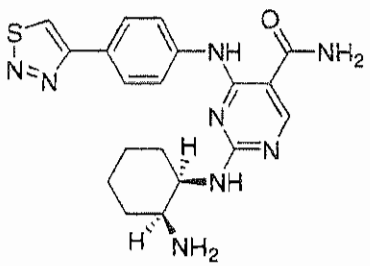


[0411] Step 1: Compound **81.1** was prepared using the same synthetic scheme demonstrated in Example 5 for **77.3** with 4-(thiazol-4-yl)aniline to replace aniline **77.1**. MS found for $C_{15}H_{13}N_5OS_2$ as $(M+H)^+$ 344.1.

[0412] Step 2: Compound **81.1** (100 mg, 0.29 mmol) was dissolved in 4 mL NMP. To it was added MCPBA (65% pure, 93 mg, 0.35 mmol). It was stirred at RT for 45 minutes. To it were then added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2** (0.3 M, 2 mL, 0.60 mmol) and DIEA (156 µL, 0.90 mmol). The mixture was stirred for 1 hour at 90°C bath. This mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ aqueous solution twice and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford crude compound **81.3**. MS found for $C_{25}H_{31}N_7O_3S$ as $(M+H)^+$ 510.2.

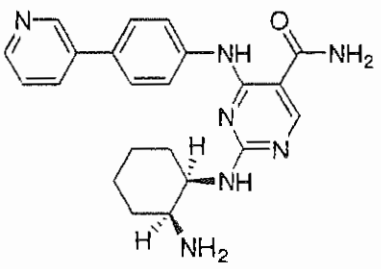
[0413] Step 3: Compound **81.3** was stirred in a 1:1 mixture of TFA and dichloromethane at RT for 10 minutes. It was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound. MS found for $C_{20}H_{23}N_7OS$ as $(M+H)^+$ 410.2. UV λ=239, 313 nm. NMR (CD_3OD): δ 9.07 (d, J=2.0 Hz, 1H), 8.53 (s, 1H), 8.01 (d, J=8.8 Hz, 2H), 7.91 (s, 1H), 7.71 (d, J=7.2 Hz, 2H), 4.40 (m, 1H), 3.74 (m, 1H), 1.94-1.59 (m, 8H) ppm.

Example 10. 4-(4-(1,2,3-thiadiazol-4-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



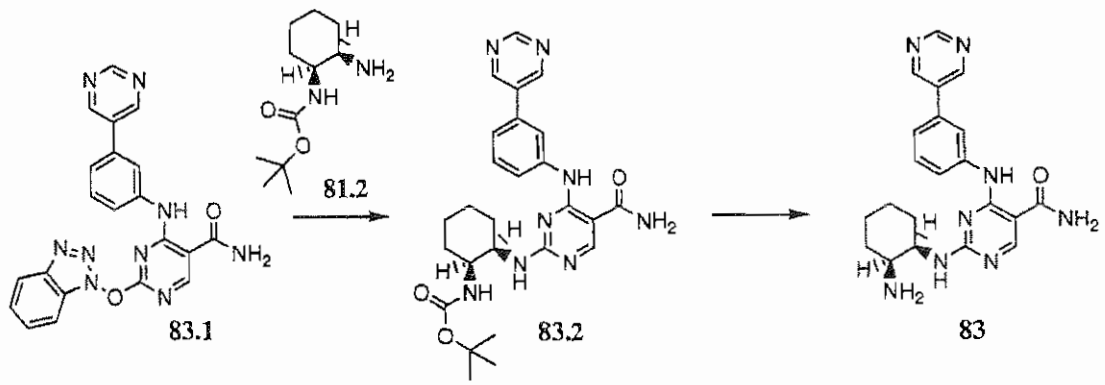
[0414] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 and Example 9 with 4-(1,2,3-thiadiazol-4-yl)aniline to replace aniline **74.1**. MS found for $C_{19}H_{22}N_8OS$ as $(M+H)^+$ 411.2. UV λ=233, 308 nm. NMR (CD_3OD): δ 9.24 (s, 1H), 8.56 (s, 1H), 8.15 (d, J=5.6 Hz, 2H), 7.84 (m, 2H), 4.43 (m, 1H), 3.76 (m, 1H), 1.91-1.60 (m, 8H) ppm.

Example 11. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyridin-3-yl)phenylamino)pyrimidine-5-carboxamide



[0415] The title compound was prepared using the same synthetic scheme demonstrated in Example 5 with pyridine-3-boronic acid to replace pyridine-4-boronic acid **77.3**. MS found for $C_{22}H_{25}N_7O$ as $(M+H)^+$ 404.2. UV λ=240, 311 nm. NMR (CD_3OD) δ 9.05 (d, J=2.0 Hz, 1H), 8.70 (dd, J=5.6, 1.2 Hz, 1H), 8.61 (d, J=6.8 Hz, 1H), 8.56 (s, 1H), 7.93-7.81 (m, 5H), 4.45 (m, 1H), 3.75 (m, 1H), 1.92-1.59 (m, 8H) ppm.

Example 12. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyrimidin-5-yl)phenylamino)pyrimidine-5-carboxamide



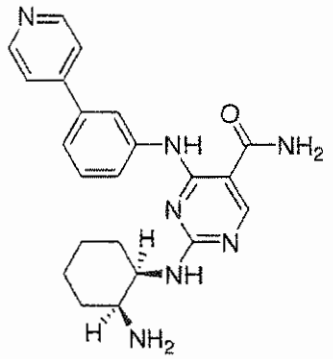
[0416] Step 1: Compound **83.1** was prepared using the same synthetic scheme demonstrated in Example 1 for **72.7** with 3-(pyrimidin-5-yl)aniline to replace aniline **72.4**. MS found for $C_{21}H_{15}N_9O_2$ as $(M+H)^+$ 426.1.

[0417] Step 2: Compound **83.1** (150 mg, 0.35 mmol) was dissolved in 5 mL NMP. To it were added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2** (0.3 M, 2.3 mL, 0.70 mmol) and DIEA (185 μL, 1.06 mmol). The mixture was stirred for 40 minutes at 90°C bath. This mixture was diluted with ethyl acetate, washed with brine three times. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford crude compound **83.2**. MS found for $C_{26}H_{32}N_8O_3$ as $(M+H)^+$ 505.2.

[0418] Step 3: Compound **83.2** was stirred in a 1:1 mixture of TFA and dichloromethane at RT for 15 minutes. It was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound. MS found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.2. UV λ=245

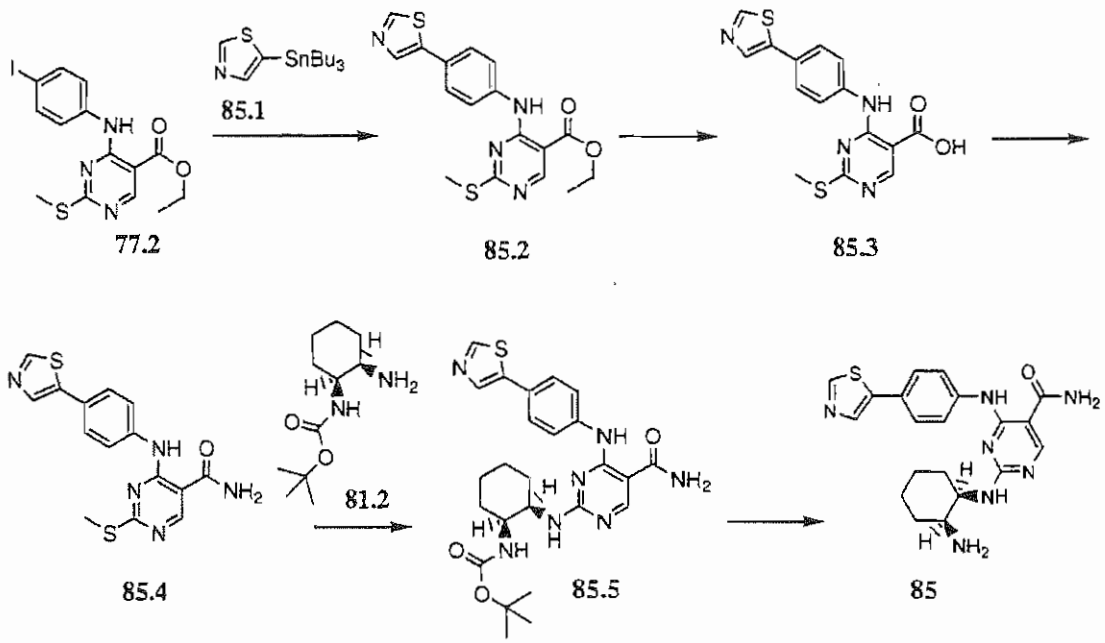
nm. NMR (CD_3OD): δ 9.17 (s, 1H), 9.10 (s, 2H), 8.55 (s, 1H), 8.11 (m, 1H), 7.70 (m, 1H), 7.58 (m, 2H), 4.37 (m, 1H), 3.61 (m, 1H), 1.91-1.50 (m, 8H) ppm.

Example 13. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyridin-4-yl)phenylamino)pyrimidine-5-carboxamide



[0419] The title compound was prepared using the same synthetic scheme demonstrated in Example 5 and Example 9 with pyridine-3-boronic acid to replace pyridine-4-boronic acid **77.3**. MS found for $C_{22}H_{25}N_7O$ as $(M+H)^+$ 404.2. UV λ=240, 312 nm.

Example 14. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(thiazol-5-yl)phenylamino)pyrimidine-5-carboxamide



[0420] Step 1: Iodobenzene **77.2** (400 mg, 0.96 mmol) was dissolved in 10 mL toluene. To it were added 5-tributylstannylthiazole (430 mg, 1.15 mmol) and $Pd(PPh_3)_4$ (115 mg, 0.1 mmol). The mixture was degassed using argon stream for 3 minutes and refluxed under an argon atmosphere for 1 hour. It was concentrated in vacuo and subjected to silica flash

column to isolate compound **85.2** (160 mg, 45%). MS found for $C_{17}H_{16}N_4O_2S_2$ as $(M+H)^+$ 373.1.

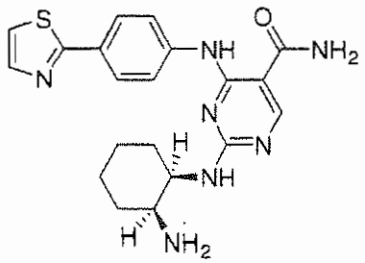
[0421] Step 2: Ethyl ester **85.2** (160 mg, 0.43 mmol) was dissolved in 30 mL THF. To it were added lithium hydroxide hydrate (55 mg, 1.3 mmol) and 5 mL water. The mixture was stirred for 2 hours at RT. It was concentrated in vacuo to remove THF and carefully treated with 1N HCl till pH reaching 3. A light yellow solid crashed out from the solution. It was isolated using a Büchner funnel, washed with cold water, dried in vacuum oven to give compound **85.3** (120 mg, 81%). MS found for $C_{15}H_{12}N_4O_2S_2$ as $(M+H)^+$ 345.1.

[0422] Step 3: Carboxylic acid **85.3** (100 mg, 0.29 mmol) was dissolved in 10 mL DMF. To it were added EDC hydrochloride (86 mg, 0.45 mmol) and HOBt hydrate (61 mg, 0.45 mmol). The mixture was stirred at RT for 1 hour. To it was then added ammonia (commercial 0.5N solution in dioxane, 3 mL, 1.5 mmol). The mixture was stirred for overnight. It was then concentrated in vacuo to remove dioxane. To it was added water 100 mL. A light yellow solid crashed out. It was isolated using a Büchner funnel, washed with cold water, dried in vacuum oven to give compound **85.4** (75 mg, 76%). MS found for $C_{15}H_{13}N_5OS_2$ as $(M+H)^+$ 344.1.

[0423] Step 4: Compound **85.4** (75 mg, 0.22 mmol) was dissolved in 5 mL NMP. To it was added MCPBA (65% pure, 64 mg, 0.24 mmol). It was stirred at RT for 30 minutes. To it were then added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2** (0.3 M, 1.5 mL, 0.45 mmol) and DIEA (115 µL, 0.66 mmol). The mixture was stirred for 90 minutes at 90°C bath. This mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ aqueous solution twice and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford crude compound **85.5**. MS found for $C_{25}H_{31}N_7O_3S$ as $(M+H)^+$ 510.2.

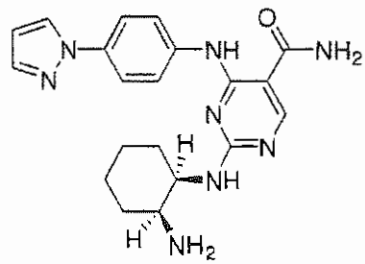
[0424] Step 5: Compound **85.5** was stirred in a 1:1 mixture of TFA and dichloromethane at RT for 30 minutes. It was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound. MS found for $C_{20}H_{23}N_7OS$ as $(M+H)^+$ 410.2. UV λ=240, 318 nm.

Example 15. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(thiazol-2-yl)phenylamino)pyrimidine-5-carboxamide



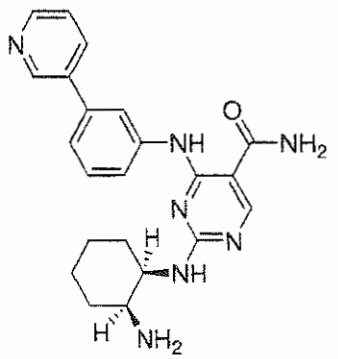
[0425] The title compound was prepared using the same synthetic scheme demonstrated in Example 14 with 2-tributylstannylthiazole to replace 5-tributylstannylthiazole **85.1**. MS found for $C_{20}H_{23}N_7OS$ as $(M+H)^+$ 410.2. UV λ=243, 332 nm. NMR (CD_3OD): δ 8.53 (s, 1H), 8.00 (d, J=8.0 Hz, 2H), 7.86 (d, J=3.2 Hz, 1H), 7.77 (d, J=8.0 Hz, 2H), 7.61 (d, J=3.2 Hz, 1H), 4.42 (m, 1H), 3.74 (m, 1H), 1.92-1.60 (m, 8H) ppm.

Example 16. 4-(4-(1H-pyrazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



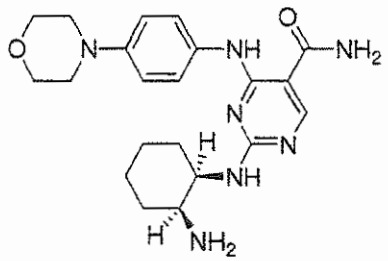
[0426] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 and Example 9. MS found for $C_{20}H_{24}N_8O$ as $(M+H)^+$ 393.2. UV λ=240, 302 nm. NMR (CD_3OD): δ 8.41 (s, 1H), 8.12 (m, 1H), 7.70 (d, J=8.4 Hz, 2H), 7.63 (d, J=7.2 Hz, 2H), 7.62 (s, 1H), 6.43 (dd, J=2.4, 2.0 Hz, 1H), 4.27 (m, 1H), 3.60 (m, 1H), 1.83-1.45 (m, 8H) ppm.

Example 17. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyridin-3-yl)phenylamino)pyrimidine-5-carboxamide



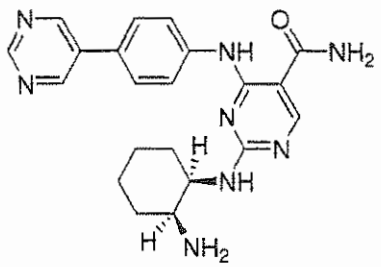
[0427] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 and Example 9 with 3-(pyridin-3-yl)aniline to replace aniline **74.1**. MS found for $C_{22}H_{25}N_7O$ as $(M+H)^+$ 404.2. UV λ=248 nm. NMR (CD_3OD): δ 9.05 (s, 1H), 8.73 (m, 1H), 8.59 (m, 1H), 8.54 (s, 1H), 8.00 (broad s, 1H), 7.92 (m, 1H), 7.80 (m, 1H), 7.63-7.61 (m, 2H), 4.33 (m, 1H), 3.62 (m, 1H), 1.91-1.47 (m, 8H) ppm.

Example 18. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-morpholinophenylamino)pyrimidine-5-carboxamide



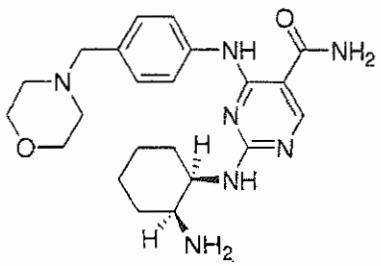
[0428] The title compound was prepared using the same synthetic scheme demonstrated in Example 5 and Example 9 with 4-morpholinoaniline to replace aniline **74.1**. MS found for $C_{21}H_{29}N_7O_2$ as $(M+H)^+$ 412.2. UV λ=243, 294 nm. NMR (CD_3OD): δ 8.45 (s, 1H), 7.49 (d, J=8.4 Hz, 2H), 7.04 (d, J=9.2 Hz, 2H), 4.30 (m, 1H), 3.85 (m, 4H), 3.71 (m, 1H), 3.19 (m, 4H), 1.88-1.56 (m, 8H) ppm.

Example 19. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyrimidin-5-yl)phenylamino)pyrimidine-5-carboxamide



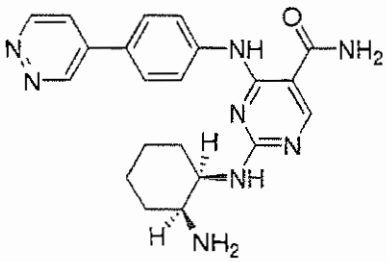
[0429] The title compound was prepared using the same synthetic scheme demonstrated in Example 5 and Example 9 with pyrimidine-5-boronic acid to replace pyridine-4-boronic acid **77.3**. MS found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.2. UV λ=242, 307 nm. NMR (CD_3OD): δ 9.13 (s, 1H), 9.08 (s, 2H), 8.55 (s, 1H), 7.82 (m, 4H), 4.44 (m, 1H), 3.74 (m, 1H), 1.95-1.58 (m, 8H) ppm.

Example 20. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(morpholinomethyl)phenylamino)pyrimidine-5-carboxamide



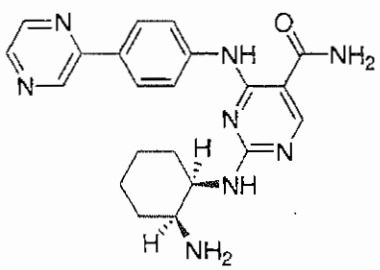
[0430] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 and Example 9 with 4-(morpholinomethyl)aniline to replace aniline **74.1**. MS found for $C_{22}H_{31}N_7O_2$ as $(M+H)^+$ 426.3. UV λ=244, 293 nm.

Example 21. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyridazin-4-yl)phenylamino)pyrimidine-5-carboxamide



[0431] The title compound was prepared using the same synthetic scheme demonstrated in Example 14 with 4-tributylstannylpyridazine to replace 5-tributylstannylthiazole **85.1**. MS found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.3. UV λ=239, 327 nm. NMR (CD_3OD): δ 9.59 (m, 1H), 9.21 (d, J=9.2 Hz, 1H), 8.58 (s, 1H), 8.08 (m, 1H), 7.96-7.85 (m, 5H), 4.47 (m, 1H), 3.77 (m, 1H), 1.93-1.59 (m, 8H) ppm.

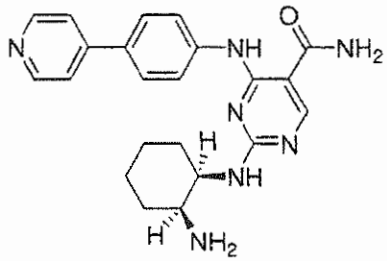
Example 22. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyrazin-2-yl)phenylamino)pyrimidine-5-carboxamide



[0432] The title compound was prepared using the same synthetic scheme demonstrated in Example 14 with 2-tributylstannylpyrazine to replace 5-tributylstannylthiazole **85.1**. MS

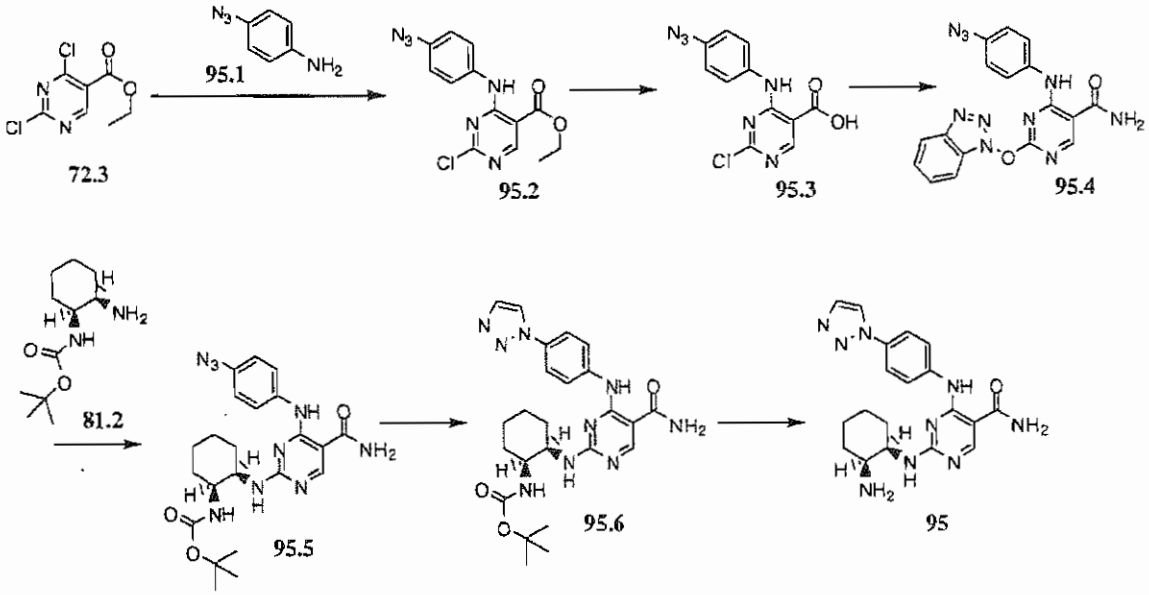
found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.3. UV λ=235, 319 nm. NMR (CD_3OD): δ 9.11 (s, 1H), 8.66 (broad s, 1H), 8.56 (s, 1H), 8.51 (broad s, 1H), 8.14 (m, 2H), 7.85 (m, 2H), 4.44 (m, 1H), 3.77 (m, 1H), 1.92-1.58 (m, 8H) ppm.

Example 23. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyridin-4-yl)phenylamino)pyrimidine-5-carboxamide



[0433] The title compound was prepared using the same synthetic scheme demonstrated in Example 5 and Example 9. MS found for $C_{22}H_{25}N_7O$ as $(M+H)^+$ 404.2. UV λ=239, 334 nm. NMR (CD_3OD): δ 8.76 (d, J=6.8 Hz, 2H), 8.60 (s, 1H), 8.29 (d, J=6.4 Hz, 2H), 8.05-7.96 (m, 4H), 4.49 (m, 1H), 3.76 (m, 1H), 1.93-1.60 (m, 8H) ppm.

Example 24. 4-(4-(1H-1,2,3-triazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0434] Step 1: Compound **72.3** (1.18 g, 5.3 mmol) was dissolved in 40 mL NMP and stirred at RT. To it were added 4-azidoaniline hydrochloride **95.1** (1.00 g, 5.9 mmol) and then DIEA (2.21 mL, 12.7 mmol) dropwise using syringe. The mixture was stirred for 1 hour and

diluted with ethyl acetate. It was washed with brine four times, dried and concentrated in vacuo to afford compound **95.2** (1.59 g, 94%). MS found for $C_{13}H_{11}ClN_6O_2$ as $(M+H)^+$ 319.2.

[0435] Step 2: Ethyl ester **95.2** (1.59 g, 5.0 mmol) was dissolved in 50 mL THF. To it were added lithium hydroxide hydrate (420 mg, 10 mmol) and 5 mL water. The mixture was stirred for 4 hours and to it was carefully added 3N HCl solution till pH reaching 3. The mixture was concentrated in vacuo to remove THF. The residue was taken into ethyl acetate and washed with brine twice. It was dried and concentrated in vacuo to give compound **95.3** (1.58 g, 99%) as a solid. MS found for $C_{11}H_7ClN_6O_2$ as $(M+H)^+$ 291.2.

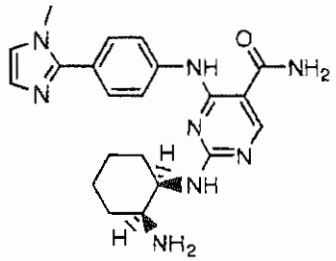
[0436] Step 3: Carboxylic acid **95.3** (1.58 g, 5.0 mmol) was dissolved in 40 mL DMF. To it were added EDC hydrochloride (1.44 g, 7.5 mmol) and HOBt hydrate (1.02 g, 7.5 mmol). The mixture was stirred at RT for 50 minutes. To it was then added ammonia (commercial 0.5N solution in dioxane, 50 mL, 25 mmol). The mixture was stirred for 7 hours. It was then concentrated in vacuo and a solid crashed out. It was collected, washed and dried in vacuum oven to afford compound **95.4** (1.30 g, 67%). MS found for $C_{17}H_{12}N_{10}O_2$ as $(M+H)^+$ 389.3.

[0437] Step 4: Compound **95.4** (300 mg, 0.77 mmol) was dissolved in 20 mL NMP. To it were added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2** (0.3 M, 5.1 mL, 1.5 mmol) and DIEA (400 μL, 2.3 mmol). The mixture was stirred for 90 minutes at 90°C bath. This mixture was diluted with ethyl acetate, washed with brine three times. The organic phase was dried over $MgSO_4$, concentrated in vacuo and subjected to flash column to afford compound **95.5** (420 mg, 90%). MS found for $C_{22}H_{29}N_9O_3$ as $(M+H)^+$ 467.3.

[0438] Step 5: Compound **95.5** (420 mg, 0.70 mmol) was stirred in 10 mL methanol. To it were added trimethylsilylacetylene (200 mg, 1.4 mmol), CuI (400 mg, 2.1 mmol) and DBU (313 μL, 2.1 mmol). The mixture was stirred at RT for 4 hours. It was diluted with ethyl acetate, washed with saturated ammonium chloride aqueous solution and brine twice. The organic phase was dried, filtered and concentrated in vacuo to afford crude compound **95.6**. MS found for $C_{24}H_{31}N_9O_3$ as $(M+H)^+$ 494.4.

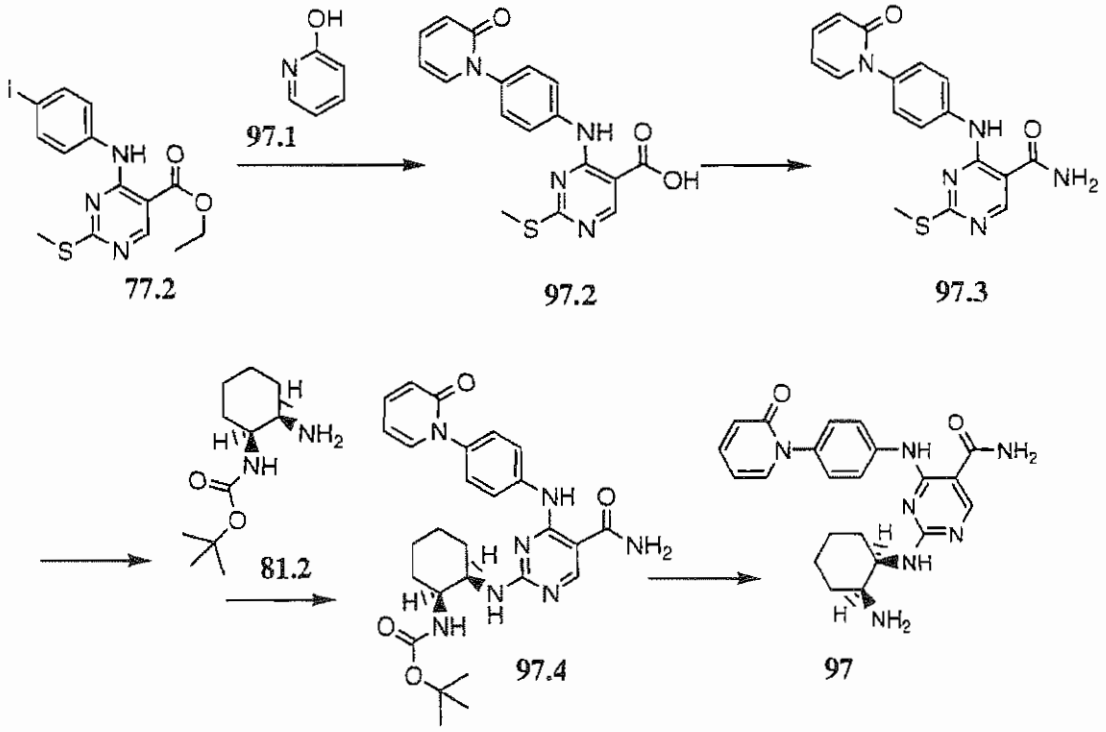
[0439] Step 6: Crude compound **95.6** was stirred in a 1:1 mixture of TFA and dichloromethane at RT for 90 minutes. It was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV λ=242, 300 nm.

Example 25. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(1-methyl-1H-imidazol-2-yl)phenylamino)pyrimidine-5-carboxamide



[0440] The title compound was prepared using the same synthetic scheme demonstrated in Example 14 with 1-methyl-2-tributylstannylimidazole to replace 5-tributylstannylthiazole **85.1**. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 407.4. UV λ=241, 300 nm. NMR (CD_3OD): δ 8.97 (s, 1H), 8.59 (s, 1H), 7.90 (m, 2H), 7.64 (m, 3H), 4.46 (m, 1H), 3.91 (s, 3H), 3.73 (m, 1H), 1.92-1.58 (m, 8H) ppm.

Example 26. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(2-oxopyridin-1(2H)-yl)phenylamino)pyrimidine-5-carboxamide



[0441] Step 1: Iodobenzene **77.2** (440 mg, 1.06 mmol) was dissolved in 10 mL DMSO. To it were added 2-hydroxypyridine **97.1** (202 mg, 2.12 mmol), K_2CO_3 (293 mg, 2.12 mmol), CuI (61 mg, 0.32 mmol) and 8-hydroxyquinoline (46 mg, 0.32 mmol). The mixture was stirred in 120°C bath for 5 hours. To the mixture were added lithium hydroxide hydrate (126

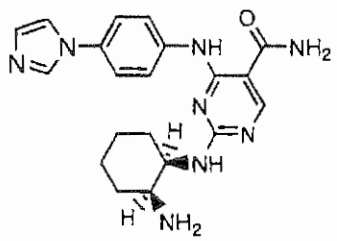
mg, 3 mmol) and 10 mL water. The mixture was stirred for overnight. To it was carefully added 1N HCl till pH reaching 3. The mixture was filtered through celite and subjected to reverse phase prep HPLC to isolate compound **97.2** (75 mg, 20%). MS found for $C_{17}H_{14}N_4O_3S$ as $(M+H)^+$ 354.3.

[0442] Step 2: Carboxylic acid **97.2** (75 mg, 0.21 mmol) was dissolved in 10 mL DMF. To it were added EDC hydrochloride (61 mg, 0.32 mmol) and HOBt hydrate (44 mg, 0.32 mmol). The mixture was stirred at RT for 90 minutes. To it was then added ammonia (commercial 0.5N solution in dioxane, 2 mL, 1 mmol). The mixture was stirred for 2 hours. It was then concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate compound **97.3** (40 mg, 53%). MS found for $C_{17}H_{15}N_5O_2S$ as $(M+H)^+$ 355.3.

[0443] Step 3: Compound **97.3** (40 mg, 0.11 mmol) was dissolved in 5 mL NMP. To it was added MCPBA (65% pure, 37 mg, 0.14 mmol). It was stirred at RT for 1 hour. To it were then added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2** (0.3 M, 0.73 mL, 0.22 mmol) and DIEA (115 μL, 0.66 mmol). The mixture was stirred for 1 hour at 90°C bath. This mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ aqueous solution twice and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford crude compound **97.3**. MS found for $C_{27}H_{33}N_7O_4$ as $(M+H)^+$ 520.4.

[0444] Step 4: Compound **97.4** was stirred in a 4:1 mixture of TFA and dichloromethane at 50° for 1 hour. It was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound. MS found for $C_{22}H_{25}N_7O_2$ as $(M+H)^+$ 420.4. UV λ=241, 296 nm.

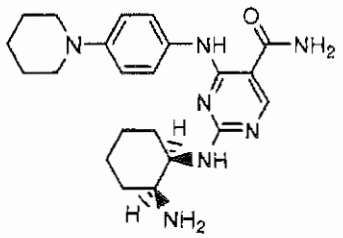
[0445] Example 27. 4-(4-(1H-imidazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0446] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 and Example 9 with 4-(1H-imidazol-1-yl)aniline to replace aniline **74.1**. MS found for $C_{20}H_{24}N_8O$ as $(M+H)^+$ 393.4. UV λ=246, 292 nm. NMR (CD_3OD): δ 9.41 (s, 1H),

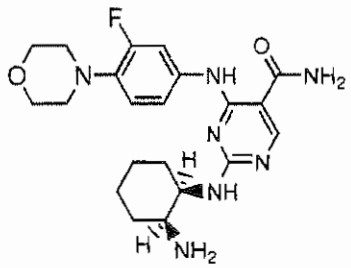
8.59 (s, 1H), 8.05-7.95 (m, 3H), 7.79-7.76 (m, 3H), 4.46 (m, 1H), 3.71 (m, 1H), 1.93-1.59 (m, 8H) ppm.

Example 28. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(piperidin-1-yl)phenylamino)pyrimidine-5-carboxamide



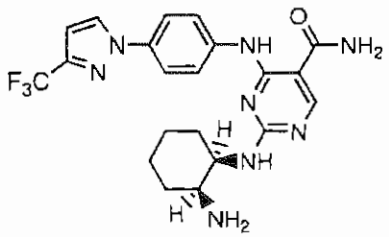
[0447] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 and Example 9 with 4-(piperidin-1-yl)aniline to replace aniline **72.4**. MS found for $C_{22}H_{31}N_7O$ as $(M+H)^+$ 410.4. UV λ=246, 287 nm. NMR (CD_3OD): δ 8.55 (s, 1H), 7.81 (m, 2H), 7.59 (m, 2H), 4.41 (m, 1H), 3.71 (m, 1H), 3.58 (m, 4H), 2.02 (m, 4H), 1.90-1.80 (m, 8H), 1.60 (m, 2H) ppm.

Example 29. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-fluoro-4-morpholinophenylamino)pyrimidine-5-carboxamide



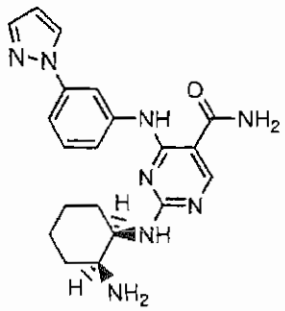
[0448] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 and Example 1 with 3-fluoro-4-morpholinoaniline to replace aniline **72.4**. MS found for $C_{21}H_{28}FN_7O_2$ as $(M+H)^+$ 430.4. UV λ=239, 309 nm. NMR (CD_3OD): δ 8.49 (s, 1H), 7.63 (m, 1H), 7.22 (m, 1H), 7.08 (dd, J=9.6, 8.8 Hz, 1H), 4.34 (m, 1H), 3.85 (m, 4H), 3.76 (m, 1H), 3.08 (m, 4 H), 1.92-1.58 (m, 8H) ppm.

Example 30. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide



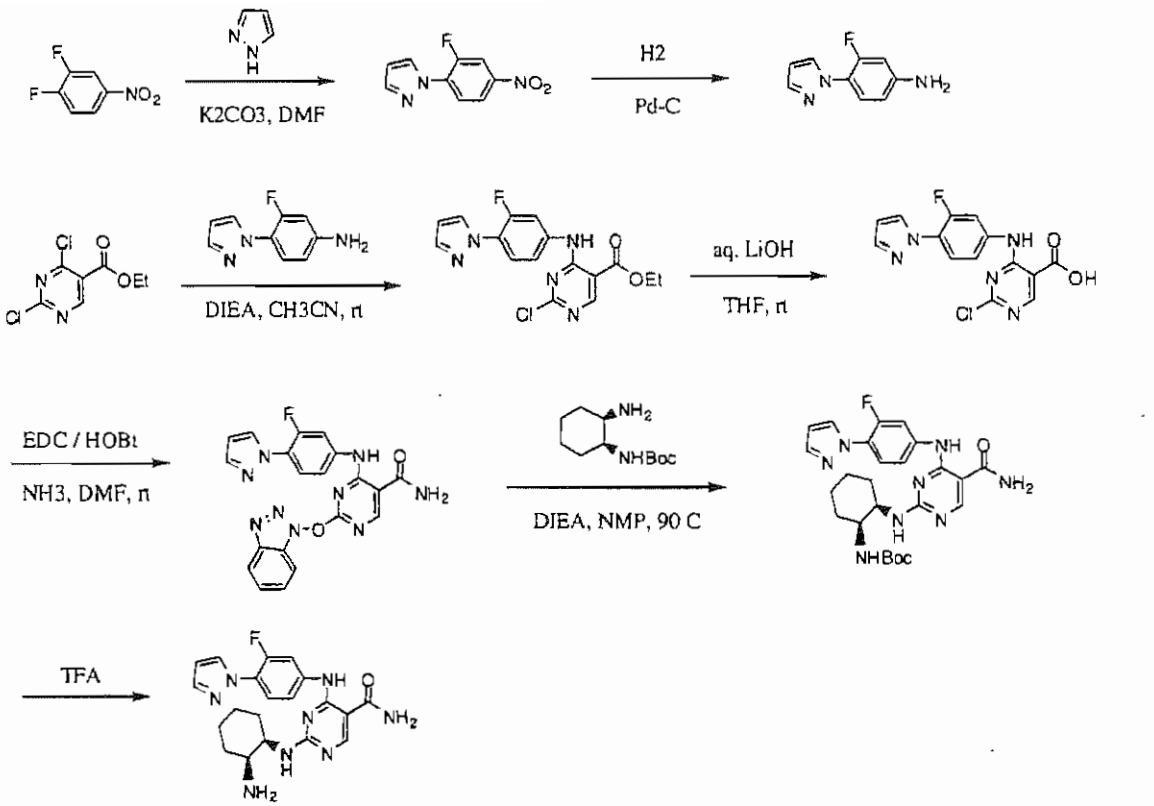
[0449] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 and Example 9 with 4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)aniline to replace aniline **74.1**. MS found for $C_{21}H_{23}F_3N_8O$ as $(M+H)^+$ 461.4. UV λ=241, 236 nm. NMR (CD_3OD): δ 8.54 (s, 1H), 8.38 (broad s, 1H), 7.85-7.80 (m, 4H), 6.84 (d, J=2.0 Hz, 1H), 4.41 (m, 1H), 3.71 (m, 1H), 1.91-1.59 (m, 8H) ppm.

Example 31. 4-(3-(1H-pyrazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0450] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 and Example 9 with 3-(1H-pyrazol-1-yl)aniline to replace aniline **74.1**. MS found for $C_{20}H_{24}N_8O$ as $(M+H)^+$ 393.4. UV λ=247 nm.

Example 32. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-fluoro-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide



[0451] A mixture of 3,4-difluoronitrobenzene (1.00 mL, 9.03 mmol), pyrazole (0.615 g, 9.04 mmol) and K2CO3 (2.50 g, 18.1 mmol) in DMF (10 mL) was stirred at room temperature overnight. Water (30 mL) was added to induce precipitation. The precipitate was collected, dried on vacuum to give1-(2-fluoro-4-nitrophenyl)-1H-pyrazole as a solid (1.80 g). MS 208.3 (M+H)

[0452] A suspension of 1-(2-fluoro-4-nitrophenyl)-1H-pyrazole (1.80 g, 8.70 mmol) and Pd-C (10%, 0.200 g) in MeOH (20 mL) (containing 10 drops of 6N HCl) was hydrogenated under balloon H2 overnight. The mixture was filtered through celite. The filtrate was concentrated in vacuo. The residue was dried on vacuum to give 3-fluoro-4-(1H-pyrazol-1-yl)benzenamine as a solid (1.55 g). MS 178.3 (M+H)

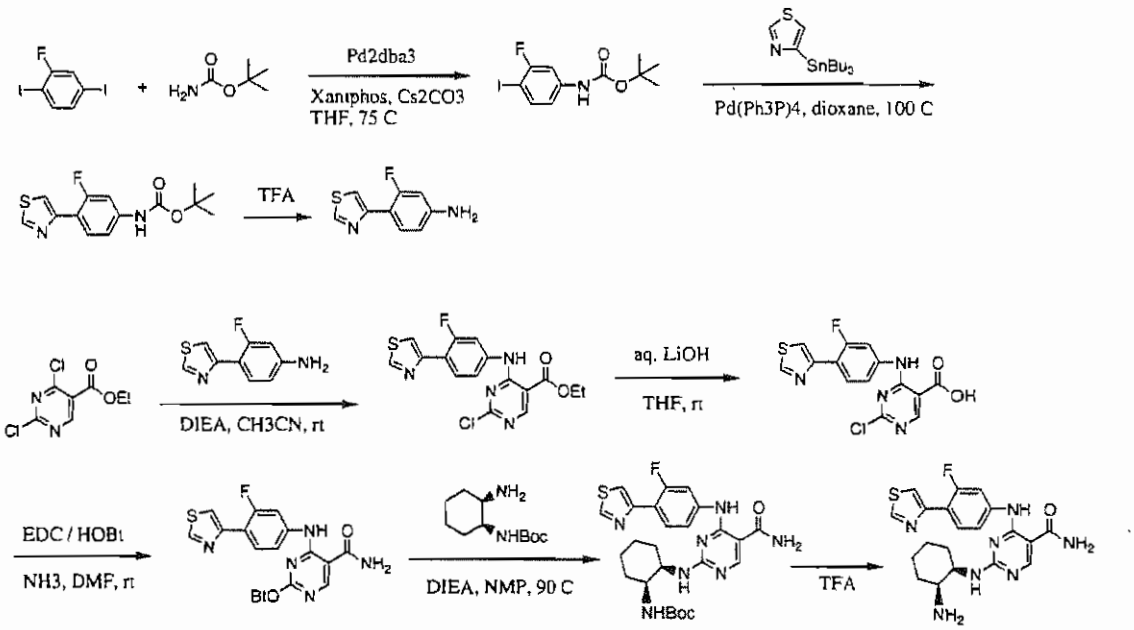
[0453] To a solution of ethyl 2,4-dichloropyrimidine-5-carboxylate (280 mg, 1.27 mmol) and 3-fluoro-4-(1H-pyrazol-1-yl)benzenamine (230 mg, 1.30 mmol) in CH_3CN (8 mL) at room temperature, DIEA (0.442 mL, 2.54 mmol) was added. The mixture was stirred at room temperature for 48 h. Water (15 mL) was added to induce precipitation. The precipitate was collected, dried on vacuum to give ethyl 2-chloro-4-(3-fluoro-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxylate as a solid (275 mg). MS 362.3 and 364.3 (M+H, Cl pattern)

[0454] To a solution of ethyl 2-chloro-4-(3-fluoro-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxylate (275 mg, 0.761 mmol) in THF (4 mL), aq. 1N LiOH (1.25 mL, 1.25 mmol) was added. The mixture was stirred at room temperature overnight. Upon acidification of the mixture with 1N HCl, white solids precipitated out, which were collected, and dried on vacuum to give 2-chloro-4-(3-fluoro-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxylic acid (230 mg). MS 334.3 and 336.3 (M+H, Cl pattern)

[0455] To a solution of 2-chloro-4-(3-fluoro-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxylic acid (230 mg, 0.690 mmol) and HOBt (158 mg, 1.03 mmol) in DMF (4 mL), EDC (200 mg, 1.04 mmol) was added. The mixture was stirred at room temperature for 1.5 h. Ammonia (0.5 M in dioxane, 6.00 mL, 3.00 mmol) was added. It was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with 1 N HCl, then with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo to give 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(3-fluoro-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide (184 mg). MS 432.4 (M+H)

[0456] A solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (0.30 M in NMP, 2.00 mL, 0.600 mmol) in NMP (2 mL) was added to 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(3-fluoro-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide (184 mg, 0.427 mmol). DIEA (0.150 mL, 0.863 mmol) was also added. The mixture was stirred at 90 C overnight. After being cooled to room temperature, water was added to induce precipitation. The precipitate was collected, then dissolved in CH_2Cl_2 (5 mL) and TFA (4 mL). The solution was stirred at room temperature for 30 min. It was concentrated in vacuo. The residue was purified by HPLC to give the titled compound (103 mg). MS 411.5 (M+H). UV λ=238.8, 304.8 nm.

Example 33. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-fluoro-4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxamide



[0457] A mixture of 2,5-diiodofluorobenzene (1.36 g, 3.90 mmol), tert-butylcarbamate (0.454 g, 3.88 mmol), xantphos (0.233 g, 0.40 mmol) and Cs_2CO_3 (dry powder, 2.48 g, 7.61 mmol) in THF (12 mL) was degassed with Ar before being charged with $Pd_2(dba)3$ (0.071 g, 0.078 mmol). It was stirred at 75 C overnight. After being cooled to room temperature, water and EtOAc were added. The organic phase was separated, dried over Na_2SO_4, concentrated in vacuo. The residue was loaded to a flash column, eluted with 0-10% EtOAc in hexane to give tert-butyl 3-fluoro-4-iodophenylcarbamate (716 mg).

[0458] A solution of tert-butyl 3-fluoro-4-iodophenylcarbamate (500 mg, 1.48 mmol) and 4-(tributylstannyl)thiazole (0.578 mL, 1.80 mmol) in dioxane (6 mL) was degassed with Ar before being charged with Pd(Ph3P)4 (170 mg, 0.147 mmol). It was stirred at 100 C for 34 h, then concentrated in vacuo. The residue was loaded to a flash column, eluted with 0-25% EtOAc in hexane to give tert-butyl 3-fluoro-4-(thiazol-4-yl)phenylcarbamate (270 mg). MS 295.3 (M+H)

[0459] A solution of tert-butyl 3-fluoro-4-(thiazol-4-yl)phenylcarbamate (270 mg, 0.92 mmol) in CH_2Cl_2 (2 mL) and TFA (4 mL) was stirred at room temperature for 60 min. It was then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), which was washed with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo to give 3-fluoro-4-(thiazol-4-yl)benzenamine (145 mg) as free base. MS 195.2 (M+H)

[0460] To a solution of ethyl 2,4-dichloropyrimidine-5-carboxylate (165 mg, 0.746 mmol) and 3-fluoro-4-(thiazol-4-yl)benzenamine (145 mg, 0.747 mmol) in CH_3CN (5 mL) at room

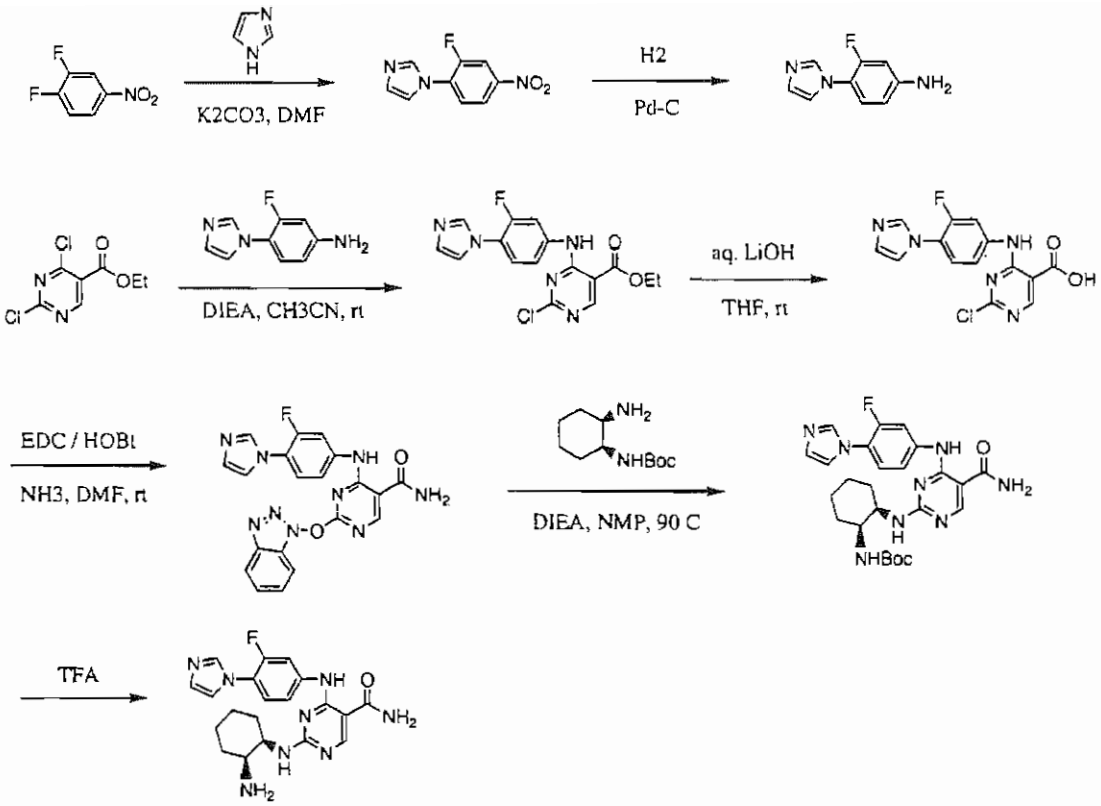
temperature, DIEA (0.260 mL, 1.49 mmol) was added. The mixture was stirred at room temperature overnight, during which time solids precipitated out. The precipitate was collected, dried on vacuum to give ethyl 2-chloro-4-(3-fluoro-4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxylate as a solid (186 mg). MS 379.3 and 381.3 (M+H, Cl pattern)

[0461] To a suspension of ethyl 2-chloro-4-(3-fluoro-4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxylate (186 mg, 0.491 mmol) in THF (4 mL), aq. 1N LiOH (1.00 mL, 1.00 mmol) was added. The suspension became clear with stirring. The mixture was then stirred at room temperature overnight. Upon acidification of the mixture with 1N HCl, white solids precipitated out, which were collected, and dried on vacuum to give 2-chloro-4-(3-fluoro-4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxylic acid (158 mg). MS 351.2 and 353.3 (M+H, Cl pattern)

[0462] To a solution of 2-chloro-4-(3-fluoro-4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxylic acid (158 mg, 0.450 mmol) and HOBt (103 mg, 0.673 mmol) in DMF (4 mL), EDC (130 mg, 0.678 mmol) was added. The mixture was stirred at room temperature for 1 h. Ammonia (0.5 M in dioxane, 4.50 mL, 2.25 mmol) was added. It was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo. The residue was dissolved in H_2O and CH_3CN (50:50). The insoluble was collected and dried on vacuum to give 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(3-fluoro-4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxamide as a solid (36 mg). MS 449.4 (M+H)

[0463] A solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (0.30 M in NMP, 1.00 mL, 0.300 mmol) in NMP (1 mL) was added to 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(3-fluoro-4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxamide (12 mg, 0.027 mmol). DIEA (0.050 mL, 0.29 mmol) was also added. The mixture was stirred at 90 C for 1h. After being cooled to room temperature, TFA (1 mL) was added. The solution was stirred at room temperature for 60 min. The mixture was purified by HPLC to give the titled compound (5 mg). MS 428.4 (M+H). UV λ=229.8, 313.8 nm.

Example 34. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-fluoro-4-(1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxamide



[0464] A mixture of 3,4-difluoronitrobenzene (1.00 mL, 9.03 mmol), imidazole (0.615 g, 9.04 mmol) and K2CO3 (2.50 g, 18.1 mmol) in DMF (10 mL) was stirred at room temperature overnight. Water (20 mL) was added to induce precipitation. The precipitate was collected, dried on vacuum to give 1-(2-fluoro-4-nitrophenyl)-1H-imidazole as a solid (1.81 g). MS 208.2 (M+H)

[0465] A mixture of 1-(2-fluoro-4-nitrophenyl)-1H-imidazole (1.81 g, 8.74 mmol) and Pd-C (10%, 0.200 g) in MeOH (20 mL) (containing 10 drops of 6N HCl) was hydrogenated under balloon H2 overnight. The mixture was filtered through celite. The filtrate was concentrated in vacuo. The residue was dried on vacuum to give 3-fluoro-4-(1H-imidazol-1-yl)benzenamine as a solid (1.37 g). MS 178.3 (M+H)

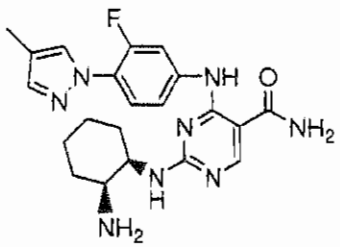
[0466] To a solution of ethyl 2,4-dichloropyrimidine-5-carboxylate (280 mg, 1.27 mmol) and 3-fluoro-4-(1H-imidazol-1-yl)benzenamine (230 mg, 1.30 mmol) in CH_3CN (8 mL) at room temperature, DIEA (0.442 mL, 2.54 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, dried over Na_2SO_4, concentrated in vacuo to give ethyl 2-chloro-4-(3-fluoro-4-(1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxylate as a solid (383 mg). MS 362.4 and 364.3 (M+H, Cl pattern)

[0467] To a solution of ethyl 2-chloro-4-(3-fluoro-4-(1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxylate (383 mg, 1.06 mmol) in THF (5 mL), aq. 1N LiOH (2.00 mL, 2.00 mmol) was added. The mixture was stirred at room temperature overnight. THF was removed in vacuo. Upon acidification with 1N HCl, the mixture was purified by HPLC to give 2-chloro-4-(3-fluoro-4-(1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxylic acid (68 mg). MS 334.1 and 336.1 (M+H, Cl pattern)

[0468] To a solution of 2-chloro-4-(3-fluoro-4-(1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxylic acid (68 mg, 0.20 mmol) and HOBt (63 mg, 0.41 mmol) in DMF (2 mL), EDC (60 mg, 0.31 mmol) was added. The mixture was stirred at room temperature for 1.5 h. Ammonia (0.5 M in dioxane, 0.800 mL, 0.40 mmol) was added. It was stirred at room temperature overnight. More EDC (100 mg, 0.52 mmol) was added. It was stirred for another 24 h. Water and EtOAc were added. The organic phase was separated, washed with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo to give 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(3-fluoro-4-(1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxamide (57 mg). MS 432.2 (M+H)

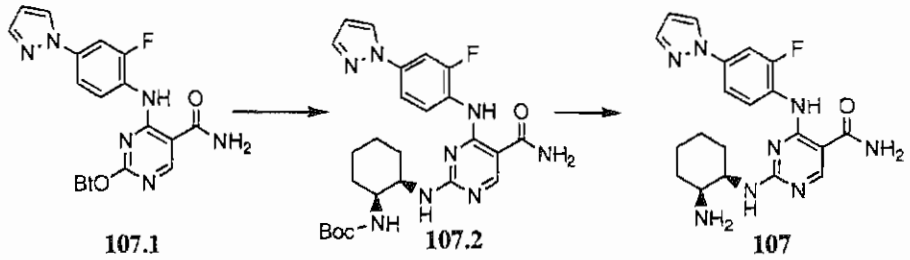
[0469] A solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (0.30 M in NMP, 1.00 mL, 0.300 mmol) in NMP (1 mL) was added to 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(3-fluoro-4-(1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxamide (57 mg, 0.13 mmol). DIEA (0.100 mL, 0.57 mmol) was also added. The mixture was stirred at 90 C for 1h. After being cooled to room temperature, water and EtOAc were added. The organic phase was separated, washed with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) and TFA (1 mL). The solution was stirred at room temperature for 60 min. It was concentrated in vacuo. The residue was purified by HPLC to give the titled compound (23 mg). MS 411.3 (M+H). UV λ=247.8, 299.8 nm..

Example 35. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-fluoro-4-(4-methyl-1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide



The titled compound was prepared analogously according to the procedure described in Example 34. MS 425.3 (M+H). UV λ=247.8, 311.8 nm.

Example 36. 2-((1R,2S)-2-aminocyclohexylamino)-4-(2-fluoro-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide

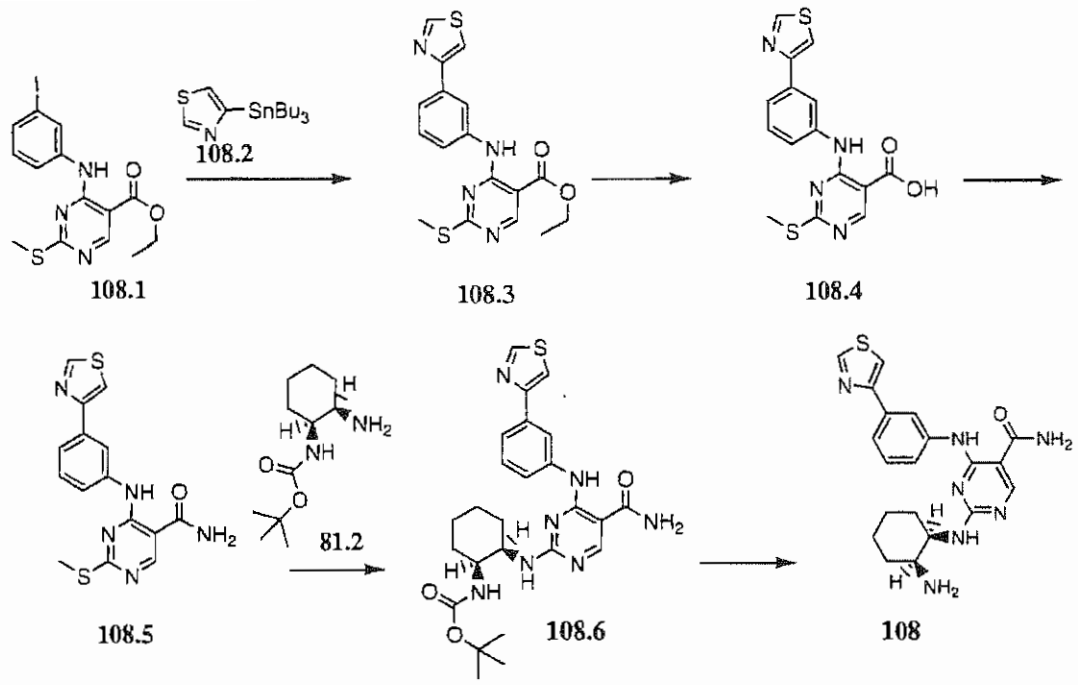


107.1 **107.2** **107**

[0470] Compound **107.1** was synthesized as demonstrated in Example 1 for **72.7** using 2-fluoro-4-(1H-pyrazol-1-yl)aniline to replace **72.4**.

To **107.1** (0.054 g, 0.125 mmol) was added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2** (0.3 M, 0.6 mL, 0.18 mmol) and DIEA (33 μL, 0.18 mmol). After stirred for 2 h at 65°C bath, the mixture was diluted with water, the resulting precipitates were collected by filtration to give **107.2**. To a mixture of **107.2** in DCM (0.5 mL) was added TFA (0.5 mL), after stirred at room temperature for 10 min, the solution was concentrated and the residue was purified by preparative HPLC to give title compound **107**. MS found for $C_{20}H_{23}FN_8O$ as $(M+H)^+$ 411.1. UV: λ = 201.6, 240.4, 289.0.

Example 37. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxamide



[0471] Step 1: To a mixture of Iodobenzene **108.1** (200 mg, 0.46 mmol) in toluene (2 mL) was added 5-tributylstannylthiazole **108.2** (173 mg, 0.46 mmol) and $Pd(PPh_3)_4$ (53 mg, 0.046 mmol). The mixture was degassed using argon stream for 3 minutes and refluxed under an argon atmosphere for 2 hour. It was concentrated in vacuo and subjected to silica flash column to isolate compound **108.3** (100 mg).

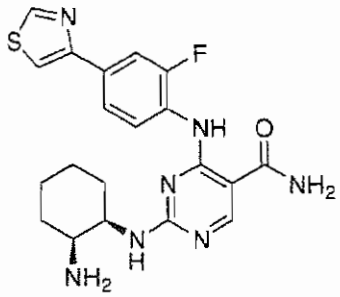
[0472] Step 2: To a mixture of Ethyl ester **108.3** (84 mg, 0.22 mmol) in THF (0.8 mL) was added a solution of lithium hydroxide hydrate (8 mg, 0.35 mmol) in water (0.5 mL). After stirred for 2 hours at RT, it was concentrated in vacuo to remove THF and carefully treated with 1N HCl till pH reaching 3. The resulting precipitates were collected by filtration to give compound **108.4** (74 mg).

[0473] Step 3: To a mixture of carboxylic acid **108.4** (74 mg) in DMF (1 mL) were added EDC hydrochloride (60 mg) and HOBt hydrate (48 mg). The mixture was stirred at RT for 1 hour. To it was then added ammonia (commercial 0.5N solution in dioxane, 1 mL). The mixture was stirred for 1 h at room temperature. It was then concentrated in vacuo to remove dioxane. To it was added water, the precipitates were collected by filtration to give compound **108.5**.

[0474] Step 4: Compound **108.5** (55 mg, 0.16 mmol) was dissolved in 0.3 mL NMP. To it was added MCPBA (65% pure, 47 mg, 0.18 mmol). It was stirred at RT for 30 minutes. To it were then added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **57.2** (0.3 M,

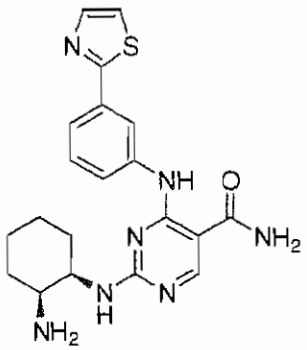
0.8 mL, 0.24 mmol) and DIEA (57 μL, 0.32 mmol). The mixture was stirred for 60 minutes at 80°C bath. This mixture was diluted with water, the resulting precipitates was collected by filtration to five **108.6**, which was stirred in a 1:1 mixture of TFA and dichloromethane at RT for 30 minutes. It was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound. MS found for $C_{20}H_{23}N_7OS$ as $(M+H)^+$ 410.2. UV: λ = 202.8, 245.2.

Example 38. 2-((1R,2S)-2-aminocyclohexylamino)-4-(2-fluoro-4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxamide



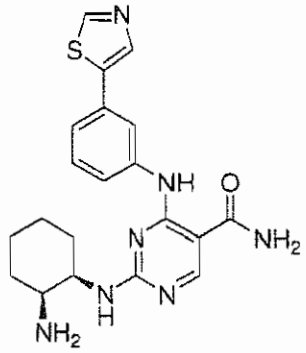
[0475] The title compound was synthesized as demonstrated in Example 14. MS found for $C_{20}H_{22}FN_7OS$ as $(M+H)^+$ 428.5. UV: λ = 240.4, 312.8

Example 39. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(thiazol-2-yl)phenylamino)pyrimidine-5-carboxamide



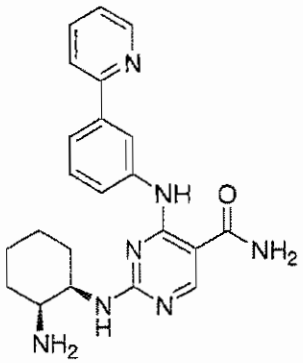
[0476] The title compound was synthesized as demonstrated in Example 37 using 2-tributylstannylthiazole to replace 5-tributylstannylthiazole **108.2**. MS found for $C_{20}H_{23}N_7OS$ as $(M+H)^+$ 410.2 UV: λ = 206.3, 242.8, 291.4

Example 40. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(thiazol-5-yl)phenylamino)pyrimidine-5-carboxamide



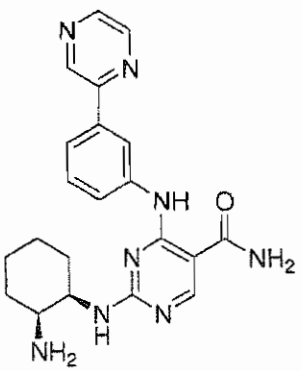
[0477] · The title compound **111** was synthesized as demonstrated in Example 37 using 4-tributylstannylthiazole to replace 5-tributylstannylthiazole **108.2**. MS found for $C_{20}H_{23}N_7OS$ as $(M+H)^+$ 410.5 UV: λ = 201.6, 244.0, 277.1

Example 41. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyridin-2-yl)phenylamino)pyrimidine-5-carboxamide



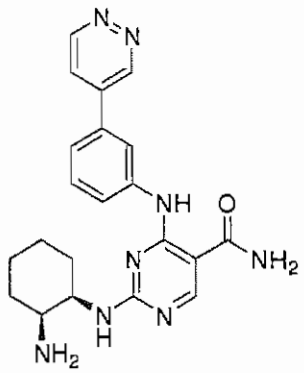
[0478] The title compound was synthesized as demonstrated in Example 37 using 2-tributylstannylpyridine to replace 5-tributylstannylthiazole **108.2**. MS found for $C_{22}H_{25}N_7O$ as $(M+H)^+$ 404.2; UV: λ = 242.8, 292.6

Example 42. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyrazin-2-yl)phenylamino)pyrimidine-5-carboxamide



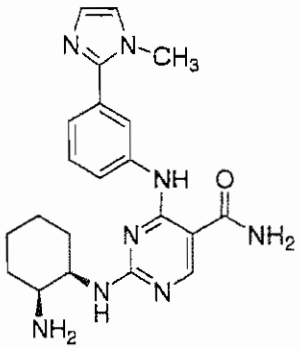
[0479] The title compound was synthesized as demonstrated in Example 37 using 2-tributylstannylpyrazine to replace 5-tributylstannylthiazole **108.2**. MS found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.3 UV: λ = 244.0, 289.0

Example 43. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyridazin-4-yl)phenylamino)pyrimidine-5-carboxamide



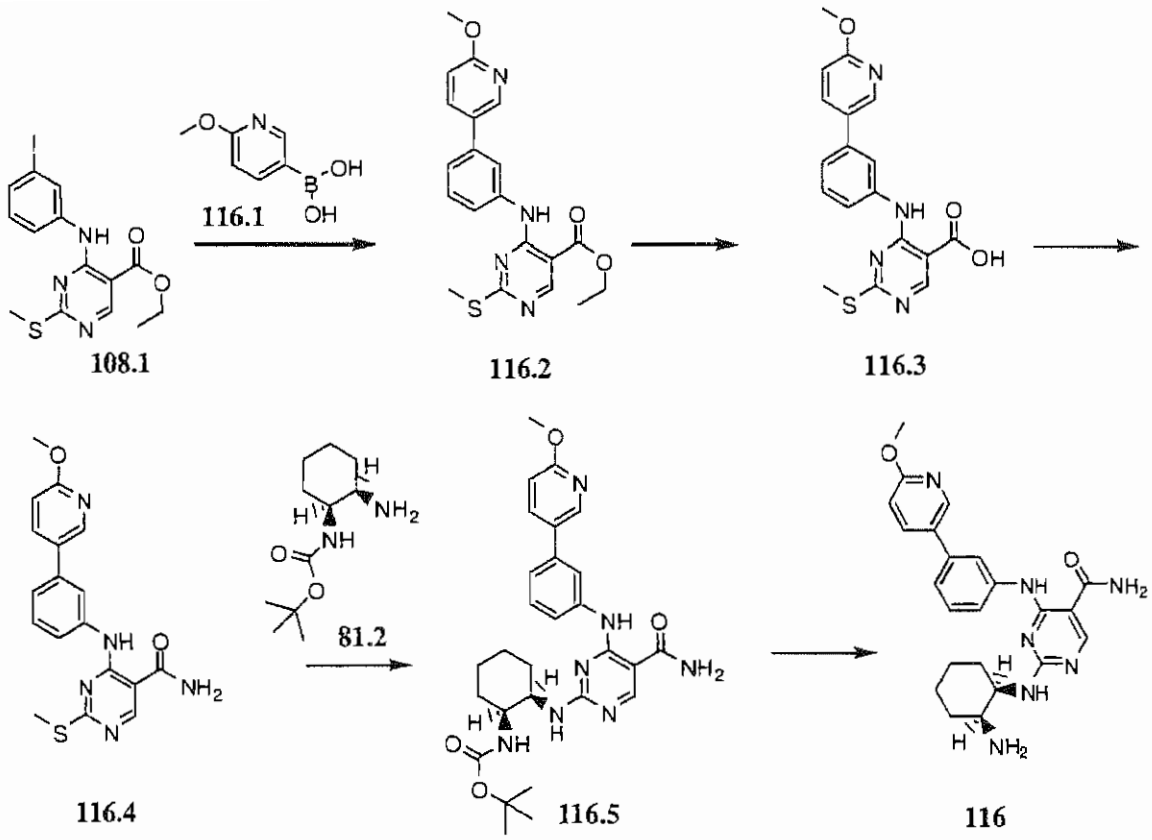
[0480] The title compound was synthesized as demonstrated in Example 37 using 4-tributylstannylpyridazine to replace 5-tributylstannylthiazole **108.2**. MS found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.2 UV: λ = 246.3

Example 44. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(1-methyl-1H-imidazol-2-yl)phenylamino)pyrimidine-5-carboxamide



[0481] The title compound was synthesized as demonstrated in Example 37 using 1-methyl-2-tributylstannyl-1H-imidazole to replace 5-tributylstannylthiazole **108.2**. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 407.2. UV: λ = 242.8

Example 45. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(6-methoxypyridin-3-yl)phenylamino)pyrimidine-5-carboxamide



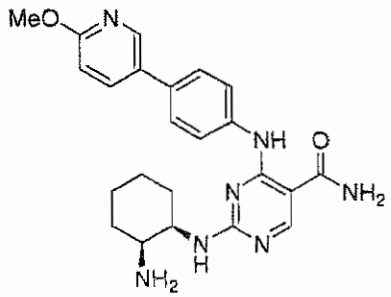
[0482] Step 1: To a mixture of Iodobenzene **108.1** (300 mg, 0.72 mmol) in p-dioxane (5 mL) were added 6-methoxypridin-3-ylboronic acid **116.1** (121 mg, 0.80 mmol) and 1M Na_2CO_3 (21. mL) followed by $PdCl2(PPh_3)_2$ (51 mg, 0.07 mmol). The mixture was degassed using argon stream for 3 minutes and heated at 85 °C under an argon atmosphere for 2 hour. It was dilted with DCM, the organic layer was washed with Sat. $NaHCO_3$, brine, dried and concentrated to give crude residue, which was purified by column chromatography to give **116.2** (160 mg).

[0483] Step 2: To a mixture of Ethyl ester **116.2** (160 mg) in THF (1.6 mL) was added a solution of lithium hydroxide hydrate (20 mg) in water (1 mL). After stirred for 24 hours at RT, it was concentrated in vacuo to remove THF and carefully treated with 1N HCl till pH reaching 3. The resulting precipitates were collected by filtration to give compound **116.3**.

[0484] Step 3: To a mixture of carboxylic acid **116.3** in DMF (1.8 mL) were added EDC hydrochloride (193 mg) and HOBt hydrate (153 mg). The mixture was stirred at RT for 10 min. To it was then added ammonia (commercial 0.5N solution in dioxane, 2 mL). The mixture was stirred for 1 h at room temperature. It was then concentrated in vacuo to remove dioxane. To it was added water, the precipitates were collected by filtration to give compound **116.4**.

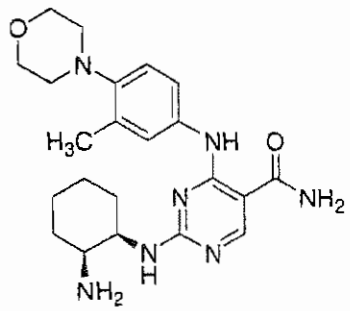
[0485] Step 4: Compound **116.4** (80 mg, 0.22 mmol) was dissolved in 0.5 mL NMP. To it was added MCPBA (65% pure, 64 mg, 0.24 mmol). It was stirred at RT for 30 minutes. To it were then added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2** (0.3 M, 1.2 mL, 0.3 mmol) and DIEA (78 μL, 0.44 mmol). The mixture was stirred for 60 minutes at 85°C bath. This mixture was diluted with water, the resulting precipitates was collected by filtration to give **116.5**, which was stirred in a 1:1 mixture of TFA and dichloromethane at RT for 30 minutes. It was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound. MS found for $C_{23}H_{27}N_7O_2$ as $(M+H)^+$ 434.3 UV: λ = 247.5

Example 46. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(6-methoxypyridin-3-yl)phenylamino)pyrimidine-5-carboxamide



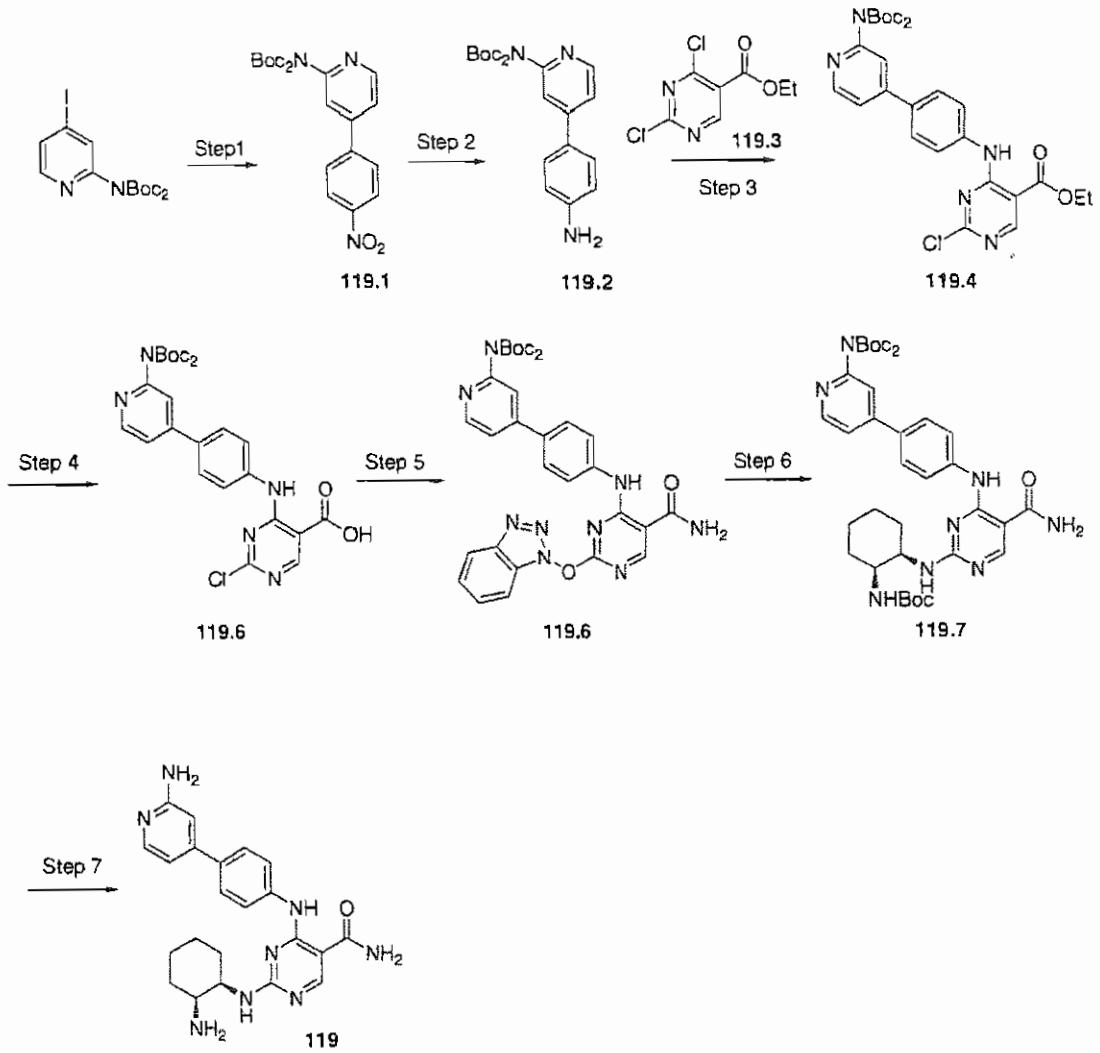
[0486] The title compound was synthesized as demonstrated in Example 45 using ethyl-4-(4-iodophenylamino)-2-(methylthio)pyrimidine-5-carboxylate to replace **108.1**. MS found for $C_{23}H_{27}N_7O_2$ as $(M+H)^+$ 434.3. **UV: λ** = 240.4, 306.8

Example 47. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-methyl-4-morpholinophenylamino)pyrimidine-5-carboxamide



[0487] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 and Example 9 with 3-methyl-4-morpholinoaniline to replace aniline **72.4**. MS found for $C_{22}H_{31}N_7O_2$ as $(M+H)^+$ 426.3. UV: λ = 240.4, 296.1

Example 48 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(2-aminopyridin-4-yl)phenylamino)pyrimidine-5-carboxamide



[0488] Step 1: A mixture of 4-Nitro-phenyl-Boronic acid (159 mgs, 0.95 mmol), N,N-Bis(*tert*-butyloxycarbonyl)amino-4-Iodo pyridine (US6831175) (200 mgs, 0.47 mmol), potassium carbonate (329 mgs, 2.38 mmol), Tetrakis(triphenylphosphine)-palladium(0) (220 mgs, 0.19 mmol), DME (5 mL), water (0.6 mL) was heated in microwave (Emry's Optimizer) at 120°C for 15 min. The reaction was repeated four more times. The combined reactions were poured into ethyl acetate and washed with water (2x), brine (1x) and concentrated. The concentrate was then purified by flash column chromatography on silica gel (3:7 Ethyl acetate/Hexanes) to provide N,N-Bis(*tert*-butyloxycarbonyl)amino-(4-nitrophenyl)pyridine **119.1**. MS found for $C_{21}H_{25}N_3O_6$ as $(M+H)^+$ 416.0.

[0489] Step 2: Compound **119.1** (955 mgs, 2.3 mmol) was dissolved in ethanol (40 mL) with few drops of acetic acid and hydrogenated at 1 atmosphere of hydrogen in the presence

of 10% Pd/C (wet) for 5h. The reaction was filtered, concentrated to give **119.2** (782 mgs, 88%) as dark brown solid. MS found for $C_{21}H_{27}N_3O_4$ as $(M+H)^+$ 386.0.

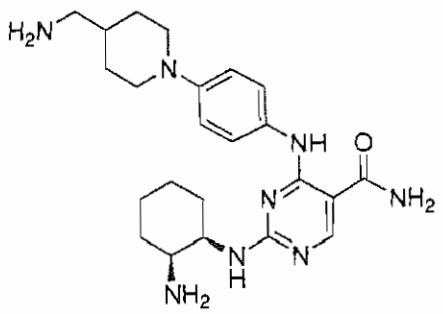
[0490] Step 3: To a solution of Dichloropyrimidine **119.3** (180 mgs, 0.816 mmol) in acetonitrile (3 mL) was added a suspension of **119.2** (314 mgs, 0.816 mmol), diisopropylamine (0.16 mL, 0.897 mmol) in acetonitrile (8 mL) at 0 °C. Reaction mixture was then slowly warmed to rt and stirred overnight. The reaction mixture was then diluted with water and extracted with ethylacetate (2x). The combined ethyl acetate layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield **119.4**. MS found for $C_{28}H_{32}ClN_5O_6$ as $(M+H)^+$ 570.0.

[0491] Step 4: Crude ethyl ester **119.4** (460 mgs, 0.81 mmol) was diluted with 1,4-dioxane (5 mL) followed by aqueous lithium hydroxide (1.0 M, 0.8 mL, 0.8 mmol) and stirred at rt until all starting material had been converted to the carboxylic acid. The reaction was then diluted with water (30 mL) and acidified with 1N HCl (1.0 mL). The resulting suspension was then filtered, washed with water and dried giving 385 mgs of the carboxylic acid **119.5** (88%). MS found for $C_{26}H_{28}ClN_5O_6$ as $(M+H)^+$ 542.0.

[0492] Step 5: To carboxylic acid **119.5** (385 mgs, 0.71 mmol), EDC (204 mgs, 1.06 mmol), HOBt (163 mgs, 1.06 mmol) in N,N-dimethylformamide (3.6 mL) was added ammonia (0.5 M in 1,4-dioxane, 3.6 mL, 1.8 mmol) and stirred overnight. The reaction mixture was then diluted with water and the precipitate collected by filtration affording the desired product **119.6** (394 mgs, 87%). MS found for $C_{32}H_{33}N_9O_6$ as $(M+H\text{-}Boc)^+$ 540.0.

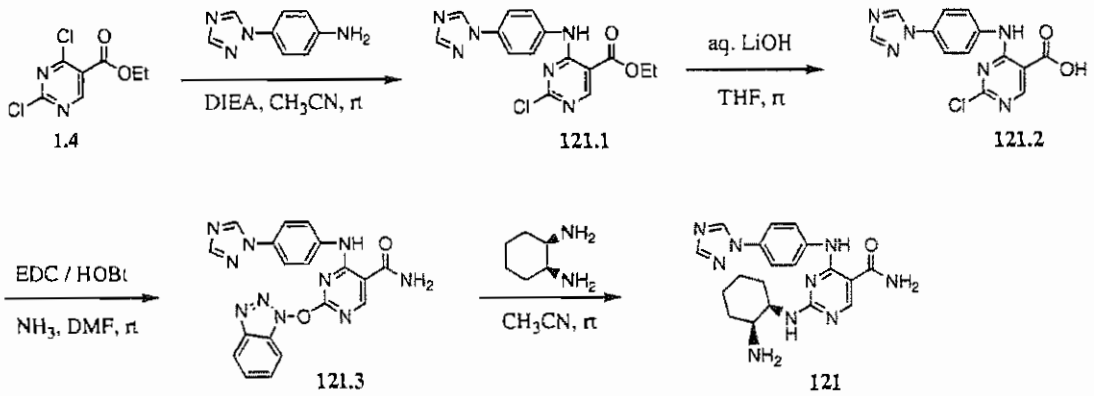
[0493] Step 6 and Step 7: A mixture of Benzotriazolyl ether **119.6** (90 mgs, 0.140 mmol), *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (36 mgs, 0.170 mmol), DIPEA (0.07 mL, 0.420 mmol) in iso-propanol (2 mL) was heated in microwave (Emry's Optimizer) at 130°C for 20 min. The reaction mixture was concentrated and then was treated with 4.0M HCl in dioxane (6.0 mL). After 1h at rt, concentrate the reaction mixture and diluted with water and acetonitrile and directly purified by preparative HPLC affording the desired product **119** (43.6 mgs, 75%) as tan solid, after lyophilization. MS found for $C_{22}H_{26}F_2N_8O$ as $(M+H)^+$ 419.5.

Example 49. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(4-(aminomethyl)piperidin-1-yl)phenylamino)pyrimidine-5-carboxamide



[0494] The above compound was prepared using *tert*-butyl (1-(4-aminophenyl)piperidin-4-yl)methylcarbamate (prepared from 4-Fluoronitrobenzene) using a procedure similar to that described in Example 48. MS found for $C_{23}H_{34}N_8O$ as $(M+H)^+$ 439.6.

Example 50. 4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexyl-amino)pyrimidine-5-carboxamide



1.4 121.1 121.2 121.3 121

Ethyl 4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-chloropyrimidine-5-carboxylate **121.1**:

[0495] To a solution of ethyl 2, 4-dichloropyrimidine-5-carboxylate (1.4) (600 mg, 2.714 mmol), in CH_3CN (12 mL), was added DIEA (0.750 mL, 4.313 mmol, 1.589 equiv), followed by 4-(1H-1, 2, 4-triazol-1-yl)aniline (465 mg, 2.902 mmol, 1.07 equiv). The mixture was stirred at room temperature for 20 h, then diluted with water (6 x) to precipitate ii. The solid product was collected by filtration, rinsed with water (100 mL), and air dried; Yield, 850 mg (91 %).

4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-chloropyrimidine-5-carboxylic acid **121.2**:

[0496] To a solution of Ethyl 4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-chloropyrimidine-5-carboxylate (ii) (870 mg, 2.523 mmol), in THF (12 mL), was added 1M LiOH (3.30 mL, 3.30 mmol, 1.30 equiv), and the mixture was stirred at room temperature for 3h. Then THF was rotavopped off, and the aqueous mixture was acidified with 2N HCl to pH

2. The precipitated solid product was collected by filtration, rinsed with water, and air dried; yield 712 mg (89 %).

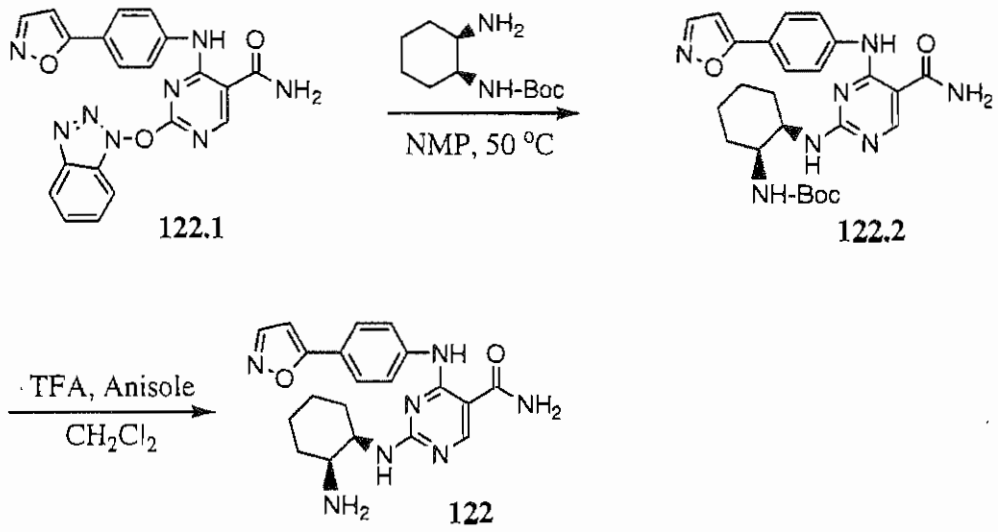
4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-(1H-benzo[d][1,2,3]triazol-1-yloxy) pyrimidine-5-carboxamide **121.3**:

[0497] To a solution of 4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-chloropyrimidine-5-carboxylic acid (iii) (730 mg, 2.305 mmol) in DMF (15 mL), at room temperature, was added HOBt (470 mg, 3.478 mmol, 1.508 equiv), and EDC.HCl (690 mg, 3.599 mmol, 1.561 equiv), and the mixture was stirred for 45 minutes. Then cooled it to 0 °C, and treated with 0.5 M NH3 in dioxane (14.0 ml, 7.0 mmol, 3.0 equiv), and stirred the mixture at room temperature for 18 h. Then diluted it with water (7 x) to precipitate iv. Collected it by filtration, rinsed with water, and air dried; yield 841 mg (88 %). MS: 415.1 (M+H), and 437.1 (M+Na).

4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)- pyrimidine-5-carboxamide **121**:

[0498] To a solution of cis-cyclohexane-1, 2-diamine (100 mg, 0.876 mmol, 6.08 equiv), in CH_3CN (1. 50 mL), was added 4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-(1H-benzo[d][1,2,3]triazol-1-yloxy)pyrimidine-5-carboxamide (iv) (60 mg, 0.144 mmol), and the mixture was stirred for 19h. Then it was diluted with water (8 x), and the solid product was collected by filtration, rinsed with water, and air dried. It was purified by RP HPLC to afford it as its TFA salt; yield 59 mg (81 %). MS: 394.1 (M+H), and 416.1 (M+Na).

Example 51. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(isoxazol-5-yl)phenylamino)pyrimidine-5-carboxamide:



[0499] 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(4-(isoxazol-5-yl)phenylamino)pyrimidine-5-carboxamide **122.1**: This compound was prepared using the procedure deasribed for the synthesis of **121.3** starting from ethyl 2, 4-dichloropyrimidine-5-carboxylate (1.4) and 4-(isoxazol-5-yl)aniline.

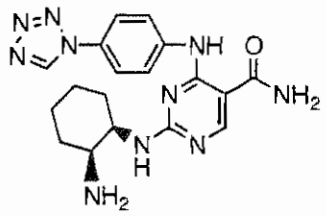
tert-butyl (1S,2R)-2-(5-carbamoyl-4-(4-(isoxazol-5-yl)phenylamino)pyrimidin-2-ylamino)cyclohexylcarbamate **122.2**:

[0500] The compound 210.1 (100 mg, 0.241 mmol), in N-methyl pyrrolidinone (NMP) was mixed with tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (0.3 mmol, 1.244 equiv), and DIEA (0.120 mL, 0.690 mmol, 2.83 equiv), and heated to 50 °C for 4 h. Then it was partitioned between EtOAc and water.The combined EtOAc extract was dried over anhydrous Na_2SO_4 and concentrated to yield 210.2, which was used as such for the next reaction.

2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(isoxazol-5-yl)phenylamino)pyrimidine-5-carboxamide **122**:

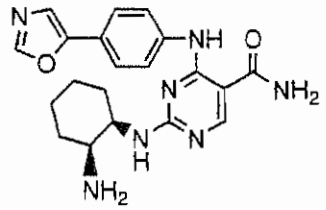
[0501] The crude **122.2** was diluted with CH_2Cl_2 (5 mL) and anilsole (0.700 mL, excess) was added, followed by CF_3COOH (5 mL). The mixture was stirred at room temperature for 5 h, and then concentrated to dryness. It was purified by RP-HPLC to yield pure 210 as colorless puffs, 101 mg (83 %). MS: 394.3 (M + H).

Example 52. 4-(4-(1H-tetrazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide:



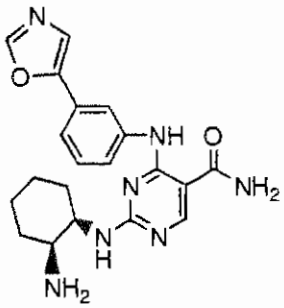
[0502] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(1H-tetrazol-1-yl)aniline in step 1. MS: 395.28 (M + H).

Example 53. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(oxazol-5-yl)phenylamino) pyrimidine-5-carboxamide:



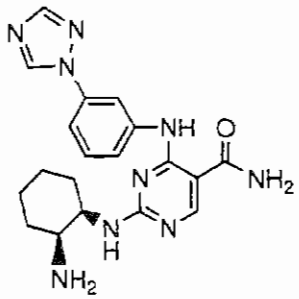
[0503] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(oxazol-5-yl)aniline in step 1.

Example 54. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(oxazol-4-yl)phenylamino) pyrimidine-5-carboxamide:



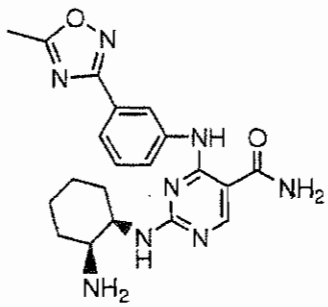
[0504] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(oxazol-4-yl)aniline in step 1. MS: 394.28 (M + H).

Example 55. 4-(3-(1H-1,2,4-triazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino) pyrimidine 5-carboxamide:



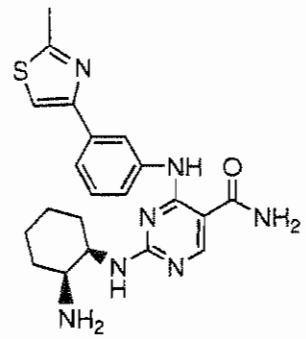
[0505] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(1H-1,2,4-triazol-1-yl)aniline in step 1.MS: 394.2 (M + H).

Example 56. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(5-methyl-1,2,4-oxadiazol-3-yl)phenylamino)pyrimidine-5-carboxamide:



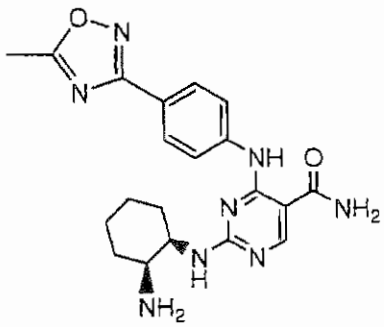
[0506] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(5-methyl-1,2,4-oxadiazol-3-yl)aniline in step 1. MS: 409.28 (M + H).

Example 57. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2-methylthiazol-4-yl)phenylamino) pyrimidine-5-carboxamide:



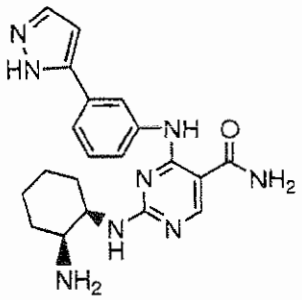
[0507] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(2-methylthiazol-4-yl)aniline in step 1. MS: 424.37 (M + H).

Example 58. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenylamino) pyrimidine-5-carboxamide:



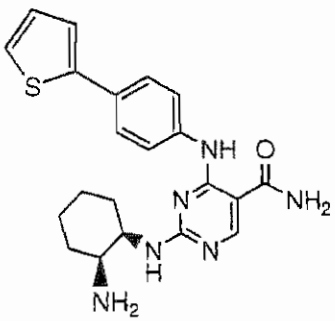
This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(5-methyl-1,2,4-oxadiazol-3-yl)aniline in step 1. MS: 409.5 (M + H).

Example 59. 4-(3-(1H-pyrazol-5-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexyl amino) pyrimidine-5-carboxamide:



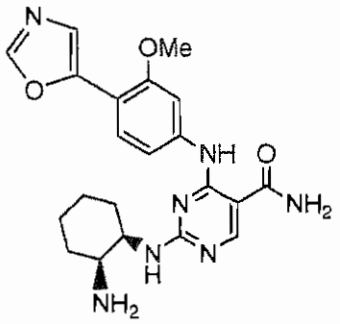
[0508] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(1H-pyrazol-5-yl)aniline in step 1. MS: 393.0 (M + H).

Example 60. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(thiophen-2-yl)phenylamino) pyrimidine-5-carboxamide:



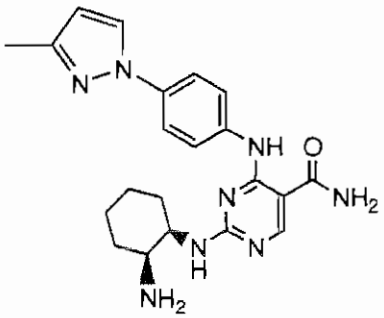
[0509] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(thiophen-2-yl)aniline in step 1. MS: 410.0 (M+ H).

Example 61. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-methoxy-4-(oxazol-5-yl)phenylamino) pyrimidine-5-carboxamide:



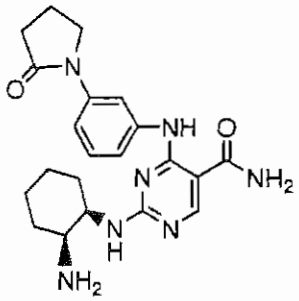
[0510] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-methoxy-4-(oxazol-5-yl)aniline in step 1. MS: 424.5 (M + H).

Example 62. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(3-methyl-1H-pyrazol-1-yl)phenylamino) pyrimidine-5-carboxamide:



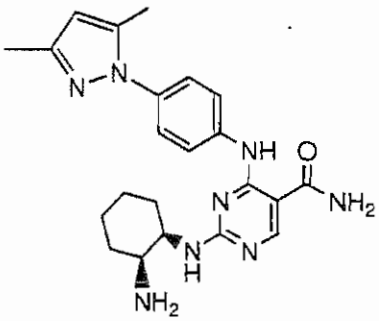
[0511] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(3-methyl-1H-pyrazol-1-yl)aniline in step 1. MS: 407.5 (M + H).

Example 63. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2-oxopyrrolidin-1-yl)phenylamino) pyrimidine-5-carboxamide:



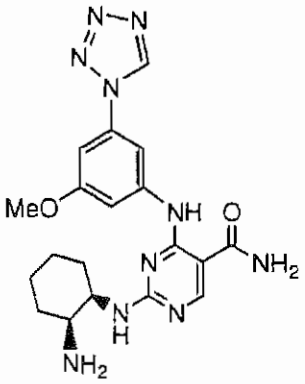
[0512] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 1-(3-aminophenyl)pyrrolidin-2-one in step 1. MS: 410.5 (M + H).

Example 64. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(3,5-dimethyl-1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide:



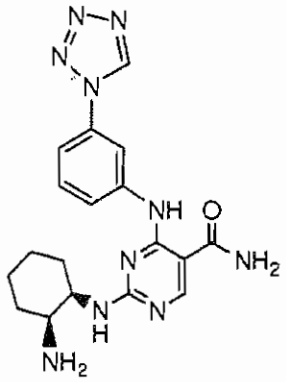
[0513] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(3,5-dimethyl-1H-pyrazol-1-yl)aniline in step 1. MS: 421.5 (M + H).

Example 65. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-methoxy-5-(1H-tetrazol-1-yl)phenylamino)pyrimidine-5-carboxamide:



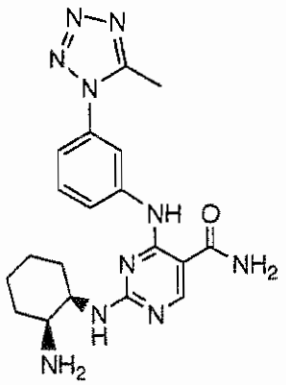
[0514] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-methoxy-5-(1H-tetrazol-1-yl)aniline in step 1. MS: 425.4 (M + H).

Example 66. 4-(3-(1H-tetrazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexyl amino)pyrimidine-5-carboxamide:



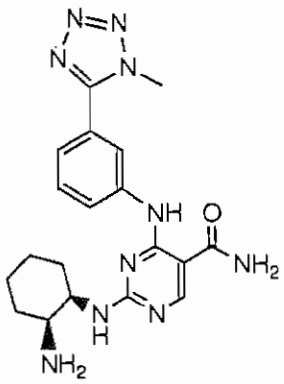
[0515] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(1H-tetrazol-1-yl)aniline in step 1. MS: 395.5 (M + H).

Example 67. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(5-methyl-1H-tetrazol-1-yl)phenylamino) pyrimidine-5-carboxamide:



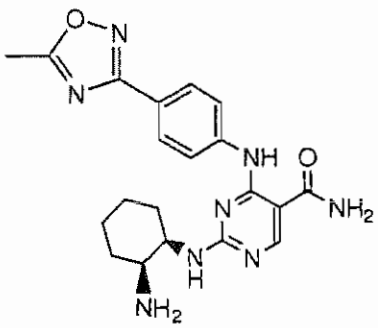
[0516] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(5-methyl-1H-tetrazol-1-yl)aniline in step 1. MS: 409.5 (M + H).

Example 68. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(1-methyl-1H-tetrazol-5-yl) phenylamino) pyrimidine-5-carboxamide:



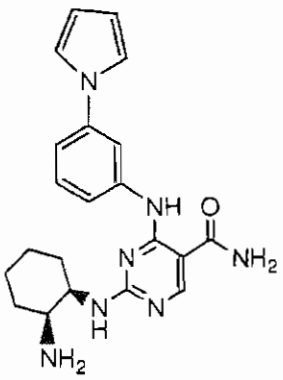
[0517] This compound was synthesised using the synthetic scheme described for the synthesis of compound 122, and using 3-(1-methyl-1H-tetrazol-5-yl)aniline in step 1. MS: 409.5 (M + H).

Example 69. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenylamino) pyrimidine-5-carboxamide:



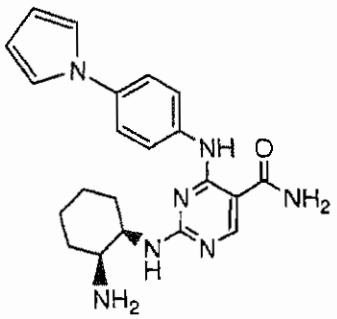
[0518] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(5-methyl-1,2,4-oxadiazol-3-yl)aniline in step 1. MS: 409.5 (M + H).

Example 70. 4-(3-(1H-pyrrol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino) pyrimidine-5-carboxamide:



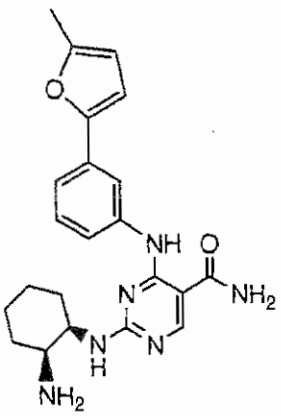
[0519] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(1H-pyrrol-1-yl)aniline in step 1. MS: 392.5 (M + H).

Example 71. 4-(4-(1H-pyrrol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino) pyrimidine-5-carboxamide:



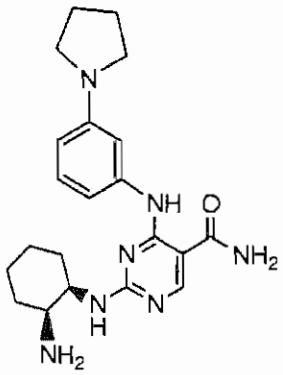
[0520] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(1H-pyrrol-1-yl)aniline in step 1. MS: 392.4 (M + H).

Example 72. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(5-methylfuran-2-yl)phenylamino) pyrimidine-5-carboxamide:



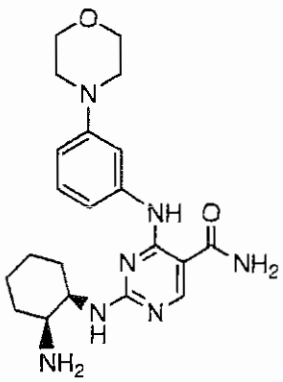
[0521] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(5-methylfuran-2-yl)aniline in step 1. MS: 407.5 (M + H).

Example 73. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyrrolidin-1-yl)phenylamino) pyrimidine-5-carboxamide:



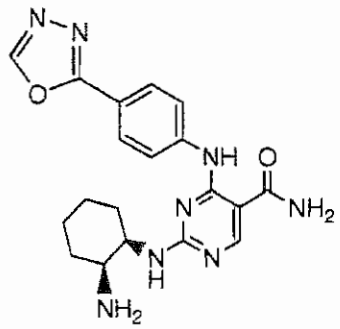
[0522] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-(pyrrolidin-1-yl)aniline in step 1. MS: 396.6 (M + H).

Example 74. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-morpholinophenylamino) pyrimidine-5-carboxamide:



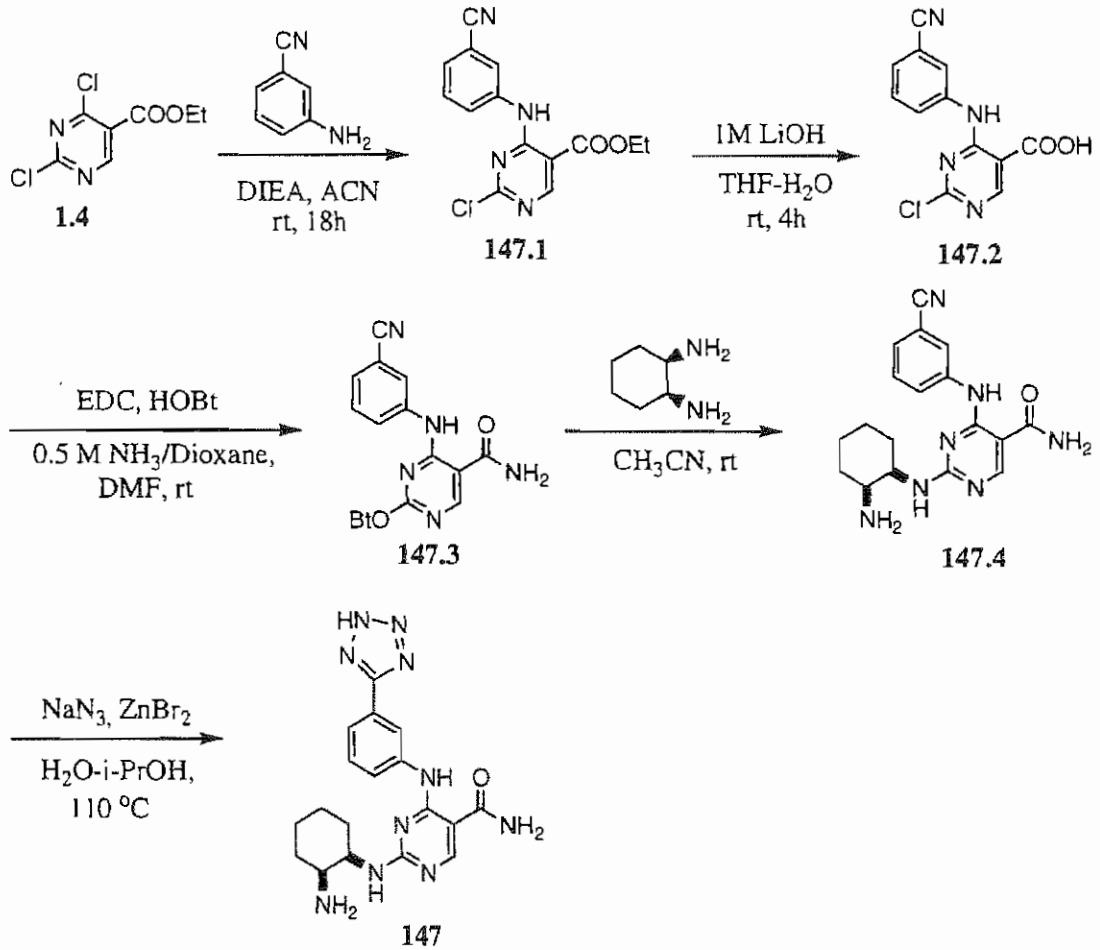
This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 3-morpholinoaniline in step 1. MS: 412.5 (M + H).

Example 75. 4-(4-(1,3,4-oxadiazol-2-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexyl amino)pyrimidine-5-carboxamide:



[0523] This compound was synthesised using the synthetic scheme described for the synthesis of compound **122**, and using 4-(1,3,4-oxadiazol-2-yl)aniline in step 1. MS: 395.3 (M + H).

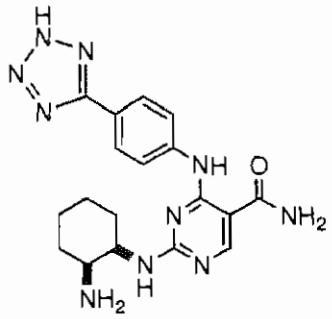
Example 76. 4-(3-(2H-tetrazol-5-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexyl amino) pyrimidine-5-carboxamide:



[0524] Compound **147.4**: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-cyanophenylamino) pyrimidine-5-carboxamide was synthesized using the procedure described for the synthesis of Example 77. MS: 352.2 (M + H).

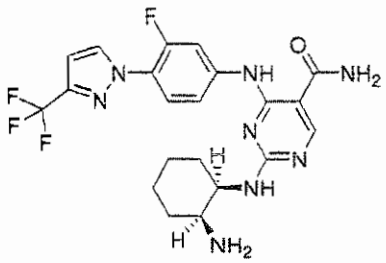
[0525] Compound **147**: 4-(3-(2H-tetrazol-5-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide was synthesized by reacting compound **147.4** (75 mg, 0.213 mmol), sodium azide (90 mg, 1.384 mmol, 6.5 equiv), and zinc bromide (53 mg, 0.235 mmol) in isopropanol/water (1:1) (4 mL) heated to reflux for 14 hrs, when an HPLC analysis showed a complete reaction. Then cooled the reaction mixture to 0 °C, and acidified with 3N HCl to pH 1, filtered through celite, concentrated the filtrate to dryness to yield the title compound, 179, purified it by RP-HPLC. MS: 395.1 (M + H), 417.2 (M + Na).

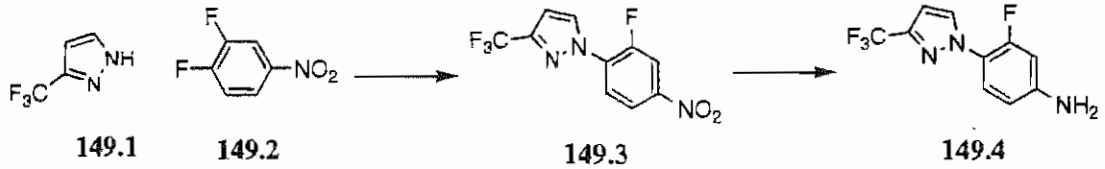
[0526] Example 78. 4-(4-(2H-tetrazol-5-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexyl amino)pyrimidine-5-carboxamide:



[0527] This compound was synthesised using the synthetic scheme described for the synthesis of Example 5, and using 4-cyanoaniline in step 1. MS: 395.1 (M + H), 417.2 (M + Na).

[0528] Example 79. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-fluoro-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide





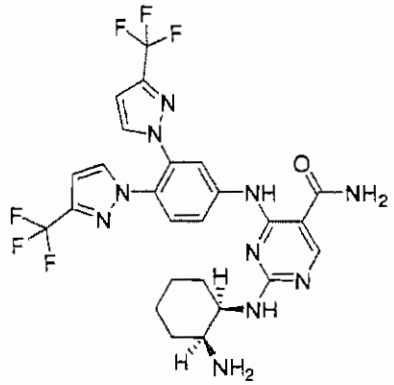
149.1 **149.2** **149.3** **149.4**

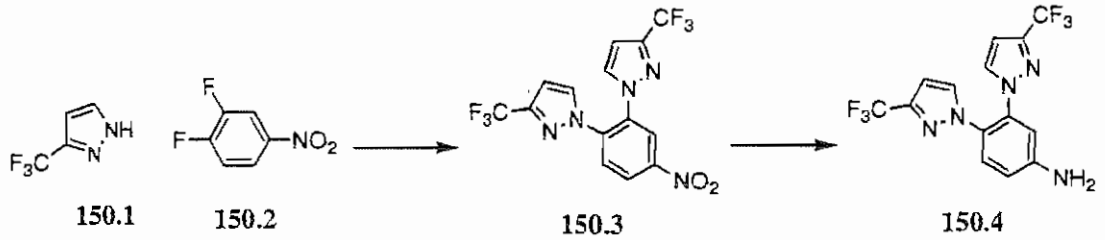
[0529] The mixture of trifluoromethylpyrazole **149.1** (1.00 g, 7.35 mmol), 3,4-difluoro-1-nitrobenzene **149.2** (0.68 mL, 6.13 mmoL) and cesium carbonate (3.00 g, 9.2 mmol) in 20 mL dry DMF was stirred in 50°C bath for 4 hours. It was diluted with 300 mL ethyl acetate and washed with water 4 times. The organic phase was dried over $MgSO_4$ and filtered to yield a solution of crude product **149.3**. To this solution was added catalytic amount of 10% Pd/C. To this stirred suspention was amounted a hydrogen balloon for overnight. The mixture was filtered and concentrated in vacuo to afford crude aniline **149.4**. MS found for $C_{10}H_7F_4N_3$ as $(M+H)^+$ 246.3. It was purified using flash column.

[0530] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with aniline **149.4** to replace aniline **74.1**. MS found for $C_{21}H_{22}F_4N_8O$ as $(M+H)^+$

479.3. UV λ=243, 302 nm. NMR (CD_3OD): δ 8.47 (s, 1H), 8.07 (broad s, 1H), 7.84 (m, 1H), 7.72 (m, 1H), 7.39 (m, 1H), 6.74 (d, J=2.0 Hz, 1H), 4.33 (m, 1H), 3.66 (m, 1H), 1.83-1.49 (m, 8H) ppm.

Example 80. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3,4-bis(3-(trifluoromethyl)-1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide



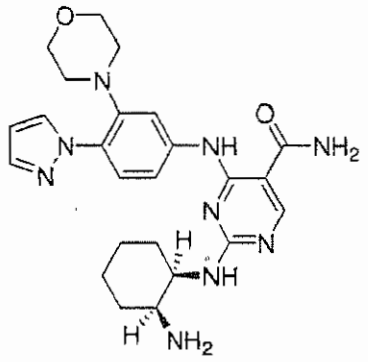


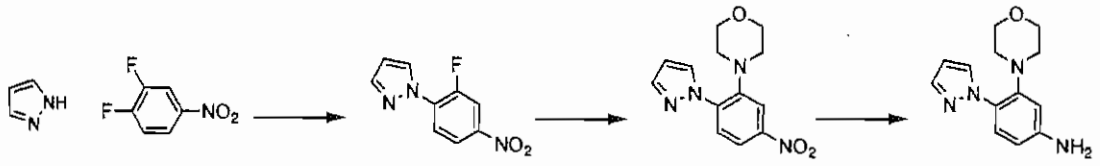
150.1 150.2 150.3 150.4

[0531] The mixture of trifluoromethylpyrazole **150.1** (2.00 g, 14.7 mmol), 3,4-difluoro-1-nitrobenzene **150.2** (1.17 g, 7.3 mmoL) and cesium carbonate (5.5 g, 17 mmol) in 30 mL dry DMF was stirred in 50°C bath for overnight. It was diluted with 300 mL ethyl acetate and washed with water four times. The organic phase was dried over $MgSO_4$ and filtered to yield a solution of crude product **150.3**. To this solution was added catalytic amount of 10% Pd/C. To this stirred suspention was amounted a hydrogen balloon for overnight. The mixture was filtered and concentrated in vacuo to afford crude aniline **150.4**. MS found for $C_{14}H_9F_6N_5$ as $(M+H)^+$ 362.2. It was purified using flash column.

[0532] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 with aniline **150.4** to replace aniline**74.1**. MS found for $C_{25}H_{24}F_6N_{10}O$ as $(M+H)^+$ 595.3. UV λ=246, 301 nm. NMR (CD_3OD): δ 8.61 (s, 1H), 8.45 (broad s, 1H), 7.78-7.65 (m, 4H), 6.75 (d, J=2.0 Hz, 1H), 6.72 (d, J=2.4 Hz, 1H), 4.41 (m, 1H), 3.59 (m, 1H), 1.86-1.48 (m, 8H) ppm.

[0533] Example 81. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-morpholino-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide



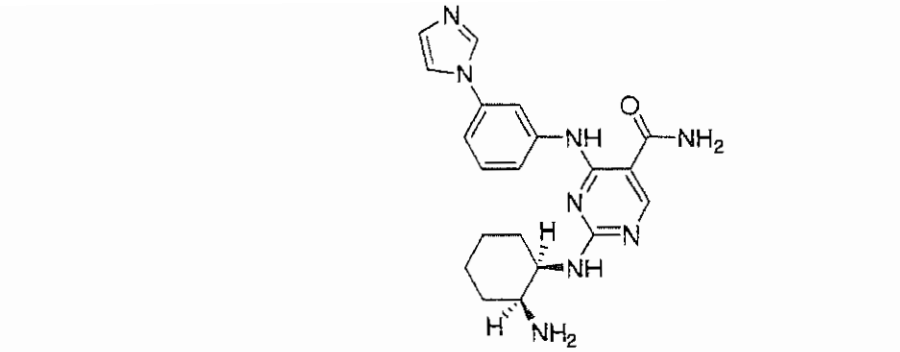


151.1 151.2 151.3 151.4 151.5

[0534] The mixture of pyrazole **151.1** (0.50 g, 7.4 mmol), 3,4-difluoro-1-nitrobenzene **151.2** (0.68 mL, 6.1 mmoL) and cesium carbonate (3.0 g, 9.2 mmol) in 15 mL dry NMP was stirred in a sealed tube in 80°C bath for 3 hours to give compound **151.3**. To the reaction sealed tube was then added morpholine (1.6 mL, 18.4 mmol). The mixture was stirred in 120°C bath for over 24 hours. It was diluted with 300 mL ethyl acetate and washed with water four times. The organic phase was dried over $MgSO_4$ and filtered to yield a solution of crude product **151.4**. To this solution was added catalytic amount of 10% Pd/C. To this stirred suspention was amounted a hydrogen balloon for overnight. The mixture was filtered and concentrated in vacuo to afford crude aniline **151.5**. MS found for $C_{13}H_{16}N_4O$ as $(M+H)^+$ 245.2. It was purified using flash column.

[0535] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with aniline **151.5** to replace aniline **74.1**. MS found for $C_{24}H_{31}N_9O_2$ as $(M+H)^+$ 478.3. UV λ=247 nm.

[0536] Example 82. 4-(3-(1H-imidazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide

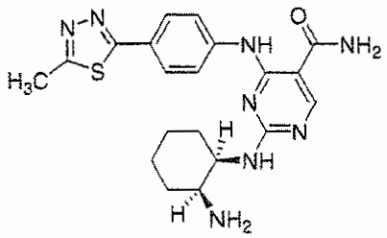


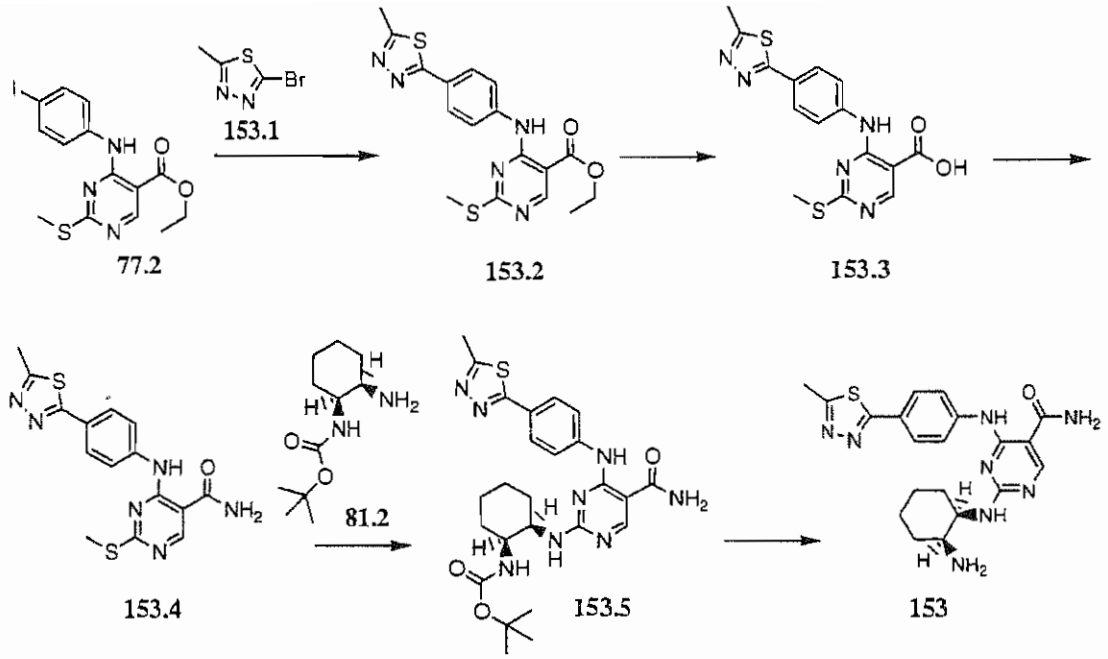
152.1 152.2 152.3 152.4

[0537] The mixture of imidazole **152.1** (0.64 g, 9.4 mmol), 3-fluoro-1-nitrobenzene **152.2** (0.50 mL, 4.7 mmoL) and cesium carbonate (3.1 g, 9.4 mmol) in 15 mL dry NMP was stirred in a sealed tube in 120°C bath for 3 hours. It was diluted with 300 mL ethyl acetate and washed with water four times. The organic phase was dried over $MgSO_4$ and filtered to yield a solution of crude product **152.3**. To this solution was added catalytic amount of 10% Pd/C. To this stirred suspention was amounted a hydrogen balloon for overnight. The mixture was filtered and concentrated in vacuo to afford crude aniline **152.4**. MS found for $C_9H_9N_3$ as $(M+H)^+$ 160.1.

[0538] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 with aniline **152.4** to replace aniline **74.1**. MS found for $C_{24}H_{31}N_9O_2$ as $(M+H)^+$ 478.3. UV λ=241 nm.

[0539] Example 83. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)phenylamino)pyrimidine-5-carboxamide





[0540] Step 1: Iodobenzene **77.2** (500 mg, 1.2 mmol) was dissolved in 12 mL dioxane in a sealed tube. To it were added bromothiadiazole **153.1** (240 mg, 1.3 mmol), hexamethylditin (0.25 mL, 1.2 mmol) and $Pd(PPh_3)_4$ (280 mg, 0.24 mmol). The mixture was degassed using argon stream for 3 minutes and stirred in 110°C bath for 90 min. It was concentrated in vacuo and subjected to silica flash column to isolate compound **153.2** (130 mg, 28%). MS found for $C_{17}H_{17}N_5O_2S_2$ as $(M+H)^+$ 388.1.

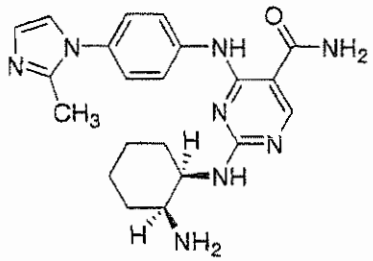
[0541] Step 2: Ethyl ester **153.2** (130 mg, 0.34 mmol) was dissolved in 20 mL THF. To it were added lithium hydroxide hydrate (42 mg, 1.0 mmol) and 3 mL water. The mixture was stirred for 2 hours at RT. It was concentrated in vacuo to remove THF and carefully treated with 1N HCl till pH reaching 3. A yellow solid crashed out from the solution. It was isolated using a Büchner funnel, washed with cold water, dried in vacuum oven to give compound **153.3**. MS found for $C_{15}H_{13}N_5O_2S_2$ as $(M+H)^+$ 360.1.

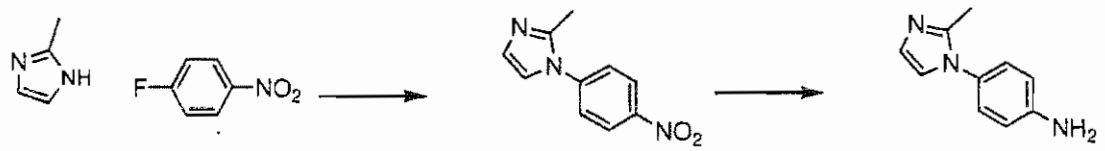
[0542] Step 3: Carboxylic acid **153.3** (0.34 mmol) was dissolved in 10 mL DMF. To it were added EDC hydrochloride (100 mg, 0.51 mmol) and HOBt hydrate (70 mg, 0.51 mmol). The mixture was stirred at RT for 1 hour. To it was then added ammonia (commercial 0.5N solution in dioxane, 3.4 mL, 1.7 mmol). The mixture was stirred for overnight. It was then concentrated in vacuo to remove dioxane. The mixture was then subjected to reverse phase preparative HPLC to isolate compound **153.4** (22 mg, 18% for 2 steps). MS found for $C_{15}H_{14}N_6OS_2$ as $(M+H)^+$ 359.1.

[0543] Step 4: Compound **153.4** (22 mg, 0.06 mmol) was dissolved in 5 mL NMP. To it was added MCPBA (65% pure, 21 mg, 0.072 mmol). It was stirred at RT for 2 hours. To it were then added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2** (0.3 M, 0.4 mL, 0.12 mmol) and DIEA (31 μL, 0.18 mmol). The mixture was stirred for 80 minutes at 90°C bath. This mixture was diluted with ethyl acetate, washed with saturated Na_2CO_3 aqueous solution twice and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford crude compound **153.5**. MS found for $C_{25}H_{32}N_8O_3S$ as $(M+H)^+$ 525.3.

[0544] Step 5: Compound **153.5** was stirred in a 1:1 mixture of TFA and dichloromethane at RT for 1 hour. It was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate the title compound. MS found for $C_{20}H_{24}N_8OS$ as $(M+H)^+$ 425.3. UV λ=241, 319 nm.

[0545] Example 84. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(2-methyl-1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxamide





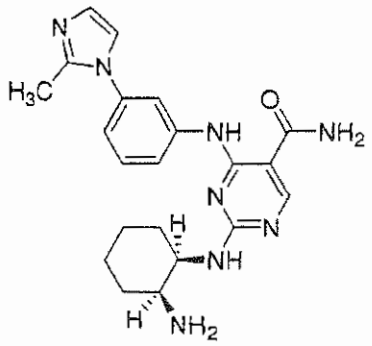
154.1 **154.2** **154.3** **154.4**

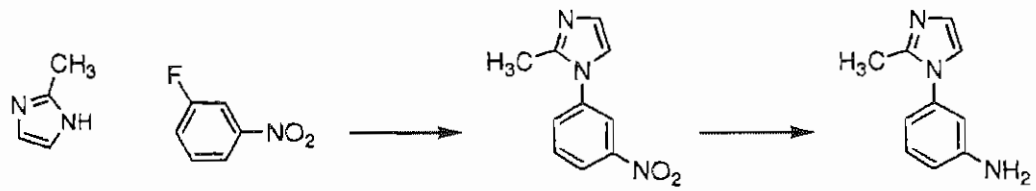
[0546] The mixture of 2-methylimidazole **154.1** (1.52 g, 18.6 mmol), 4-fluoro-1-nitrobenzene **154.2** (1.0 mL, 9.4 mmoL) and potassium carbonate (1.30 g, 9.4 mmol) in 20 mL dry DMF was stirred in 100°C bath for overnight. It was diluted with 300 mL ethyl acetate and washed with water 4 times. The organic phase was dried over $MgSO_4$ and filtered to yield a solution of crude product **154.3**. To this solution was added catalytic amount of 10% Pd/C. To this stirred suspention was amounted a hydrogen balloon for overnight. The mixture was filtered and concentrated in vacuo to afford crude aniline **154.4**. MS found for $C_{10}H_{11}N_3$ as $(M+H)^+$ 174.1. It was purified using flash column.

[0547] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 with aniline **154.4** to replace aniline **74.1**. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$

407.3. UV λ=246, 293 nm. NMR (CD_3OD): δ 8.60 (s, 1H), 7.96 (m, 2H), 7.70 (d, J=8.4 Hz, 2H), 7.66-7.61 (m, 4H), 4.47 (m, 1H), 3.73 (m, 1H), 2.60 (s, 3H), 1.92-1.59 (m, 8H) ppm.

[0548] Example 85. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2-methyl-1H-imidazol-1-yl)phenylamino)pyrimidine-5-carboxamide



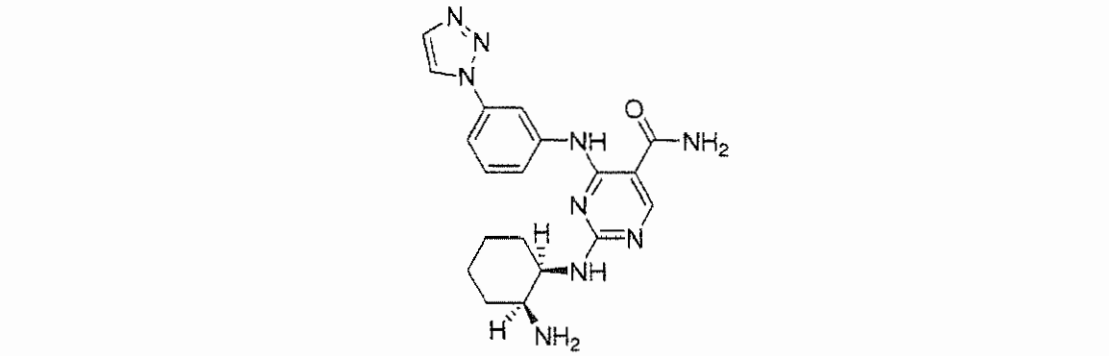


155.1 **155.2** **155.3** **155.4**

[0549] The mixture of 2-methylimidazole **155.1** (0.77 g, 9.4 mmol), 3-fluoro-1-nitrobenzene **155.2** (0.50 mL, 4.7 mmoL) and cesium carbonate (3.07 g, 9.4 mmol) in 15 mL dry NMP was stirred in 120°C bath for 6 hours. It was diluted with 300 mL ethyl acetate and washed with water 4 times. The organic phase was dried over $MgSO_4$ and filtered to yield a solution of crude product **155.3**. To this solution was added catalytic amount of 10% Pd/C. To this stirred suspention was amounted a hydrogen balloon for overnight. The mixture was filtered and concentrated in vacuo to afford crude aniline **155.4**. MS found for $C_{10}H_{11}N_3$ as $(M+H)^+$ 174.1. It was purified using flash column.

[0550] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 with aniline **155.4** to replace aniline **74.1**. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 407.3. UV λ=243, 285 nm. NMR (CD_3OD): δ 8.58 (s, 1H), 8.06 (m, 1H), 7.83 (m, 1H), 7.73-7.71 (m, 2H), 7.64 (m, 1H), 7.44 (m, 1H), 4.41 (m, 1H), 3.66 (m, 1H), 2.62 (s, 3H), 1.89-1.55 (m, 8H) ppm.

[0551] Example 86. 4-(3-(1H-1,2,3-triazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide

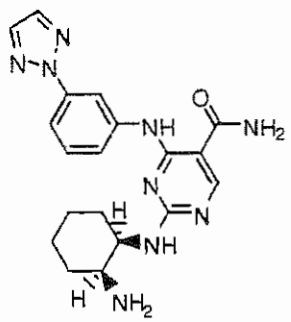


156.1 156.2 156.3 156.4 156.5 156.6

[0552] The mixture of 1H-1,2,3-triazole **156.1** (0.55 mL 9.4 mmol), 3-fluoro-1-nitrobenzene **156.2** (0.50 mL, 4.7 mmoL) and cesium carbonate (3.07 g, 9.4 mmol) in 15 mL dry NMP was stirred in 120°C bath for 17 hours. It was diluted with 300 mL ethyl acetate and washed with water 4 times. The organic phase was dried over $MgSO_4$ and filtered to yield a solution of crude products **156.3** and **156.4** in nearly 1:1 ratio. To this solution was added catalytic amount of 10% Pd/C. To this stirred suspention was amounted a hydrogen balloon for overnight. The mixture was filtered and concentrated in vacuo to afford crude anilines **156.5** and **156.6**. MS found for $C_8H_8N_4$ as $(M+H)^+$ 161.1. The two anilines were purified using flash column.

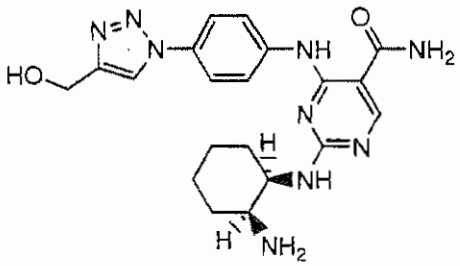
[0553] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 with aniline **156.5** to replace aniline **74.1**. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.3. UV λ=244 nm. NMR (CD_3OD): δ 8.90 (s, 1H), 8.63 (d, J=1.2 Hz, 1H), 8.57 (s, 1H), 7.95 (d, J=1.2Hz, 1H), 7.62-7.58 (m, 2H), 7.43 (m, 1H), 4.68 (m, 1H), 3.73 (m, 1H), 1.91-1.53 (m, 8H) ppm.

[0554] Example 87. 4-(3-(1H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



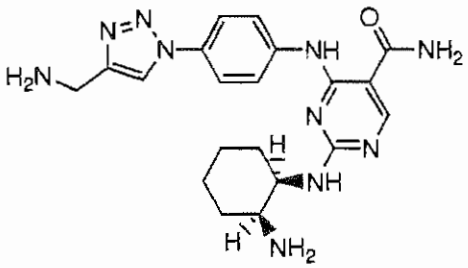
[0555] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 with aniline **156.6** (shown in Example 1) to replace aniline **74.1**. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.3. UV λ=250 nm. NMR (CD_3OD): δ 8.77 (s, 1H), 8.46 (s, 1H), 7.88 (s, 2H), 7.83 (d, J=7.6 Hz, 1H), 7.45 (dd, J=8.4, 8.0 Hz, 1H), 7.23 (d, J=8.0 Hz, 1H), 4.52 (m, 1H), 3.58 (m, 1H), 1.82-1.43 (m, 8H) ppm.

[0556] Example 88. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)phenylamino)pyrimidine-5-carboxamide



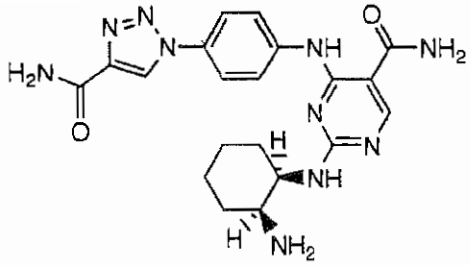
[0557] The title compound was prepared using the same synthetic scheme demonstrated in the scheme (Example 45) with propargyl alcohol to replace trimethylsilylacetylene. MS found for $C_{20}H_{25}N_9O_2$ as $(M+H)^+$ 424.3. UV λ=242, 300 nm.

[0558] Example 89. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)phenylamino)pyrimidine-5-carboxamide



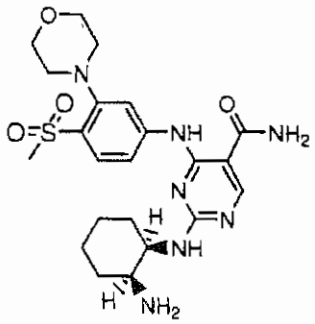
[0559] The title compound was prepared using the same synthetic scheme demonstrated in the Scheme (Example 45) with propargylamine to replace trimethylsilylacetylene. MS found for $C_{20}H_{26}N_{10}O$ as $(M+H)^+$ 423.3. UV λ=242, 301 nm.

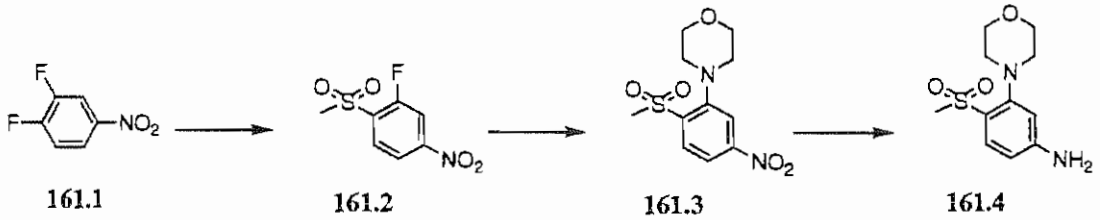
[0560] Example 90. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(4-carbamoyl-1H-1,2,3-triazol-1-yl)phenylamino)pyrimidine-5-carboxamide



[0561] The title compound was prepared using the same synthetic scheme demonstrated in the scheme (Example 45) with propynoic acid amide to replace trimethylsilylacetylene. MS found for $C_{20}H_{24}N_{10}O_2$ as $(M+H)^+$ 437.3. UV λ=242, 300 nm.

[0562] Example 91. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(methylsulfonyl)-3-morpholinophenylamino)pyrimidine-5-carboxamide





161.1 161.2 161.3 161.4

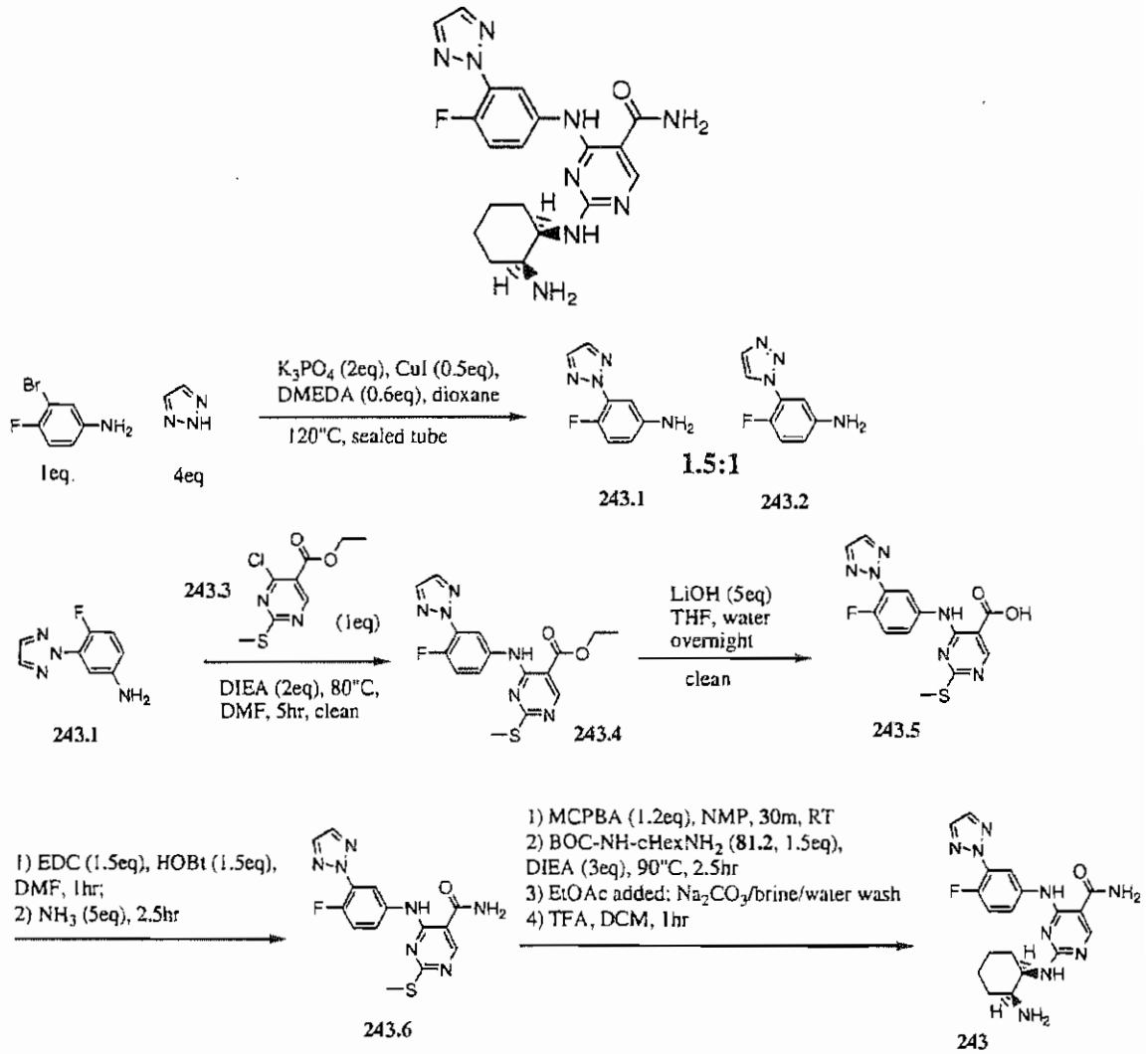
[0563] The mixture of sodium thiomethoxide (2.85 g, 40.6 mmol) and 3,4-difluoro-1-nitrobenzene **161.1** (3.0 mL, 27.1 mmoL) in 20 mL dry NMP was stirred at RT for 3 hours. It was diluted with 300 mL ethyl acetate and washed with water four times. The organic phase was dried over $MgSO_4$, concentrated in vacuo and dissolved in 270 mL DCM. To it was added MCPBA (65%, 14.3 g, 54 mmol) in small portions. The mixture was stirred for 2 hours at RT, diluted with more DCM, washed with 0.1 N NaOH three times and brine. This solution was dried over $MgSO_4$ and concentrated in vacuo to give crude **161.2**.

[0564] Crude **161.2** (490 mg, 2.2 mmol) was dissolved in 10 mL dry NMP. To it was added morpholine (1.2 mL, 6.6 mmol). The mixture was stirred at 60°C bath for 1 hour. It was diluted by ethyl acetate 300 mL, washed with brine three times, dried over $MgSO_4$ and filtered to yield a solution of crude product **161.3**. To this solution was added catalytic

amount of 10% Pd/C. To this stirred suspention was amounted a hydrogen balloon for overnight. The mixture was filtered and concentrated in vacuo to afford crude aniline **161.4**. MS found for $C_{11}H_{16}N_2O_3S$ as $(M+H)^+$ 257.1. It was purified using flash column.

[0565] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 with aniline **161.4** to replace aniline **74.1**. MS found for $C_{22}H_{31}N_7O_4S$ as $(M+H)^+$ 490.3. UV λ=249, 301 nm.

Example 92. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-fluoro-3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



[0566] Step1: The mixture of 3-bromo-4-fluoroaniline (860 mg, 4.53 mmol), 1,2,3-triazole (1.05 mL, 18.1 mmol), K_3PO_4 (1.92 g, 9.06 mmol), CuI (430 mg, 2.27 mmol), N,N'-dimethylethylenediamine (0.29 mL, 2.72 mmol) in 10 mL dioxane and 5mL DMSO was stirred in a sealed tube at 120°C for 5 days. A mixture of **243.1** and **243.2** (in 1.5:1 ratio)

along with leftover starting materials were obtained. To the mixture was poured EtOAc 250 mL. It was vigoriously stirred, washed with water and brine, dried over $MgSO_4$, filtered, concentrated in vacuo and subjected to flash column. Compound **243.1** left the column at 70% EtOAc in hexane and compound **243.2** at 90%EtOAc in hexane.

Step 2: To the mixture of aniline **243.1** (255 mg, 1.44 mmol) and ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (**243.3**, CAS 5909-24-0, 336 mg, 1.44 mmol) in 15 mL DMF was added DIEA (0.5 mL, 2.88 mmol). The mixture was stirred at 85 °C for 5 hours. To it was added 250 mL EtOAc, washed with brine x3, dried, filtered and concentrated in vacuo to afford compound **243.4** in quantatititive yield. MS found for $C_{16}H_{15}FN_6O_2S$ as $(M+H)^+$ 375.1.

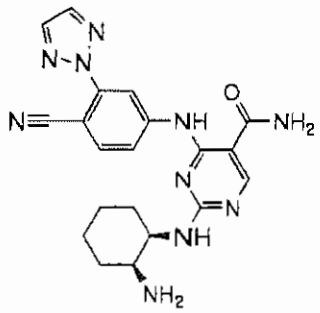
[0567] Step 3: The above prepapred compound (1.44 mmol) was dissolved in 80 mL THF and 10 mL water. To it was added LiOH hydrate (302 mg, 7.2 mmol). The mixture was stirred for overnight. It was concentrated in vacuo to remove THF. To the residue was added 1N HCl till pH reaching 2. The solid product was isolated by filtration. It was washed thoroughly with cold water and dried in vacuum oven to give compound **243.5** in quantatitive yield as a tan solid. MS found for $C_{14}H_{11}FN_6O_2S$ as $(M+H)^+$ 347.1.

[0568] Step 4: The above prepared compound **243.5** (468 mg, 1.35 mmol) was stirred in 25 mL DMF. To it were added EDC.HCl (390 mg, 2.03 mmol) and HOBt hydrate (311 mg, 2.03 mmol). The mixture was stirred for 1 hr and HPLC indicated that all the starting **243.5** had been consumed. To this mixture was then added ammonium (0.5N solution in dixoane, 8.1 mL, 4.05 mmol). The mixture was stirred for 3 hrs and concentrated in vacuo to remove dioxane. Water was added to the residue and solid crashed out. This solid was isolated by filtration, washed with cold water thoroughly and dried in vacuum oven to give compound **243.6** as a tan solid. MS found for $C_{14}H_{12}FN_7OS$ as $(M+H)^+$ 346.1.

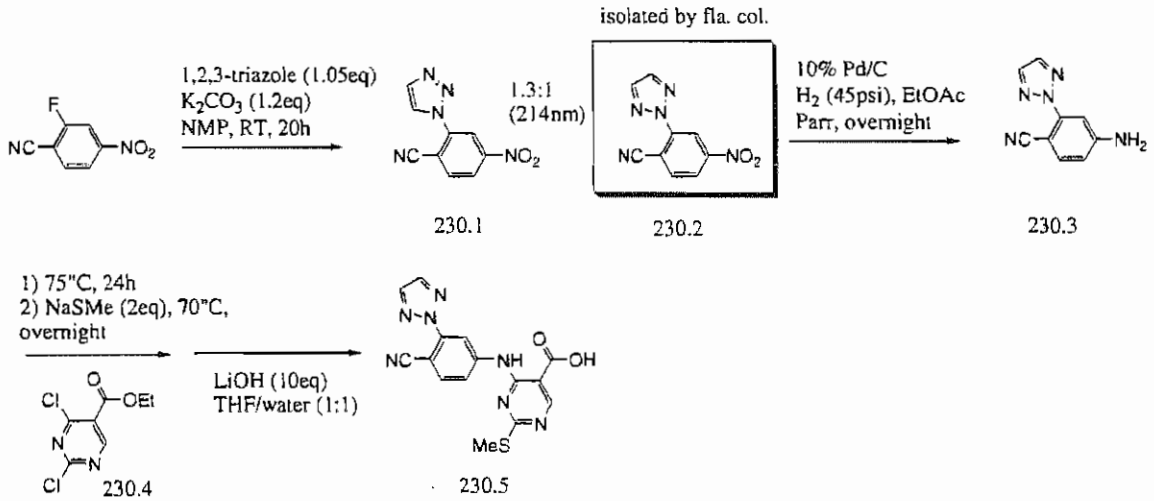
[0569] Step 5: The above prepared compound **243.6** (100 mg, 0.29 mmol) was dissolved in 5 mL NMP. To it was added MCPBA (65% pure, 92 mg, 0.35 mmol). It was stirred at RT for 30 minutes to afford a mixture of the corresponding sulfoxide and sulfone. To it then were added DIEA (160 µL, 0.90 mmol) and then tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (**81.2**, 94 mg, 0.45 mmol). The mixture was stirred for 3 hrs at 90°C bath. It was then diluted with 150 mL EtOAc, washed with sat Na_2CO_3 and brine x2, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was then exposed to 1:1 mixture of TFA and DCM for 1 hr. It was concentrated and subjected to reverse phase HPLC to isolate the title compound

243. MS found for $C_{19}H_{22}FN_9O$ as $(M+H)^+$ 412.3. UV λ=247 nm. NMR (CD_3OD): δ 8.58 (m, 1H), 8.55 (s, 1H), 8.05 (s, 2H), 7.45-7.43 (m, 2H), 4.53 (m, 1H), 3.64 (m, 1H), 1.86-1.54 (m, 8H) ppm.

Example 93. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-cyano-3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



Scheme:



[0570] Step 1: 2-fluoro-4-nitrobenzonitrile (2.98 g, 18 mmol) was dissolved in 40 mL NMP. To it were added 1,2,3-triazole (1.1 mL, 18.8 mmol) and K_2CO_3 (2.98 g, 21.6 mmol). The mixture was stirred at RT for 20 h to give compound 230.1 and 230.2 (less polar) in 1.3:1 ratio. The mixture was taken into ethyl acetate, washed with water and brine x3. It was dried, concentrated and subjected to silica flash column to isolate desired compound 230.2 using 20% ethyl acetate in hexane.

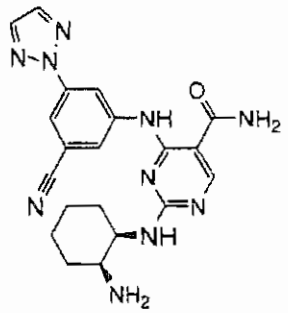
[0571] Step 2: Compound 230.2 from Step 1 was dissolved in 300 mL ethyl acetate. To it was added 500 mg 10% Pd/C. The mixture was placed on Parr shaker under 45 psi hydrogen pressure for overnight. The mixture was filtered through celite, which was thoroughly washed

using methanol. The filtrate was concentrated and subjected to silica flash column to isolate aniline 230.3 (0.59 g, 18% for 2 steps).

[0572] Step 3: Compound 230.4 (0.66 g, 3.0 mmol) was dissolved in 20 mL NMP. To it were added compound 230.3 (0.55 g, 3.0 mmol) and then DIEA (0.78 mL, 4.5 mmol). The mixture was stirred at 75°C for 24 h. To it was then added NaSMe (0.42 g, 6.0 mmol). The mixture was stirred at 70°C for overnight. The mixture was diluted with ethyl acetate, washed with brine x 4, dried, concentrated in vauo. The residue was then dissolved in 50 mL THF. To it were added $LiOH.H_2O$ (1.26 g, 30 mmol) and 50 mL water. The mixture was stirred for 90 min at RT. It was acidified using 6 N HCl till pH reaching 2. The solid precipitate was collected by filtration. It was washed with water and dried in vacuo oven. It was crude compound 230.5.

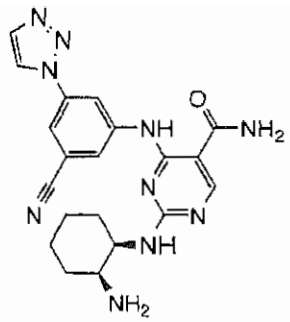
[0573] The title compound was made using the similar chemistry scheme shown for Example 93 using compound 230.5. MS found for $C_{20}H_{22}N_{10}O$ as $(M+H)^+$ 419.4. UV λ=259, 314 nm.

Example 94. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-cyano-5-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



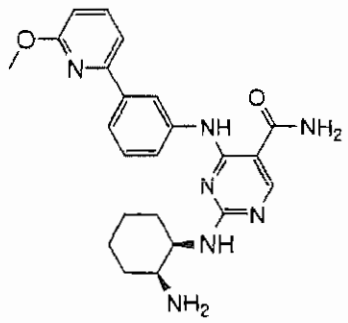
[0574] The title compound was made using the similar chemistry scheme shown for Example 92. MS found for $C_{20}H_{22}N_{10}O$ as $(M+H)^+$ 419.3. UV λ=252 nm. NMR (CD_3OD): δ 9.03 (s, 1H), 8.61 (s, 1H), 8.16 (m, 1H), 8.02 (s, 2H), 7.91 (m, 1H), 4.62 (m, 1H), 3.69 (m, 1H), 1.94-1.58(m, 8H) ppm.

Example 95. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-cyano-5-(1H-1,2,3-triazol-1-yl)phenylamino)pyrimidine-5-carboxamide

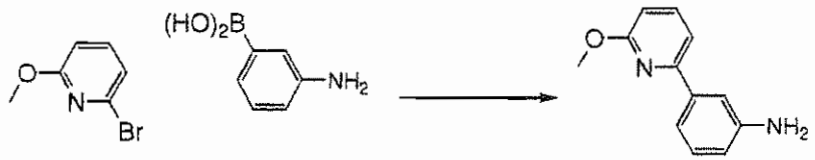


[0575] The title compound was made using the similar chemistry scheme shown for Example 93. MS found for $C_{20}H_{22}N_{10}O$ as $(M+H)^+$ 419.4. UV λ=244, 288 nm. NMR (CD_3OD): δ 9.15 (s, 1H), 8.71 (s, 1H), 8.63 (s, 1H), 7.99-7.97 (m, 3H), 4.67 (m, 1H), 3.72 (m, 1H), 1.90-1.58(m, 8H) ppm.

Example 96. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(6-methoxypyridin-2-yl)phenylamino)pyrimidine-5-carboxamide



Scheme:

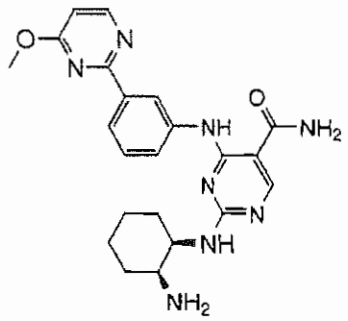


233.1 233.2 233.3

[0576] Commercially available compound 233.1 (2.3 g, 12.2 mmol) and boronic acid 233.2 (1.68 g, 12.2 mmol) were placed in 40 mL dioxane and 20 mL water. To it were added K_2CO_3 (5.05 g, 36.6 mmol) and $Pd(Ph_3P)_2Cl_2$ (0.86 g, 1.22 mmol). The mixture was bubbled with argon stream for 3 min and sent to 85°C bath under argon. The mixture was stirred for 90 min. It was concentrated in vacuo to remove dioxane. The mixture then was extracted with chloroform x4. The organic extract was dried and concentrated in vauo to afford crude aniline 233.3.

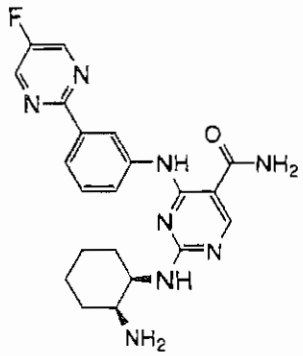
[0577] The title compound was then prepared using the similar chemistry scheme shown for Example 86 using aniline 233.3. MS found for $C_{23}H_{27}N_7O_2$ as $(M+H)^+$ 434.4. UV λ=245, 296 nm.

Example 97. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-methoxypyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



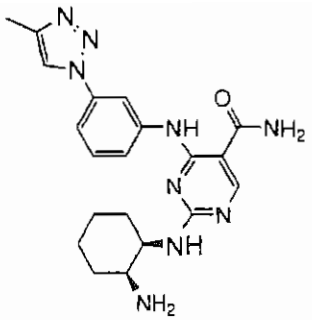
[0578] The title compound was prepared using the similar chemistry scheme shown for Example 96. MS found for $C_{22}H_{26}N_8O_2$ as $(M+H)^+$ 435.4. UV λ=250 nm. NMR (CD_3OD): δ 8.53 (s, 1H), 8.42 (s, 1H), 7.92(m, 1H), 7.77 (m, 1H), 7.54-7.50 (m, 3H), 6.79 (d, J=8.0 Hz, 1H), 4.30 (m, 1H), 4.01 (s, 3H), 3.64 (m, 1H), 1.85-1.36 (m, 8H) ppm.

Example 98. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(5-fluoropyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



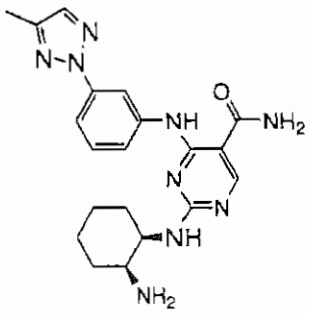
[0579] The title compound was prepared using the similar chemistry scheme shown for Example 96. MS found for $C_{21}H_{23}FN_8O$ as $(M+H)^+$ 423.3. UV λ=249 nm.

Example 99. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-methyl-1H-1,2,3-triazol-1-yl)phenylamino)pyrimidine-5-carboxamide



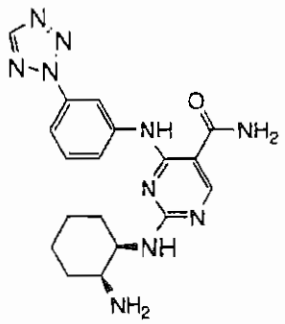
[0580] The title compound was prepared using the same synthetic scheme demonstrated in Example 86. MS found for $C_{20}H_{25}N_9O$ as $(M+H)^+$ 408.4. UV λ=245 nm.

Example 100. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-methyl-2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide

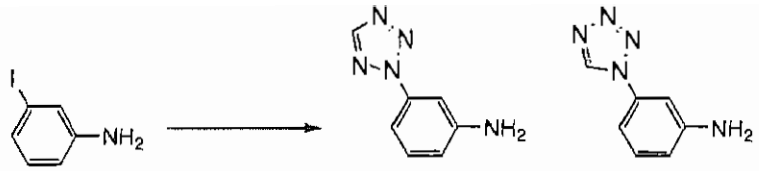


[0581] The title compound was prepared using the same synthetic scheme demonstrated in Example 87. MS found for $C_{20}H_{25}N_9O$ as $(M+H)^+$ 408.4. UV λ=251 nm.

Example 101a. 4-(3-(2H-tetrazol-2-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



Scheme:

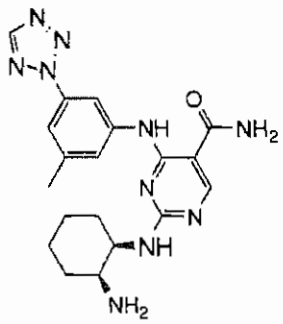


238.1 238.2

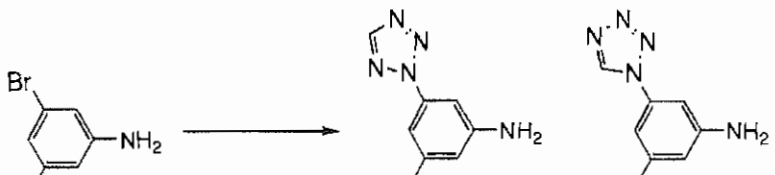
[0582] The mixture of 3-iodoaniline (0.5 mL, 4.2 mmol), tetrazole (0.88 g, 12.6 mmol), K_3PO_4 (2.67 g, 12.6 mmol), CuI (400 mg, 2.1 mmol), DMEDA (0.27 mL, 2.5 mmol) in 6 mL dioxane and 6 mL DMSO was stirred at 105°C in a sealed flask for 3 days to cleanly give a mixture of aniline 238.1 (less polar) and 238.2 in ratio of 17:1 (determined by HPLC). It was diluted with ethyl acetate, washed with water and brine x2. It was dried, concentrated and subjected to silica flash column to isolate aniline 238.1 using 40% ethyl acetate in hexane.

[0583] The title compound was prepared using the same synthetic scheme demonstrated in Example 86. MS found for $C_{18}H_{22}N_{10}O$ as $(M+H)^+$ 395.4. UV λ=250 nm. NMR (CD_3CN): δ 9.02 (s, 1H), 8.87 (s, 1H), 7.98 (d, J=8.0Hz, 1H), 7.67-7.53 (m, 3H), 4.83 (m, 1H), 3.67 (m, 1H), 1.8-1.4 (m, 8H) ppm.

Example 101b. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-methyl-5-(2H-tetrazol-2-yl)phenylamino)pyrimidine-5-carboxamide



Scheme:



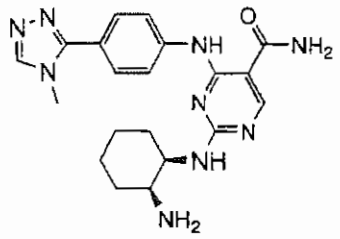
239.1 239.2

[0584] The mixture of 3-bromo-5-methylaniline.HCl (0.94 g, 4.2 mmol), tetrazole (0.88 g, 12.6 mmol), K_3PO_4 (4.45 g, 21 mmol), CuI (400 mg, 2.1 mmol), DMEDA (0.27 mL, 2.5

mmol) in 6 mL dioxane and 6 mL DMSO was stirred at 105°C in a sealed flask for 3 days to cleanly give exclusively aniline 239.1. Aniline 239.2 was not found by HPLC/LCMS. It was diluted with ethyl acetate, washed with water and brine x2. It was dried, concentrated and subjected to silica flash column to isolate aniline 239.1 using 40% ethyl acetate in hexane.

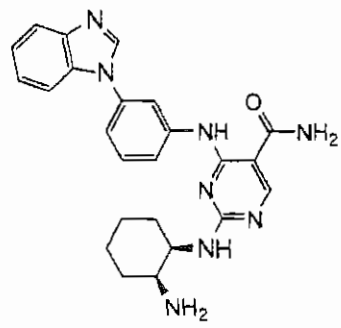
[0585] The title compound was prepared using the same synthetic scheme demonstrated in Example 86. MS found for $C_{19}H_{24}N_{10}O$ as $(M+H)^+$ 409.4. UV λ=250 nm. NMR (CD_3CN): δ 8.85 (s, 1H), 8.80 (s, 1H), 8.58 (s, 1H), 7.83 (s, 1H), 4.83 (m, 1H), 3.68 (m, 1H), 2.50 (s, 3H), 1.8-1.4 (m, 8H) ppm.

Example 102. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(4-methyl-4H-1,2,4-triazol-3-yl)phenylamino)pyrimidine-5-carboxamide

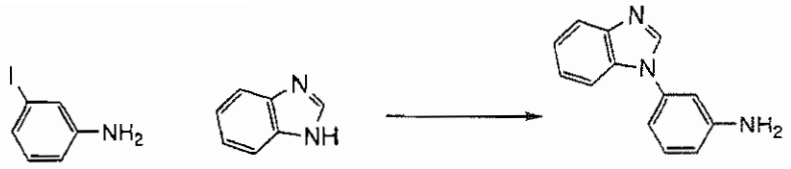


[0586] The title compound was prepared using the same synthetic scheme demonstrated in Example 86 with the corresponding aniline. MS found for $C_{20}H_{25}N_9O$ as $(M+H)^+$ 408.4. UV λ=246, 304 nm.

Example 103. 4-(3-(1H-benzo[d]imidazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



Scheme:

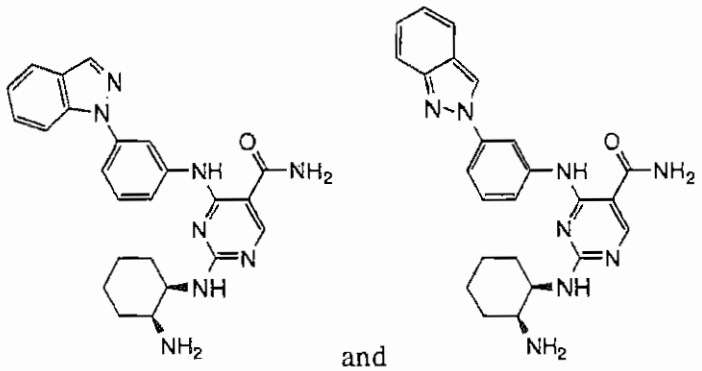


241.1

[0587] The mixture of 3-iodoaniline (0.5 mL, 4.2 mmol), benzimidazole (1.5 g, 12.6 mmol), K_3PO_4 (2.67 g, 12.6 mmol), CuI (400 mg, 2.1 mmol), DMEDA (0.27 mL, 2.5 mmol) in 6 mL dioxane and 6 mL DMSO was stirred in a sealed flask at 120°C for 2 days to cleanly afford aniline 241.1. The mixture was diluted with 300 mL ethyl acetate, washed with water and brine, dried, filtered, concentrated, subjected to silica flash column with 70% ethyl acetate in hexane to isolate aniline 241.1 (730 mg, 83%) as white solid.

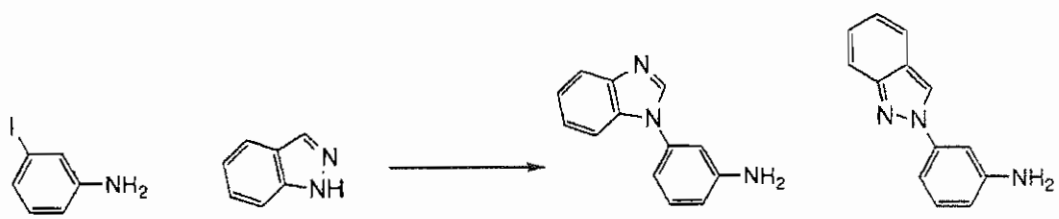
[0588] The title compound was prepared using the same synthetic scheme demonstrated in Example 89 with the aniline. MS found for $C_{24}H_{26}N_8O$ as $(M+H)^+$ 443.4. UV λ=249 nm. NMR (CD_3OD): δ 9.07 (s, 1H), 8.56 (s, 1H), 8.29 (s, 1H), 7.87(m, 1H), 7.74 (m, 3H), 7.56 (m, 3H), 4.14 (m, 1H), 3.50 (m, 1H), 1.72-1.11 (m, 8H) ppm.

Example 104. 4-(3-(1H-indazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide (242.A) and 4-(3-(2H-indazol-2-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide (242.B)



and

Scheme:

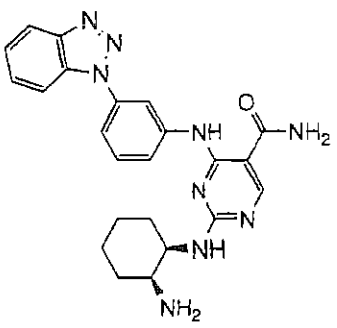


242.1 242.2

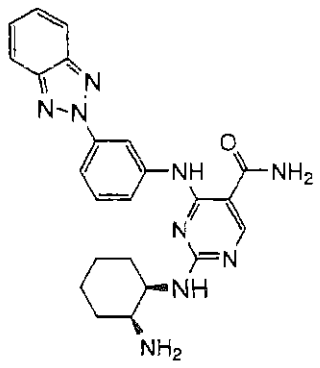
[0589] The mixture of 3-iodoaniline (0.5 mL, 4.2 mmol), indazole (1.5 g, 12.6 mmol), K_3PO_4 (2.67 g, 12.6 mmol), CuI (400 mg, 2.1 mmol), DMEDA (0.27 mL, 2.5 mmol) in 6 mL dioxane and 6 mL DMSO was stirred in a sealed flask at 120°C for 17 h to cleanly afford aniline 242.1 (less polar) and aniline 242.2 in ratio of 6.9:1 (determined by HPLC). The mixture was diluted with 300 mL ethyl acetate, washed with water and brine, dried, filtered, concentrated, subjected to silica flash column to isolate the two anilines.

[0590] The two title compounds were prepared using the same synthetic scheme demonstrated in Example 86 with the corresponding anilines. With aniline 242.1, compound 242.A was prepared: MS found for $C_{24}H_{26}N_8O$ as $(M+H)^+$ 443.4. UV λ=247, 301 nm. With aniline 242.2, compound 242.B was prepared: MS found for $C_{24}H_{26}N_8O$ as $(M+H)^+$ 443.4. UV λ=240, 295 nm. Compound 104A: NMR (CD_3OD): δ 8.57 (m, 1H), 8.56 (s, 1H), 8.31 (s, 1H), 7.87(m, 1H), 7.83 (m, 3H), 7.59 (m, 2H), 7.51 (m, 1H), 7.33 (m, 1H), 7.28 (m, 1H), 4.34 (m, 1H), 3.60 (m, 1H), 1.80-1.22 (m, 8H) ppm. Compound 104B: NMR (CD_3OD): δ 8.84 (s, 1H), 8.78 (m, 1H), 8.55 (s, 1H), 7.78-7.76 (m, 2H), 7.68 (d, J=9.2 Hz, 1H), 7.57 (m, 1H), 7.42-7.34 (m, 2H), 7.13 (m, 1H), 4.46 (m, 1H), 3.63 (m, 1H), 1.85-1.19 (m, 8H) ppm.

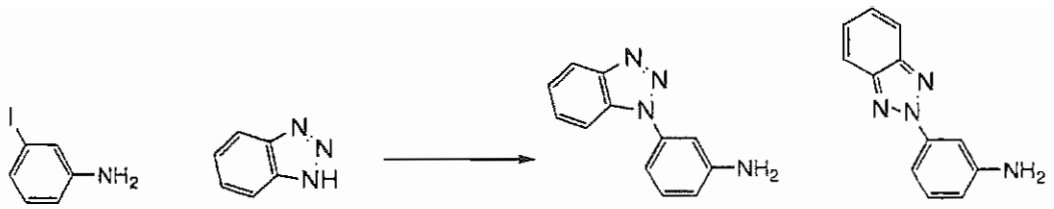
Example 105. 4-(3-(1H-benzo[d][1,2,3]triazol-1-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide (243.A) and 4-(3-(2H-benzo[d][1,2,3]triazol-2-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide (243.B)



and



Scheme:

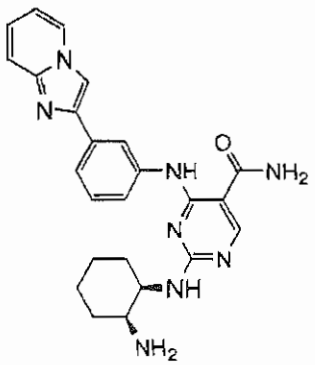


243.1 243.2

[0591] The mixture of 3-iodoaniline (0.5 mL, 4.2 mmol), indazole (1.5 g, 12.6 mmol), K_3PO_4 (2.67 g, 12.6 mmol), CuI (400 mg, 2.1 mmol), DMEDA (0.27 mL, 2.5 mmol) in 6 mL dioxane and 6 mL DMSO was stirred in a sealed flask at 120°C for 17 h to cleanly afford aniline 243.1 and aniline 243.2 (less polar) in ratio of 7.5:1 (determined by HPLC). The mixture was diluted with 300 mL ethyl acetate, washed with water and brine, dried, filtered, concentrated, subjected to silica flash column to isolate the two anilines.

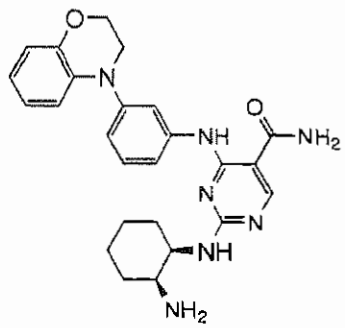
[0592] The two title compounds were prepared using the same synthetic scheme demonstrated in Example 86 with the corresponding anilines. With aniline 243.1, compound 2432.A was prepared: MS found for $C_{23}H_{25}N_9O$ as $(M+H)^+$ 444.4. UV λ=246, 291 nm. With aniline 243.2, compound 243.B was prepared: MS found for $C_{23}H_{25}N_9O$ as $(M+H)^+$ 444.4. UV λ=234, 303 nm. Compound 105A: NMR (CD_3OD): δ 8.78 (m, 1H), 8.56 (s, 1H), 8.12 (d, J=8.4 Hz, 1H), 7.95 (d, J=8.4 Hz, 1H), 7.68 (m, 3H), 7.54 (m, 1H), 7.47 (m, 1H), 4.57 (m, 1H), 3.68 (m, 1H), 1.90-1.44 (m, 8H) ppm. Compound 105B: NMR (CD_3OD): δ 9.07 (s, 1H), 8.55 (s, 1H), 8.16 (d, J=7.6 Hz, 1H), 7.92 (m, 2H), 7.59 (m, 1H), 7.49 (m, 2H), 7.42 (m, 1H), 4.61 (m, 1H), 3.67 (m, 1H), 1.93-1.59 (m, 8H) ppm.

Example 106. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(imidazo[1,2-a]pyridin-2-yl)phenylamino)pyrimidine-5-carboxamide

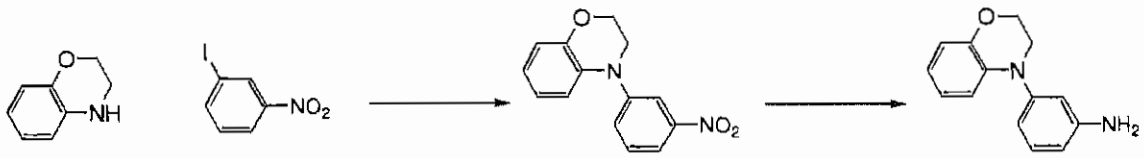


[0593] The title compound was prepared using the same synthetic scheme demonstrated in Example 86 with the biaryl aniline (commercially available). MS found for $C_{24}H_{26}N_8O$ as $(M+H)^+$ 443.4. UV λ=240, 292 nm.

Example 107. 4-(3-(2H-benzo[b][1,4]oxazin-4(3H)-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



Scheme:

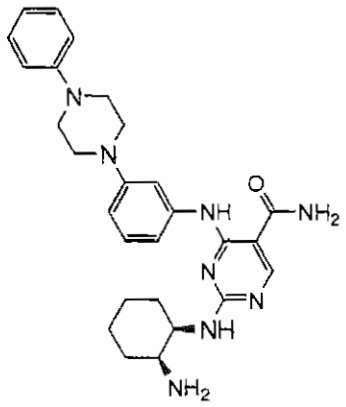


245.1 245.2 245.3 245.4

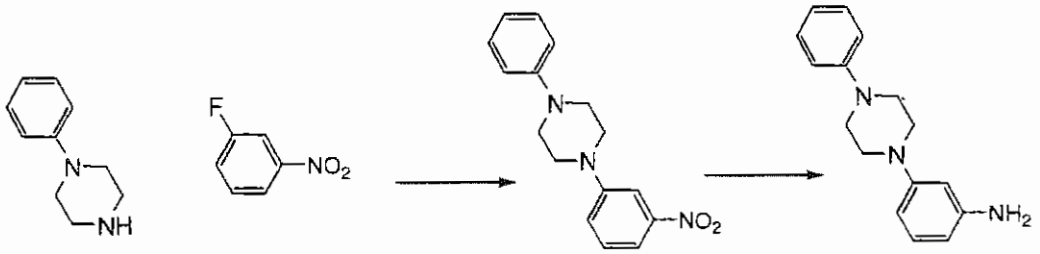
[0594] The mixture of commercially available compound 245.1 (600 mg, 4.44 mmol), 3-iodo-1-nitrobenzene (245.2, 1.11 g, 4.44 mmol), $Pd(dba)_2$ (128 mg, 0.22 mmol), $Ph_5FcP(tBu)_2$ (313 mg, 0.44 mmol) and NaOtBu (640 mg, 0.66 mmol) in 8 mL toluene was stirred at 50°C under argon for overnight (21 h). Compound 245.2 was formed cleanly. The mixture was diluted with 300 mL ethyl acetate, washed with brine x3, dried, filtered through a thin silica plug. The filtrate was subjected to treatment of 200 mg 10% Pd/C at 50 psi H_2 Parr shaker for overnight. The mixture was filtered through celite, and the celite was thoroughly washed with methanol. The filtrate was concentrated in vacuo to afford crude aniline 245.4 (870 mg, 87% for 2 steps).

[0595] The title compound was prepared using the same synthetic scheme demonstrated in Example 12 with the aniline prepared above. MS found for $C_{25}H_{29}N_7O_2$ as $(M+H)^+$ 460.4. UV λ=243, 290 nm.

Example 108. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-phenylpiperazin-1-yl)phenylamino)pyrimidine-5-carboxamide



Scheme:

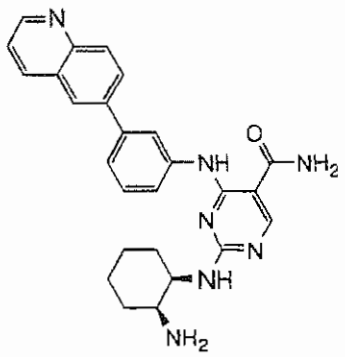


245.1 245.2

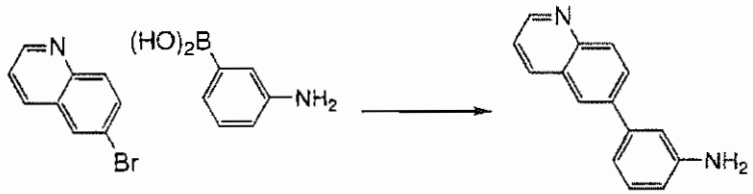
The mixture of 3-fluoro-1-nitrobenzene (1.0 mL, 9.4 mmol), N-phenylpiperazine (2.87 mL, 18.8 mmol) and cesium carbonate (6.13 g, 18.8 mmol) in NMP was stirred at 128°C for three nights. It was diluted with ethyl acetate, washed with brine x2, dried, concentrated and purified using silica flash column to afford compound 245.1 (1.19 g, 45%). It was dissolved in 200 mL ethyl acetate and treated with 500 mg 10% Pd/C under 50 psi hydrogen pressure on Parr shaker for overnight. The mixture was filtered through celite, and the celite was washed thoroughly with methanol. The filtrate was concentrated in vacuo to afford aniline 245.2.

[0596] The title compound was prepared using the same synthetic scheme demonstrated in Example 12 with the aniline prepared above. MS found for $C_{27}H_{34}N_8O$ as $(M+H)^+$ 487.5. UV λ=245 nm.

Example 109. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(quinolin-6-yl)phenylamino)pyrimidine-5-carboxamide



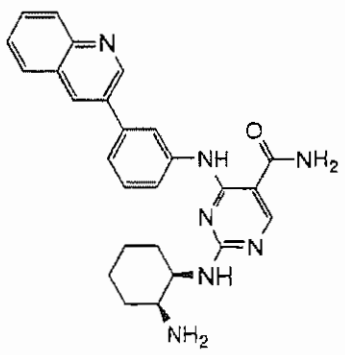
Scheme:



[0597] The mixture of 6-bromoquinoline (870 mg, 4.2 mmol), boronic acid (580 mg, 4.2 mmol), $Pd(Ph_3P)_2Cl_2$ (590 mg, 0.84 mmol), K_2CO_3 (1.74 g, 12.6 mmol) in 20 mL dioxane and 10 mL water was degassed using argon stream for 3 min and stirred at 85°C under argon for 90 min. The mixture was diluted with ethyl acetate, washed with water and brine, dried, concentrated, subjected to silica flash column with 60% ethyl acetate in hexane to isolate the featured aniline.

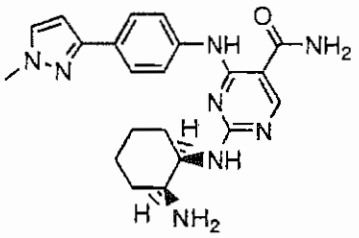
[0598] The title compound was prepared using the same synthetic scheme demonstrated in Example 86 with the aniline prepared above. MS found for $C_{26}H_{27}N_7O$ as $(M+H)^+$ 454.4. UV λ=263 nm.

Example 110. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(quinolin-3-yl)phenylamino)pyrimidine-5-carboxamide



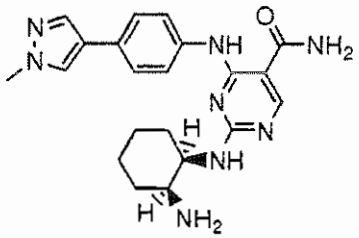
[0599] The title compound was prepared using the same synthetic scheme demonstrated in Example 109. MS found for $C_{26}H_{27}N_7O$ as $(M+H)^+$ 454.4. UV λ=249 nm.

[0600] Example 112. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(1-methyl-1H-pyrazol-3-yl)phenylamino)pyrimidine-5-carboxamide



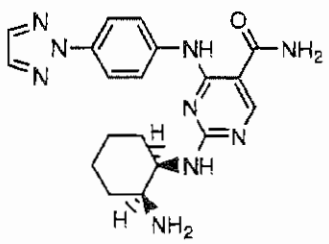
[0601] The title compound was prepared using the same synthetic scheme demonstrated in Example 83 with 3-iodo-1-methylpyrazole to replace 2-bromo-5-methyl-1,3,4-thiadiazole **153.1**. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 407.3. UV λ=240, 311 nm.

[0602] Example 113. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(1-methyl-1H-pyrazol-4-yl)phenylamino)pyrimidine-5-carboxamide



[0603] The title compound was prepared using the same synthetic scheme demonstrated in Example 83 with 4-iodo-1-methylpyrazole to replace 2-bromo-5-methyl-1,3,4-thiadiazole **153.1**. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 407.3. UV λ=239, 314 nm.

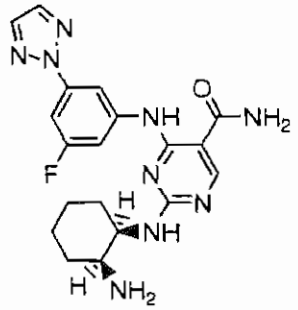
[0604] Example 114. 4-(4-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0605] The title compound was prepared using the same synthetic scheme demonstrated in Example 87 with 4-fluoro-1-nitrobenzene to replace 3-fluoro-1-nitrobenzene. MS found for

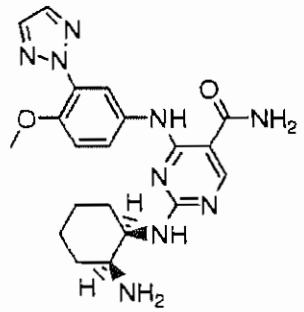
$C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.3. UV λ=239, 310 nm. NMR (CD_3OD): δ 8.54 (s, 1H), 8.12 (m, 2H), 7.93 (s, 2H), 7.81 (m, 2H), 4.40 (m, 1H), 3.73 (m, 1H), 1.94-1.58(m, 8H) ppm.

Example 115. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-fluoro-5-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



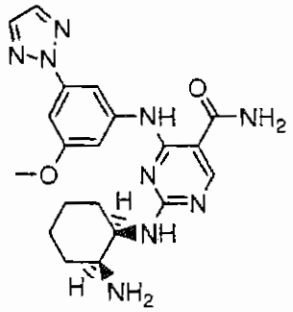
[0606] The above compound was prepared using 3-fluoro-5-iodoaniline using a procedure same as that described in Example 92. MS found for $C_{19}H_{22}FN_9O$ as $(M+H)^+$ 412.3. UV λ=250 nm.

Example 116. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-methoxy-3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



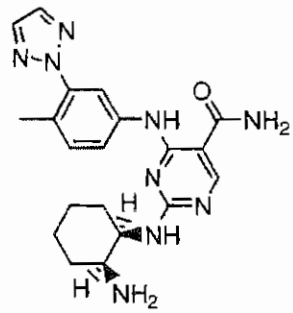
[0607] The above compound was prepared using 3-iodo-4-methoxyaniline using a procedure same as that described in Example 92. 3-Iodo-4-methoxyaniline was prepared from commercial 3-iodo-4-methoxy-1-nitrobenzene by hydrogenation with 5% sulfided Pt on carbon in EtOAc. MS found for $C_{20}H_{25}N_9O_2$ as $(M+H)^+$ 424.3. UV λ=244, 295 nm.

Example 117. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-methoxy-5-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



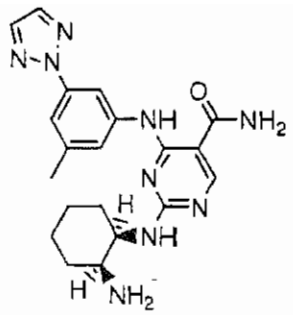
[0608] The above compound was prepared using 3-bromo-5-methoxyaniline using a procedure same as that described in Example 92. 3-Bromo-5-methoxyaniline was prepared from commercial 3-bromo-5-methoxy-1-nitrobenzene by hydrogenation with 5% sulfided Pt on carbon in EtOAc. MS found for $C_{20}H_{25}N_9O_2$ as $(M+H)^+$ 424.3. UV λ=249 nm.

Example 118. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-methyl-3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



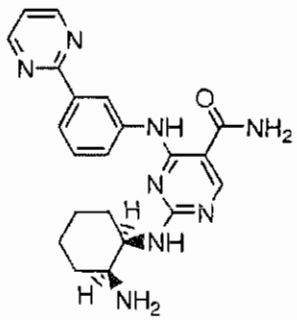
[0609] The above compound was prepared using 4-methyl-3-(2H-1,2,3-triazol-2-yl)aniline using a procedure same as that described in Example 87. 4-Methyl-3-(2H-1,2,3-triazol-2-yl)aniline was prepared from commercial 3-flouro-4-methyl-1-nitrobenzene and 1,2,3-triazole followed by hydrogenation with 10% Pd on carbon in EtOAc, as shown in Example 106. MS found for $C_{20}H_{25}N_9O$ as $(M+H)^+$ 408.3. UV λ=243, 281 nm. δ 1.5-1.9 (m, 8H), 2.36 (s, 3H), 3.60-3.70 (m, 1H), 4.40-4.50 (m, 1H), 7.35-7.43 (m, 2H), 8.00 (s, 2H), 8.28-8.33 (m, 1H), 8.53 (s, 1H)

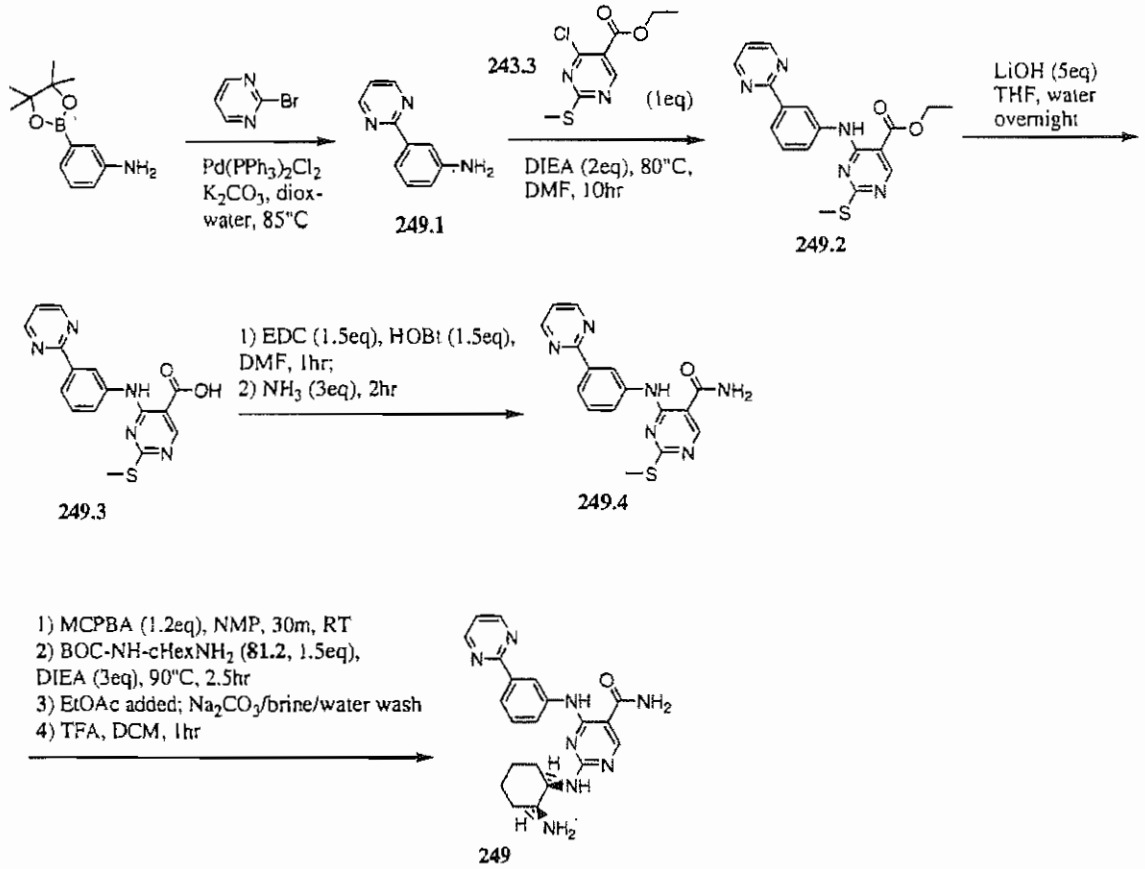
Example 119. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-methyl-5-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



[0610] The above compound was prepared using commercial 3-bromo-5-methylaniline using a procedure same as that described in Example 92. MS found for $C_{20}H_{25}N_9O$ as $(M+H)^+$ 408.3. UV λ=248 nm. δ 1.5-1.9 (m, 8H), 2.45 (s, 3H), 3.65-3.75 (m, 1H), 4.6-4.7 (s, 1H), 7.12-7.18 (m, 1H), 7.72 (s, 1H), 7.98 (s, 2H), 8.56 (s, 1H), 8.72-8.78 (m, 1H)

Example 120. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide





[0611] Step 1: The mixture of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (670 mg, 3.06 mmol), 2-bromopyrimidine (486 mg, 3.06 mmol), $Pd(PPh_3)_2Cl_2$ (430 mg, 0.61 mmol), K_2CO_3 (1.27 g, 9.18 mmol) in 20 mL dixoane and 10 mL water was degassed using Ar stream for 5 minutes and stirred at 85°C under Ar for 2 hrs. It was diluted with 300 mL EtOAc and washed with water and brine x2. The organic phase was then dried, concentrated in vacuo and subjected to flash column to give compound **249.1** (white solid, 440 mg, 84% yield, out of column with 60% EtOAc in hexane). MS found for $C_{10}H_9N_3$ as $(M+H)^+$ 172.1.

[0612] Step 2: To the mixture of aniline **249.1** (440 mg, 2.57 mmol) and ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (**243.3**, CAS 5909-24-0, 600 mg, 2.57 mmol) in 20 mL DMF was added DIEA (0.90 mL, 5.14 mmol). The mixture was stirred at 80 °C for 10 hours. To it was added 350 mL EtOAc, washed with brine x2, dried, filtered and concentrated in vacuo to afford compound **249.2** in quantatititive yield. MS found for $C_{18}H_{17}N_5O_2S$ as $(M+H)^+$ 368.1.

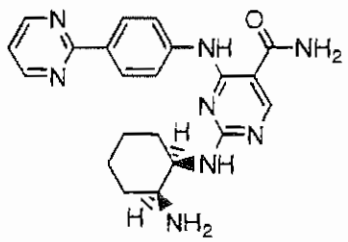
[0613] Step 3: The above prepapred compound (2.57 mmol) was dissolved in 50 mL THF and 5 mL water. To it was added LiOH hydrate (540 mg, 12.9 mmol). The mixture was stirred for overnight. It was concentrated in vacuo to remove THF. To the residue was added

1N HCl until pH reaching 2. The solid product was isolated by filtration. It was washed thoroughly with cold water and dried in vacuum oven to give compound **249.3** in quantatitive yield as a tan solid. MS found for $C_{16}H_{13}N_5O_2S$ as $(M+H)^+$ 340.1.

[0614] Step 4: The above prepared compound **249.3** (2.57 mmol) was stirred in 20 mL DMF. To it were added EDC.HCl (740 mg, 3.86 mmol) and HOBt hydrate (590 mg, 3.86 mmol). The mixture was stirred for 1 hr and HPLC indicated that all the starting **249.3** had been consumed. To this mixture was then added ammonium (0.5N solution in dixoane, 15 mL, 7.5 mmol). The mixture was stirred for 2 hrs and concentrated in vacuo to remove dioxane. Water was added to the residue and solid crashed out. This solid was isolated by filtration, washed with cold water thoroughly and dried in vacuum oven to give compound **249.4** as a tan solid. MS found for $C_{16}H_{14}N_6OS$ as $(M+H)^+$ 339.1.

[0615] Step 5: The above prepared compound **249.4** (150 mg, 0.44 mmol) was dissolved in 6 mL NMP. To it was added MCPBA (65% pure, 140 mg, 0.53 mmol). It was stirred at RT for 45 minutes to afford a mixture of the corresponding sulfoxide and sulfone. To it then were added DIEA (230 μL, 1.32 mmol) and then tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (**81.2**, 142 mg, 0.66 mmol). The mixture was stirred for 2 hrs at 90°C bath. It was then diluted with 150 mL EtOAc, washed with sat Na_2CO_3 and brine x2, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was then exposed to 1:1 mixture of TFA and DCM for 1 hr. It was concentrated and subjected to reverse phase HPLC to isolate the title compound **249**. MS found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.3. UV λ=249 nm. NMR (CD_3OD): δ 8.63 (s, 1H), 8.59 (s, 1H), 8.57 (s, 1H), 8.24 (s, 1H), 8.01 (m, 1H), 7.27 (m, 2H), 7.12 (dd, J=4.8, 4.8 Hz, 1H), 4.24 (m, 1H), 3.37 (m, 1H), 1.64-1.21 (m, 8H) ppm.

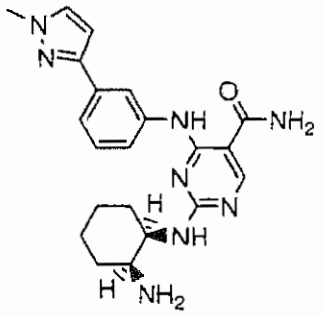
Example 121. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



[0616] The above compound was prepared using commercial 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline using a procedure same as that described in Example 120. MS found for $C_{21}H_{24}N_8O$ as $(M+H)^+$ 405.3. UV λ=231, 314 nm. NMR (CD_3OD): δ 8.83 (d,

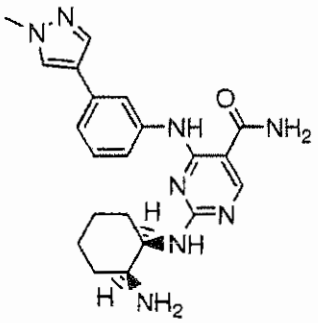
J=4.8 Hz, 2H), 8.56 (s, 1H), 8.45 (m, 2H), 7.81 (m, 2H), 7.35 (dd, J=5.2, 4.8 Hz, 1H), 4.44 (m, 1H), 3.78 (m, 1H), 1.82-1.62(m, 8H) ppm.

[0617] Example 122. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(1-methyl-1H-pyrazol-3-yl)phenylamino)pyrimidine-5-carboxamide



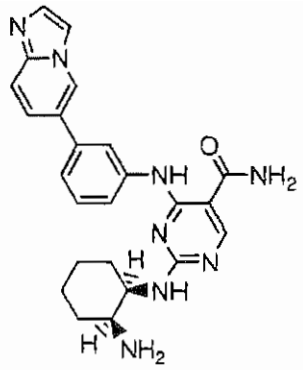
[0618] The above compound was prepared using commercial 3-iodo-1-methylpyrazole using a procedure same as that described in Example 120. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 407.3. UV λ=249 nm.

Example 123. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(1-methyl-1H-pyrazol-4-yl)phenylamino)pyrimidine-5-carboxamide



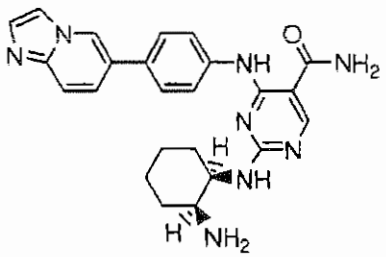
[0619] The above compound was prepared using commercial 4-iodo-1-methylpyrazole using a procedure same as that described in Example 120. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 407.3. UV λ=247 nm.

Example 124. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(imidazo[1,2-a]pyridin-6-yl)phenylamino)pyrimidine-5-carboxamide



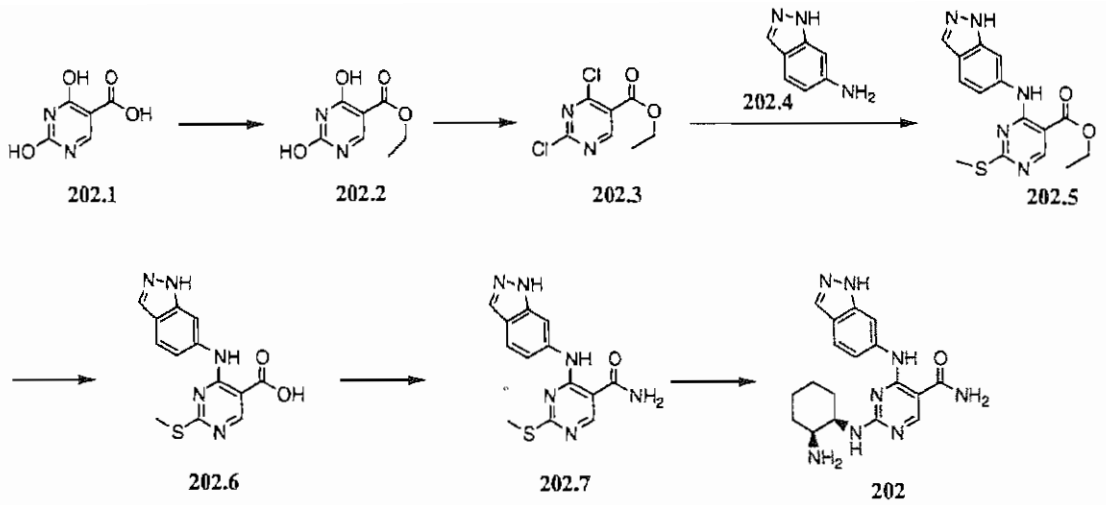
[0620] The above compound was prepared using commercial 6-bromoimidazo[1,2-a]pyridine using a procedure same as that described in Example 120. MS found for $C_{24}H_{26}N_8O$ as $(M+H)^+$ 443.3. UV λ=247 nm. NMR (CD_3OD): δ 9.17 (s, 1H), 8.57 (s, 1H), 8.31 (dd, J=9.6, 1.6 Hz, 1H), 8.30 (d, J=1.6 Hz, 1H), 8.09 (d, J=2.4 Hz, 1H), 8.03 (d, J=9.2 Hz, 1H), 7.95 (broad s, 1H), 7.87 (s, 1H), 7.63 (broad s, 2H), 4.35 (m, 1H), 3.66 (m, 1H), 1.90-1.48 (m, 8H) ppm.

Example 125. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(imidazo[1,2-a]pyridin-6-yl)phenylamino)pyrimidine-5-carboxamide



[0621] The above compound was prepared using commercial 6-bromoimidazo[1,2-a]pyridine and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline using a procedure same as that described in Example 120. MS found for $C_{24}H_{26}N_8O$ as $(M+H)^+$ 443.3. UV λ=245, 303 nm.

Example 126. 4-(1H-indazol-6-ylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0622] Step 1: To a stirring solution of carboxylic acid **202.1** (85 g, 540 mmol) in thionyl chloride (425 mL) was added pyridine (8.5 mL, 0.11 mmol), slowly. The reaction was stirred at 75°C overnight at which time it was concentrated and dried under vacuum to a light yellow powder. This yellow solid was slowly diluted with 750 mL of ethanol and refluxed overnight. The next day the reaction was determined to be complete by HPLC and then cooled in an ice bath and the solid filtered and washed with diethyl ether affording ethyl ester **202.2** as an off-white powder (91 g, 87% for two steps). MS found for $C_7H_8N_2O_4$ as $(M+H)^+$ 185.0.

[0623] Step 2: Ester **202.2** (22 g, 120 mmol) was dissolved in phosphorous oxychloride (60 mL, 600 mmol) and the mixture treated with N,N-diethylaniline (27 mL, 167 mmol) and the mixture heated to 105°C until the reaction was determined to be complete by HPLC. It was then cooled to RT and slowly added to 1 L of crushed ice resulting in the formation of a beige precipitate which was collected by filtration and dried under vacuum affording dichloride **202.3** as a light yellow powder (22.5 g, 85%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.13 (s, 1H), 4.37 (q, 2H), 1.32 (t, 3H).

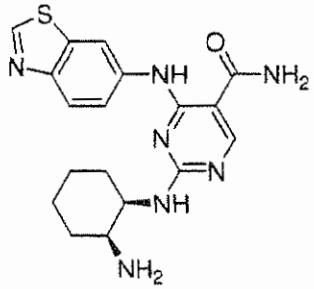
[0624] Step 3: Dichloropyrimidine **202.3** (1.04 g, 4.7 mmol) was dissolved in NMP (30 mL) and stirred in ice bath. To it were added 6-aminoindazole **202.4** (690 mg, 5.2 mmol) and then dropwise ethyldiisopropylamine (DIEA, 1.64 mL, 9.4 mmol). The mixture was stirred for 40 minutes, and to it was added sodium thiomethoxide (660 mg, 9.4 mmol). The mixture was stirred for overnight, diluted with ethyl acetate, washed with brine three times, and concentrated in vacuo to give crude compound **202.5** as a light brown solid in quantitative yield. MS found for $C_{15}H_{15}N_5O_2S$ as $(M+H)^+$ 330.1.

[0625] Step 4: Ethyl ester **202.5** (4.7 mmol) was dissolved in 60 mL THF. To it were added lithium hydroxide hydrate (236 mg, 5.6 mmol) and 20 mL water. The mixture was stirred for overnight and to it was carefully added 1N HCl solution till pH reaching 2. The mixture was concentrated in vacuo to remove THF. White solid crashed out and was isolated using a Büchner funnel. It was washed with water and dried in vacuum oven to give compound **202.6** (1.14 g, 81%) as a white solid. MS found for $C_{13}H_{11}N_5O_2S$ as $(M+H)^+$ 302.1.

[0626] Step 5: Carboxylic acid **202.6** (1.14 g, 3.8 mmol) was dissolved in 30 mL DMF. To it were added EDC hydrochloride (1.09 g, 5.7 mmol) and HOBt hydrate (770 mg, 5.7 mmol). The mixture was stirred at RT for 1 hour. To it was then added ammonia (commercial 0.5N solution in dioxane, 22 mL, 11.4 mmol). The mixture was stirred for 2 hours. It was then concentrated in vacuo and taken into water and ethyl acetate. The organic phase was separated and washed with brine four times. The organic phase was then dried over $MgSO_4$ and concentrated in vacuo to afford compound **202.7** as a light yellow solid (820 mg, 72%). MS found for $C_{13}H_{12}N_6OS$ as $(M+H)^+$ 301.1.

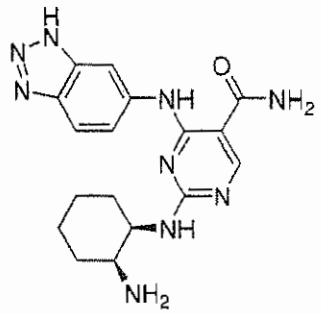
[0627] Step 6: Compound **202.7** (36 mg, 0.12 mmol) was dissolved in 3 mL NMP. To it was added MCPBA (65% pure, 48 mg, 0.18 mmol). It was stirred at RT for 30 minutes. To it then was added cis-1,2-diaminocyclohexane (71 μL, 0.60 mmol). The mixture was stirred for 90 minutes at 90°C bath. This mixture was then subjected to preparative HPLC to isolate the racemic title compound **202**. MS found for $C_{18}H_{22}N_8O$ as $(M+H)^+$ 367.2. UV λ=245, 300 nm.

Example 127. 2-((1R,2S)-2-aminocyclohexylamino)-4-(benzo[d]thiazol-6-ylamino)pyrimidine-5-carboxamide



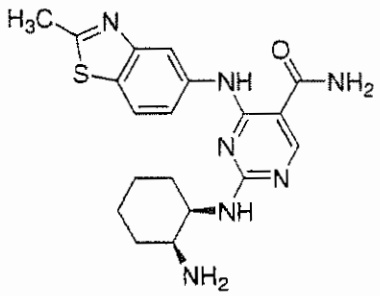
[0628] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 126 with 6-aminobenzothiazole to replace 6-aminoindazole **202.4**. MS found for $C_{18}H_{21}N_7OS$ as $(M+H)^+$ 384.2. UV λ=241, 298 nm.

Example 128. 4-(1H-benzo[d][1,2,3]triazol-6-ylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide 3



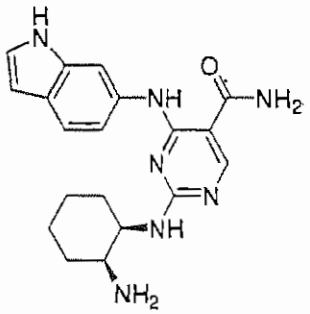
[0629] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 126 with 5/6-aminobenzotriazole to replace 6-aminoindazole **202.4**. MS found for $C_{17}H_{21}N_9O$ as $(M+H)^+$ 368.2. UV λ=246, 295 nm.

Example 129. 2-((1R,2S)-2-aminocyclohexylamino)-4-(2-methylbenzo[d]thiazol-5-ylamino)pyrimidine-5-carboxamide



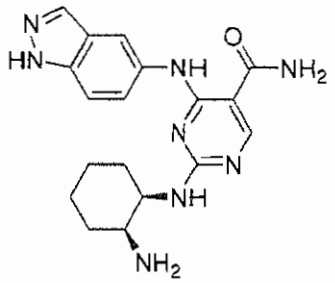
[0630] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 126 with 5-amino-2-methylbenzothiazole to replace 6-aminoindazole **202.4**. MS found for $C_{19}H_{23}N_7OS$ as $(M+H)^+$ 398.2. UV λ=246, 295 nm.

Example 130. 4-(1H-indol-6-ylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide 6



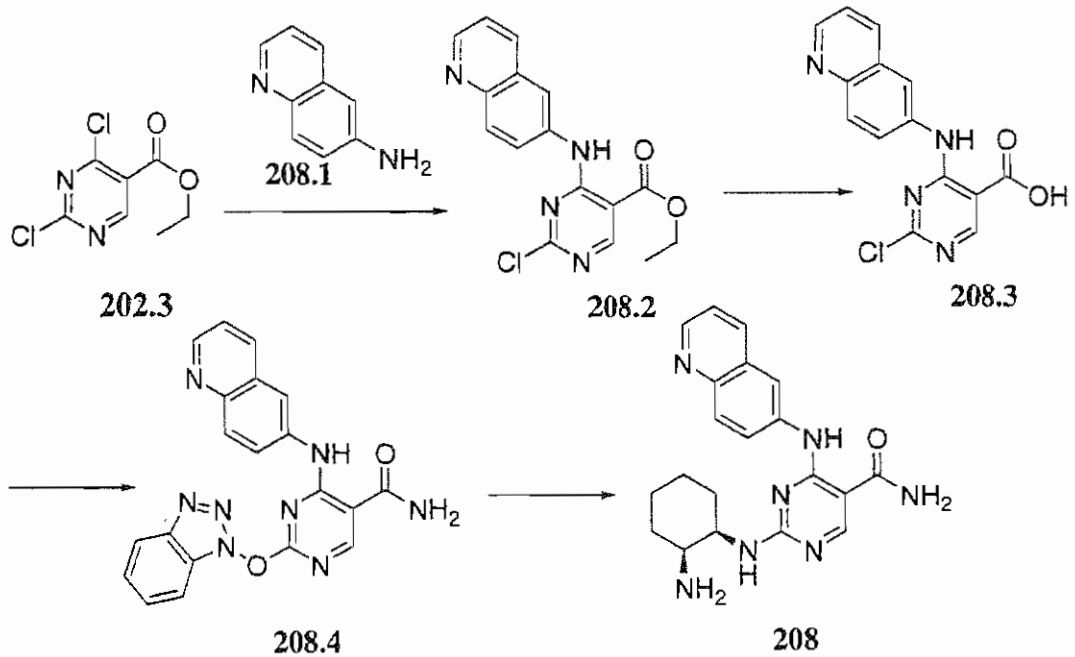
[0631] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 126 with 6-aminoindole to replace 6-aminoindazole **202.4**. MS found for $C_{19}H_{23}N_7O$ as $(M+H)^+$ 366.2. UV λ=239, 309 nm.

Example 131. 4-(1H-indazol-5-ylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0632] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 126 with 5-aminoindazole to replace 6-aminoindazole **202.4**. MS found for $C_{18}H_{22}N_8O$ as $(M+H)^+$ 367.2. UV λ=245, 294 nm.

Example 132. 2-((1R,2S)-2-aminocyclohexylamino)-4-(quinolin-6-ylamino)pyrimidine-5-carboxamide



202.3 **208.1** **208.2** **208.3** **208.4** **208**

[0633] Step 1: Dichloropyrimidine **202.3** (500 mg, 2.3 mmol) was dissolved in NMP (20 mL) and stirred in ice bath. To it were added 6-aminoquinoline **208.1** (390 mg, 2.7 mmol) and then dropwise ethyldiisopropylamine (DIEA, 0.72 mL, 4.1 mmol). The mixture was stirred for 2 hours, diluted with ethyl acetate, washed with brine three times, and concentrated

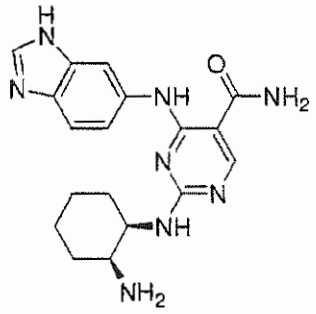
in vacuo to give crude compound **208.2** as a light brown solid in quantitative yield. MS found for $C_{16}H_{13}ClN_4O_2$ as $(M+H)^+$ 329.1.

[0634] Step 2: Ethyl ester **208.2** (2.3 mmol) was dissolved in 30 mL THF. To it were added lithium hydroxide hydrate (193 mg, 4.6 mmol) and 6 mL water. The mixture was stirred for 7 hours and to it was carefully added 1N HCl solution till pH reaching 5. The mixture was concentrated in vacuo to remove THF and was extracted with ethyl acetate 5 times. The organic phases were combined, dried and concentrated in vacuo to give crude acid **208.3**. MS found for $C_{14}H_9ClN_4O_2$ as $(M+H)^+$ 301.1.

[0635] Step 3: Carboxylic acid **208.3** (220 mg, 0.73 mmol) was dissolved in 18 mL NMP. To it were added EDC hydrochloride (210 mg, 1.1 mmol) and HOBt hydrate (150 mg, 1.1 mmol). The mixture was stirred at RT for 1 hour. To it was then added ammonia (commercial 0.5N solution in dioxane, 7.3 mL, 3.65 mmol). The mixture was stirred for 2.5 hours. It was then concentrated in vacuo and taken into water and ethyl acetate. The organic phase was separated and washed with brine three times. The organic phase was then dried over $MgSO_4$ and concentrated in vacuo to afford compound **208.4** as a solid (180 mg, 62%). MS found for $C_{20}H_{14}N_8O_2$ as $(M+H)^+$ 399.1.

[0636] Step 6: Compound **208.4** (72 mg, 0.18 mmol) was dissolved in 3 mL NMP. To it was added cis-1,2-diaminocyclohexane (100 µL, 0.90 mmol). The mixture was stirred for 90 minutes at 90°C bath. This mixture was then subjected to preparative HPLC to isolate the racemic title compound **208**. MS found for $C_{20}H_{23}N_7O$ as $(M+H)^+$ 378.2. UV λ=241, 283 nm.

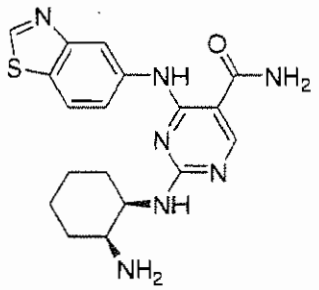
Example 133. 4-(1H-benzo[d]imidazol-6-ylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



[0637] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 132 with tert-butyl 6-amino-1H-benzo[d]imidazole-1-carboxylate

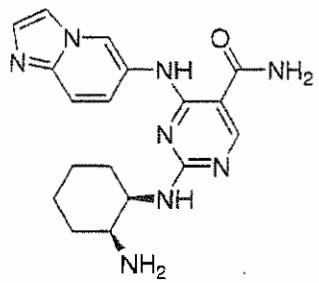
to replace 6-aminoquinoline **208.1**. MS found for $C_{18}H_{22}N_8O$ as $(M+H)^+$ 367.2. UV λ=243, 294 nm.

Example 134. 2-((1R,2S)-2-aminocyclohexylamino)-4-(benzo[d]thiazol-5-ylamino)pyrimidine-5-carboxamide



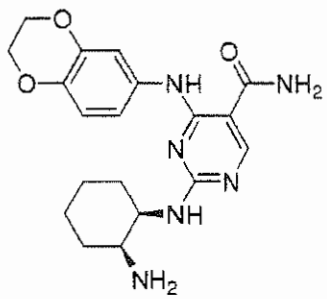
[0638] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 126 with 5-aminobenzothiazole to replace 6-aminoindazole **202.4**. MS found for $C_{18}H_{21}N_7OS$ as $(M+H)^+$ 384.2. UV λ=246, 292 nm.

Example 135. 2-((1R,2S)-2-aminocyclohexylamino)-4-(imidazo[1,2-a]pyridin-6-ylamino)pyrimidine-5-carboxamide



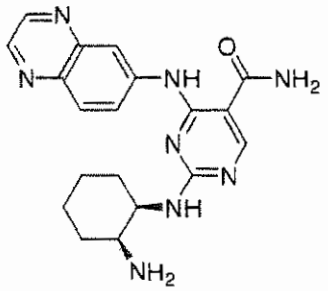
[0639] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 126 with imidazo[1,2-a]pyridin-6-amine to replace 6-aminoindazole **202.4**. MS found for $C_{18}H_{22}N_8O$ as $(M+H)^+$ 367.2. UV λ=250 nm.

Example 136. 2-((1R,2S)-2-aminocyclohexylamino)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-ylamino)pyrimidine-5-carboxamide



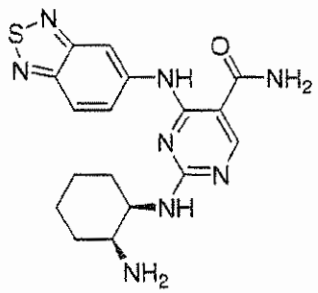
[0640] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 132 with 2,3-dihydrobenzo[b][1,4]dioxin-6-amine to replace 6-aminoquinoline **208.1**. MS found for $C_{20}H_{23}N_7O$ as $(M+H)^+$ 385.2. UV λ=240, 294 nm. NMR (CD_3OD): δ 8.45 (s, 1H), 7.31 (d, J=2.4Hz, 1H), 6.91 (dd, J=8.4, 2.0 Hz, 1H), 6.85 (d, J=8.8 Hz, 1H), 4.27 (m, 5H), 3.79 (m, 1H), 1.94-1.58 (m, 8H) ppm.

Example 137. 2-((1R,2S)-2-aminocyclohexylamino)-4-(quinoxalin-6-ylamino)pyrimidine-5-carboxamide



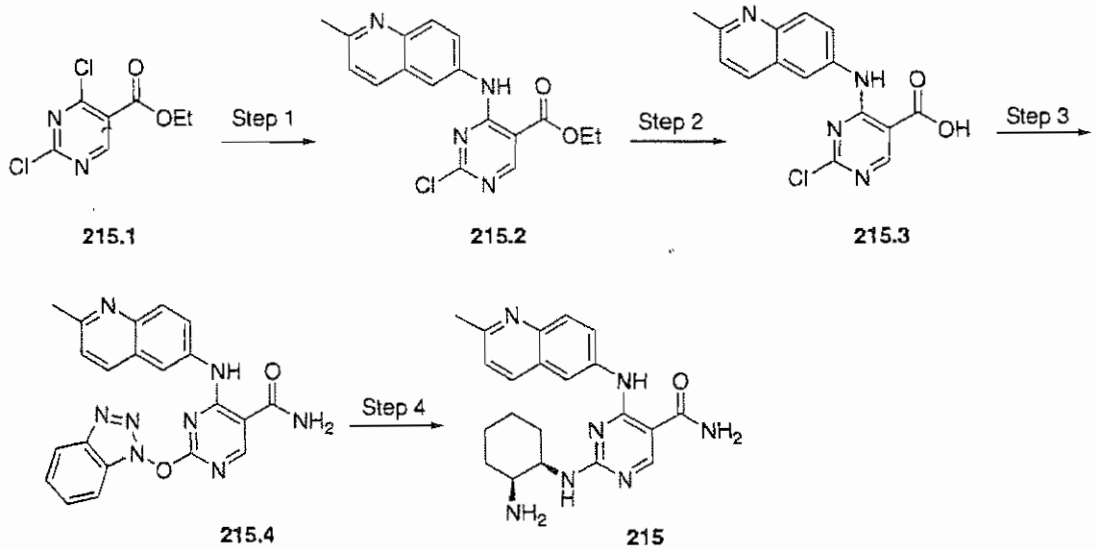
[0641] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 126 with 6-aminoquinoxaline to replace 6-aminoindazole **202.4**. MS found for $C_{19}H_{22}N_8O$ as $(M+H)^+$ 379.2. UV λ=242 nm. NMR (CD_3OD): δ 8.87 (s, 1H), 8.82 (s, 1H), 8.74 (m, 1H), 8.61 (s, 1H), 8.10 (d, J=8.8 Hz, 1H), 7.87 (d, J=8.4 Hz, 1H), 4.54 (m, 1H), 3.82 (m, 1H), 1.99-1.62 (m, 8H) ppm.

Example 138. 2-((1R,2S)-2-aminocyclohexylamino)-4-(benzo[c][1,2,5]thiadiazol-5-ylamino)pyrimidine-5-carboxamide



[0642] The above racemic compound was prepared using the same synthetic scheme demonstrated in Example 132 with 2,1,3-benzothiadiazole-5-amine to replace 6-aminoquinoline **208.1**. MS found for $C_{17}H_{20}N_8OS$ as $(M+H)^+$ 385.2. UV λ=243 nm. NMR (CD_3OD): δ 8.73 (m, 1H), 8.60 (s, 1H), 7.96 (m, 1H), 7.63 (dd, J=9.6, 2.0 Hz, 1H), 4.48 (m, 1H), 3.87 (m, 1H), 1.98-1.63 (m, 8H) ppm.

Example 139. 2-((1R,2S)-2-aminocyclohexylamino)-4-(2-methylquinolin-6-ylamino)pyrimidine-5-carboxamide



[0643] Step 1: To a solution of Dichloropyrimidine **215.1** (700 mgs, 3.16 mmol) in acetonitrile (8 mL) was added a suspension of 6-amino-2-methylquinoline (500 mgs, 3.16 mmol), diisopropylamine (0.61 mL, 3.5 mmol) in acetonitrile (10 mL) at 0 °C. Reaction mixture was then slowly warmed to rt and stirred overnight. The reaction mixture was then diluted with water and the precipitate collected by filtration affording the desired product **215.2** (964 mgs, 89%). MS found for $C_{17}H_{15}ClN_4O_2$ as $(M+H)^+$ 343.1.

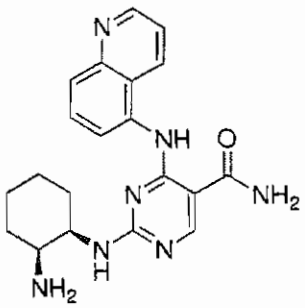
[0644] Step 2: Ethyl ester **215.2** (960 mgs, 2.81 mmol) was diluted with 1,4-dioxane (7.5 mL) and ethanol (2 mL), followed by aqueous lithium hydroxide (1.0 M, 2.8 mL, 2.8 mmol) and stirred at rt until all starting material had been converted to the carboxylic acid. The reaction was then diluted with and acidified with 1N HCl (3.0 mL). The resulting suspension was then filtered, washed with water and dried giving 870 mgs of the carboxylic acid **215.3** (98%). MS found for $C_{15}H_{11}ClN_4O_2$ as $(M+H)^+$ 316.1.

[0645] Step 3: To carboxylic acid **215.3** (870 mgs, 2.76 mmol), EDC (792 mgs, 4.14 mmol), HOBt (560 mgs, 4.14 mmol) in N,N-dimethylformamide (14 mL) was added ammonia (0.5 M in 1,4-dioxane, 14 mL, 6.9 mmol) and stirred overnight. The reaction mixture was then diluted with water (100 mL) and the precipitate collected by filtration affording the desired product **215.4** (1.10 g, 97%). MS found for $C_{21}H_{16}N_8O_2$ as $(M+H)^+$ 413.1.

[0646] Step 4: A mixture of Benzotriazolyl ether **215.4** (75 mgs, 0.182 mmol), cis-1,2-diaminocyclohexane (25 mgs, 0.218 mmol), DIPEA (0.1 mL, 0.546 mmol) in iso-propanol (3 mL) was heated in microwave (Emry's Optimizer) at 130°C for 20 min.

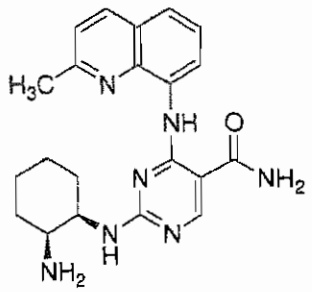
[0647] The reaction mixture was then diluted with water and acetonitrile and directly purified by preparative HPLC affording the desired product, **215**, after lyophilization. MS found for $C_{21}H_{25}N_7O$ as $(M+H)^+$ 392.2.

Example 140. 2-((1R,2S)-2-aminocyclohexylamino)-4-(quinolin-5-ylamino)pyrimidine-5-carboxamide



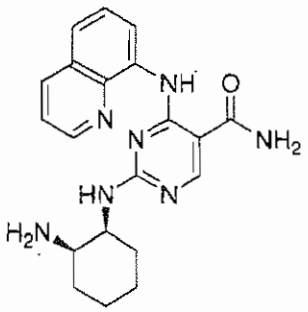
[0648] The above compound was prepared using 5-Aminoquinoline using a procedure similar to that described in Example 129. MS found for $C_{20}H_{23}N_7O$ as $(M+H)^+$ 378.3.

Example 141. 2-((1R,2S)-2-aminocyclohexylamino)-4-(2-methylquinolin-8-ylamino)pyrimidine-5-carboxamide



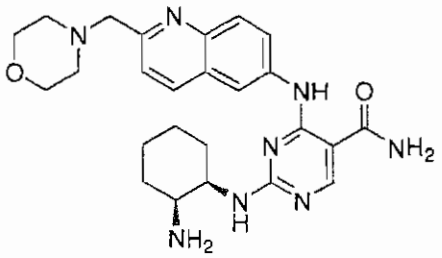
[0649] The above compound was prepared using 8-Amino-2-methylquinoline using a procedure similar to that described in Example 140. MS found for $C_{21}H_{25}N_7O$ as $(M+H)^+$ 392.3.

Example 142. 2-((1S,2R)-2-aminocyclohexylamino)-4-(quinolin-8-ylamino)pyrimidine-5-carboxamide



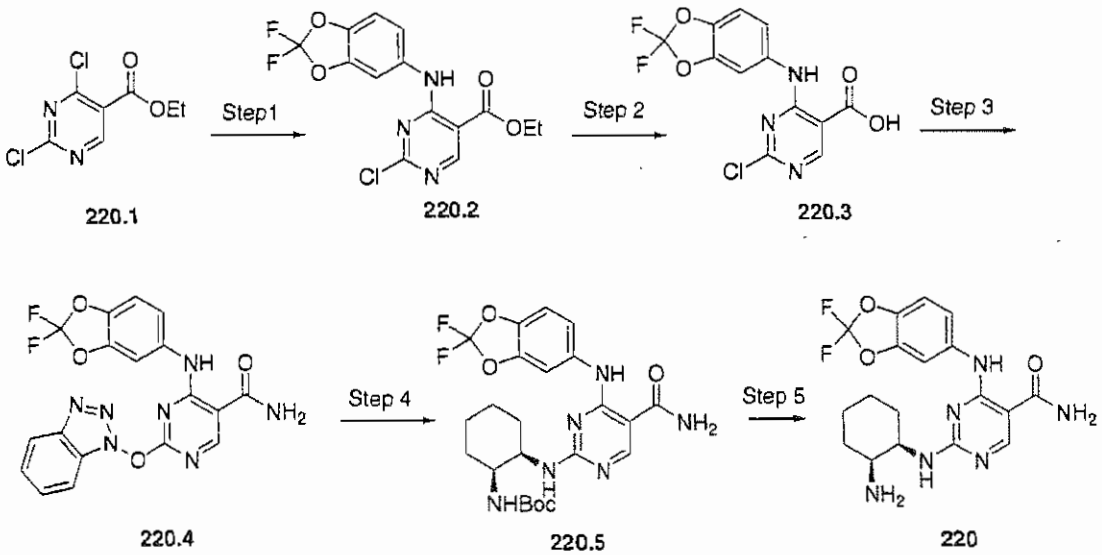
[0650] The above compound was prepared using 8-Aminoquinoline using a procedure similar to that described in Example 139. MS found for $C_{20}H_{23}N_7O$ as $(M+H)^+$ 378.3.

Example 143. 2-((1R,2S)-2-aminocyclohexylamino)-4-(2-(morpholinomethyl)quinolin-6-ylamino)pyrimidine-5-carboxamide



The above compound was prepared using 2-(morpholinomethyl)quinolin-6-amine (*J. Med.Chem* **2006**, *49*, 7095) using a procedure similar to that described in Example 139. MS found for $C_{25}H_{32}N_8O_2$ as $(M+H)^+$ 477.4.

Example 144. 2-((1R,2S)-2-aminocyclohexylamino)-4-(2,2-difluorobenzo[d][1,3]dioxol-5-ylamino)pyrimidine-5-carboxamide



[0651] Step 1: To a solution of Dichloropyrimidine **220.1** (700 mgs, 3.16 mmol) in acetonitrile (10 mL) was added a suspension of 2,2-difluoro-5-aminobenzodioxole (549 mgs, 3.16 mmol), diisopropylamine (0.61 mL, 3.5 mmol) in acetonitrile (5 mL) at 0 °C. Reaction mixture was then slowly warmed to rt and stirred overnight. The reaction mixture was then diluted with water (50 mL) and the precipitate collected by filtration affording the desired product **220.2** (1.03 g, 91%). MS found for $C_{14}H_{10}Cl\ F_2N_3O_4$ as $(M+H)^+$ 358.1.

[0652] Step 2: Ethyl ester **220.2** (1.03 g, 2.9 mmol) was diluted with 1,4-dioxane (7.5 mL) followed by aqueous lithium hydroxide (1.0 M, 2.9 mL, 2.9 mmol) and stirred at rt until all starting material had been converted to the carboxylic acid. The reaction was then diluted with water (20 mL) and acidified with 1N HCl (3.6 mL). The resulting suspension was then filtered, washed with water and dried giving 950 mgs of the carboxylic acid **220.3** (99%). MS found for $C_{12}H_6Cl\ F_2N_3O_4$ as $(M+H)^+$ 330.0.

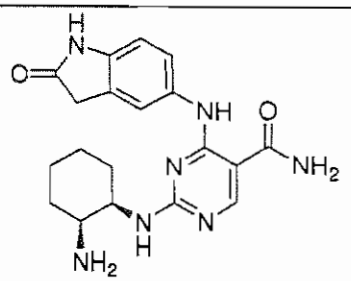
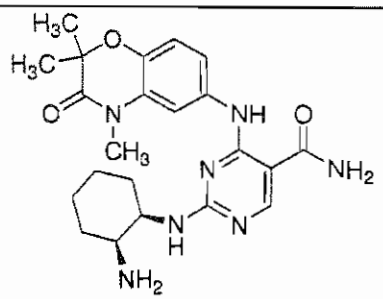
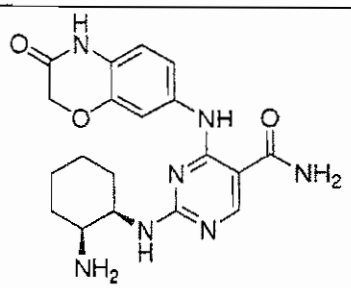
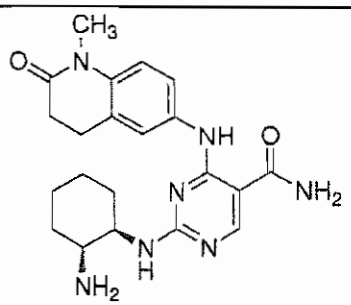
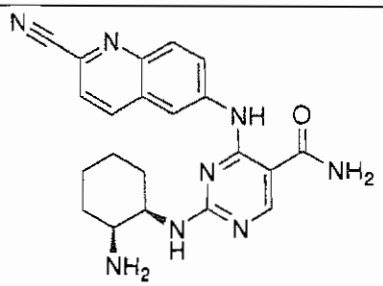
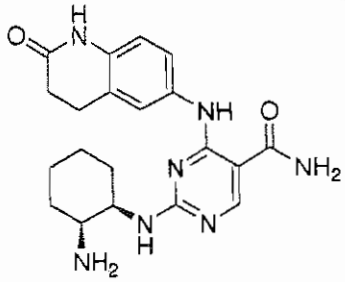
[0653] Step 3: To carboxylic acid **220.3** (950 mgs, 2.89 mmol), EDC (828 mgs, 4.33 mmol), HOBt (663 mgs, 4.33 mmol) in N,N-dimethylformamide (14 mL) was added ammonia (0.5 M in 1,4-dioxane, 14 mL, 6.9 mmol) and stirred overnight. The reaction mixture was then diluted with water (60 mL) and the precipitate collected by filtration affording the desired product **220.4** (1.26 g, 99%). MS found for $C_{18}H_{11}F_2N_7O_4$ as $(M+H)^+$ 428.2.

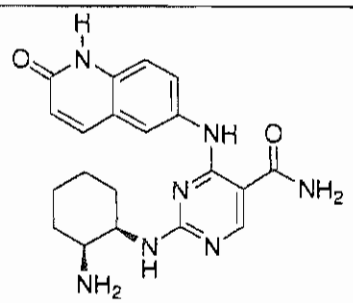
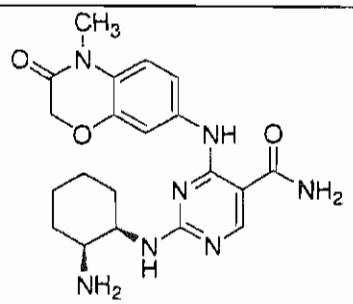
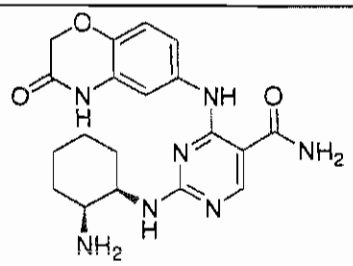
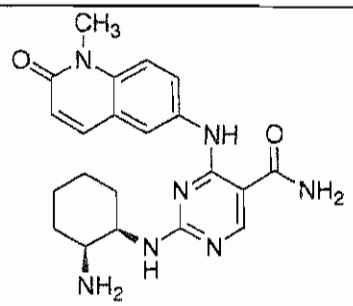
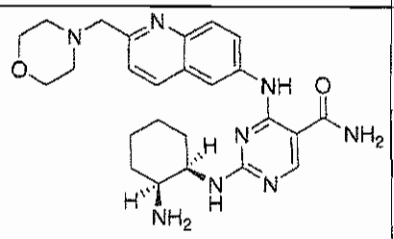
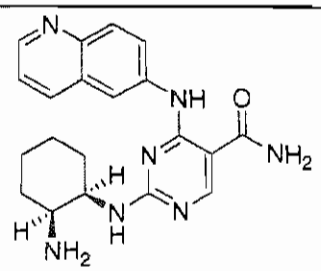
[0654] Step 4 and Step 5: A mixture of Benzotriazolyl ether **220.4** (75 mgs, 0.176 mmol), *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (45 mgs, 0.211 mmol), DIPEA (0.1 mL, 0.530 mmol) in iso-propanol (3 mL) was heated in microwave (Emry's Optimizer) at 130°C for 20 min. The reaction mixture was concentrated and then was treated with 4.0M HCl in dioxane (5.0 mL). After 1h at rt, concentrate the reaction mixture and diluted with water and acetonitrile and directly purified by preparative HPLC affording the desired product **220**, after lyophilization. MS found for $C_{18}H_{20}F_2N_6O_3$ as $(M+H)^+$ 407.28.

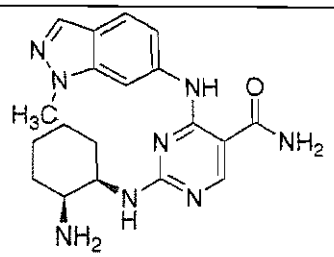
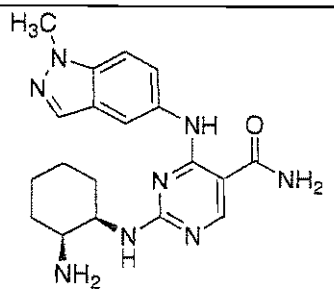
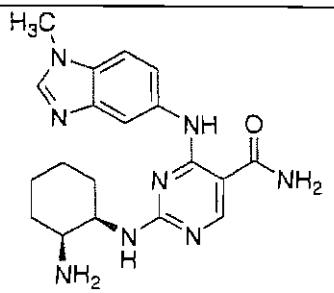
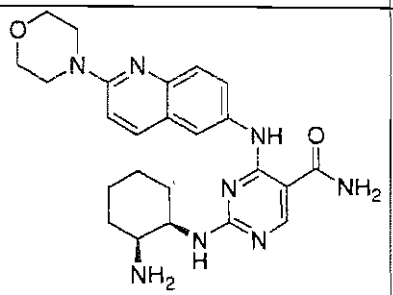
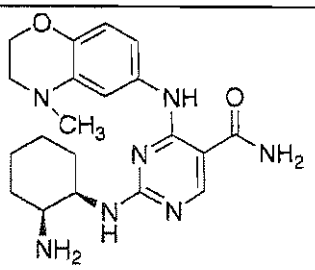
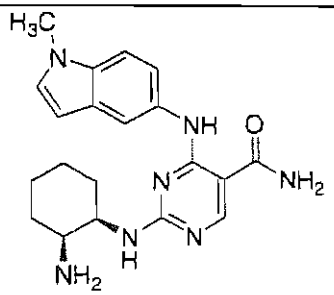
Example 145 The following compounds were prepared using a procedure similar to that described in Example 143.

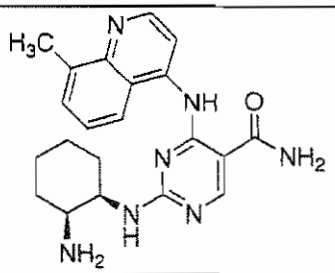
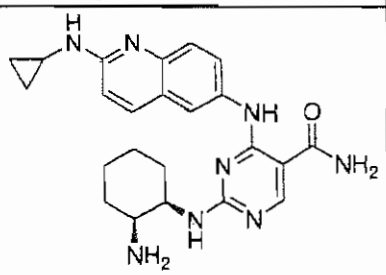
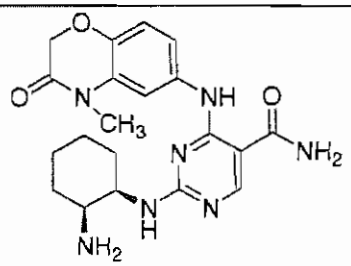
Table 1.

Ex No	Structure	MW	MS	Name

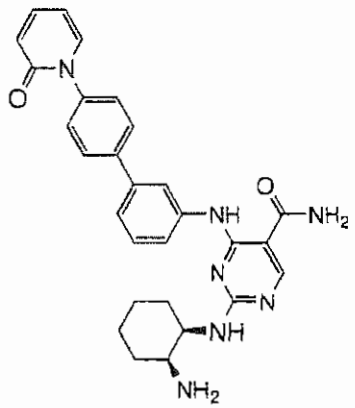
146		381.44	382.35	2-((1R,2S)-2-aminocyclohexylamino)-4-(2-oxoindolin-5-ylamino)pyrimidine-5-carboxamide
147		439.52	440.38	2-((1R,2S)-2-aminocyclohexylamino)-4-(2,2,4-trimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)pyrimidine-5-carboxamide
148		397.439	398.31	2-((1R,2S)-2-aminocyclohexylamino)-4-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-ylamino)pyrimidine-5-carboxamide
149		409.494	410.36	2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylamino)pyrimidine-5-carboxamide
150		402.462	403.32	2-((1R,2S)-2-aminocyclohexylamino)-4-(2-cyanoquinolin-6-ylamino)pyrimidine-5-carboxamide
151		395.467	396.35	2-((1R,2S)-2-aminocyclohexylamino)-4-(2-oxo-1,2,3,4-tetrahydroquinolin-6-ylamino)pyrimidin

				e-5-carboxamide
152		393.451	394.14	2-((1R,2S)-2-aminocyclohexylamino)-4-(2-oxo-1,2-dihydroquinolin-6-ylamino)pyrimidine-5-carboxamide
153		411.466	412.5	2-((1R,2S)-2-aminocyclohexylamino)-4-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-ylamino)pyrimidine-5-carboxamide
154		397.439	398.5	2-((1R,2S)-2-aminocyclohexylamino)-4-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)pyrimidine-5-carboxamide
155		407.478	408.6	2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-2-oxo-1,2-dihydroquinolin-6-ylamino)pyrimidine-5-carboxamide
156		476.585	477.6	2-((1R,2S)-2-aminocyclohexylamino)-4-(2-(morpholinomethyl)quinolin-6-ylamino)pyrimidine-5-carboxamide
157		377.452	378.5	2-((1R,2S)-2-aminocyclohexylamino)-4-(quinolin-6-ylamino)pyrimidine-5-carboxamide

158		380.46	381.1.	2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-1H-indazol-6-ylamino)pyrimidine-5-carboxamide
159		380.46	381.1	2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-1H-indazol-5-ylamino)pyrimidine-5-carboxamide
160		380.46	381.1	2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-1H-benzo[d]imidazol-5-ylamino)pyrimidine-5-carboxamide
161		462.56	463.3	2-((1R,2S)-2-aminocyclohexylamino)-4-(2-morpholinoquinolin-6-ylamino)pyrimidine-5-carboxamide
162		397.49	398.2	2-((1R,2S)-2-aminocyclohexylamino)-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)pyrimidine-5-carboxamide
163		379.47	380.4	2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-1H-indol-5-ylamino)pyrimidine-5-carboxamide

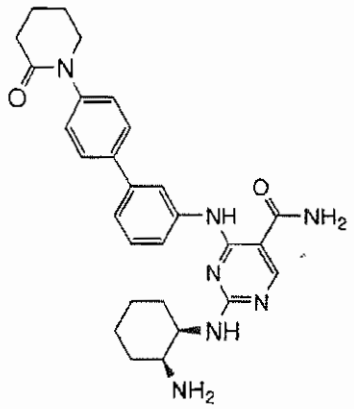
164		391.48	392.2	2-((1R,2S)-2-aminocyclohexylamino)-4-(8-methylquinolin-4-ylamino)pyrimidine-5-carboxamide
165		432.53	433.2	2-((1R,2S)-2-aminocyclohexylamino)-4-(2-(cyclopropylamino)quinolin-6-ylamino)pyrimidine-5-carboxamide
166		411.47	412.2	2-((1R,2S)-2-aminocyclohexylamino)-4-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)pyrimidine-5-carboxamide

Example 167. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4'-(2-oxopyridin-1(2H)-yl)biphenyl-3-ylamino)pyrimidine-5-carboxamide



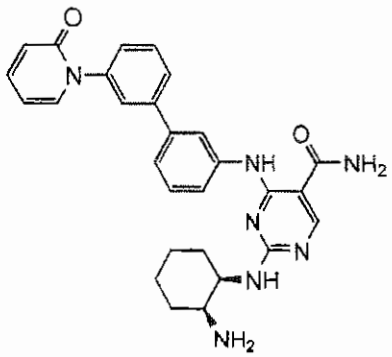
[0655] The title compound was prepared using the same synthetic scheme demonstrated in Example 120. MS found for $C_{28}H_{29}N_7O_2$ as $(M+H)^+$ 496.5. UV λ=245 nm. NMR (CD_3OD): δ 8.51 (s, 1H), 8.12 (s, 1H), 7.79 (d, J=8.8 Hz, 2H), 7.63 (m, 2H), 7.55-7.49 (m, 5H), 6.65 (m, 1H), 6.50 (m, 1H), 4.25 (m, 1H), 3.58 (m, 1H), 2.54 (t, 2H), 1.84-1.40 (m, 8H) ppm.

Example 168. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4'-(2-oxopiperidin-1-yl)biphenyl-3-ylamino)pyrimidine-5-carboxamide



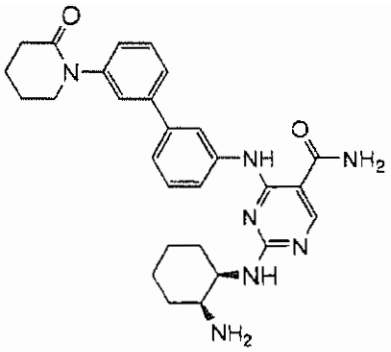
[0656] The title compound was prepared using the same synthetic scheme demonstrated in Example 120. MS found for $C_{28}H_{33}N_7O_2$ as $(M+H)^+$ 500.5. UV λ=249 nm. NMR (CD_3OD): δ 8.50 (s, 1H), 8.09 (s, 1H), 7.68 (d, J=8.8 Hz, 2H), 7.49-7.43 (m, 3H), 7.36 (d, J=8.4 Hz, 2H), 4.21 (m, 1H), 3.71 (t, 2H), 3.57 (m, 1H), 2.54 (t, 2H), 1.98 (m, 4H), 1.83-1.36 (m, 8H) ppm.

Example 169. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3'-(2-oxopyridin-1(2H)-yl)biphenyl-3-ylamino)pyrimidine-5-carboxamide



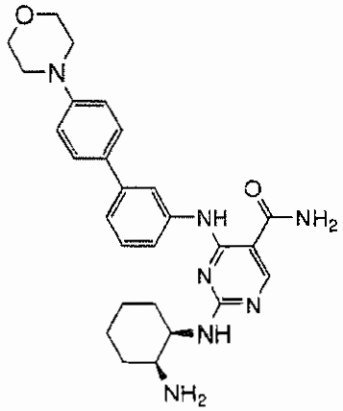
[0657] The title compound was prepared using the same synthetic scheme demonstrated in Example 120. MS found for $C_{28}H_{29}N_7O_2$ as $(M+H)^+$ 496.5. UV λ=244 nm.

Example 170 2. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3'-(2-oxopiperidin-1-yl)biphenyl-3-ylamino)pyrimidine-5-carboxamide



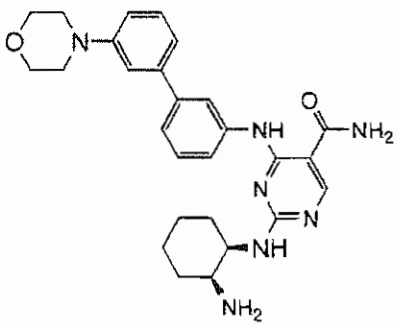
[0658] The title compound was prepared using the same synthetic scheme demonstrated in Example 120. MS found for $C_{28}H_{33}N_7O_2$ as $(M+H)^+$ 500.5. UV λ=246 nm.

Example 171. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4'-morpholinobiphenyl-3-ylamino)pyrimidine-5-carboxamide



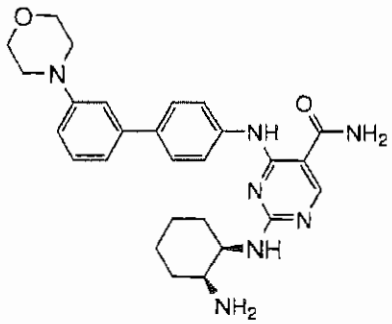
[0659] The title compound was prepared using the same synthetic scheme demonstrated in Example 120. MS found for $C_{27}H_{33}N_7O_2$ as $(M+H)^+$ 488.4. UV λ=247 nm.

Example 172. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3'-morpholinobiphenyl-3-ylamino)pyrimidine-5-carboxamide



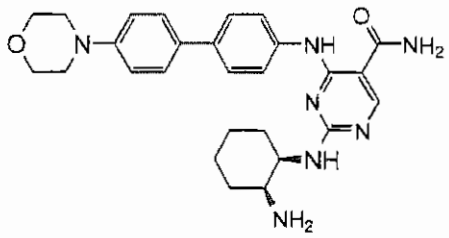
[0660] The title compound was prepared using the same synthetic scheme demonstrated in Example 120. MS found for $C_{27}H_{33}N_7O_2$ as $(M+H)^+$ 488.4. UV λ=246 nm.

Example 173. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3'-morpholinobiphenyl-4-ylamino)pyrimidine-5-carboxamide



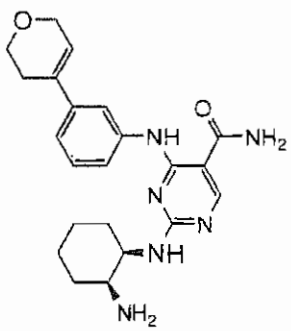
[0661] The title compound was prepared using the same synthetic scheme demonstrated in Example 120. MS found for $C_{27}H_{33}N_7O_2$ as $(M+H)^+$ 488.4. UV λ=238, 309 nm.

Example 174. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4'-morpholinobiphenyl-4-ylamino)pyrimidine-5-carboxamide

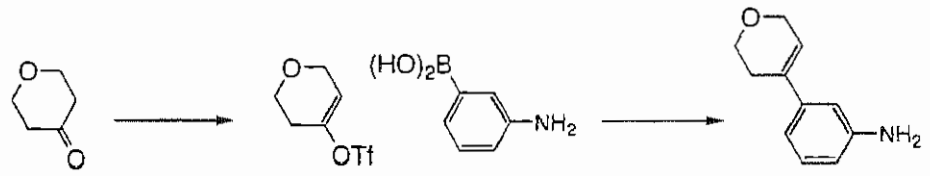


[0662] The title compound was prepared using the same synthetic scheme demonstrated in Example 120. MS found for $C_{27}H_{33}N_7O_2$ as $(M+H)^+$ 488.4. UV λ=241, 314 nm.

Example 175. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(3,6-dihydro-2H-pyran-4-yl)phenylamino)pyrimidine-5-carboxamide



Scheme:



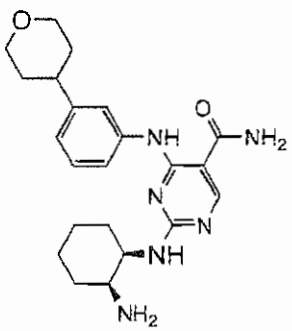
257.1 257.2 257.3 257.4

[0663] Diisopropylamine (1.63 mL, 11.68 mmol) was dissolved in 10 mL dry THF and stirred in ice bath. To it was added n-buthyl lithium (2.5 M in hexane, 4.67 mL, 11.68 mmol) dropwise. The mixture was stirred for 20 min, and sent to -78°C bath. To it was added the solution of ketone 257.1 (0.92 mL, 10 mmol) in 10 mL THF dropwise. The mixture was stirred for 30 min. To it was added the solution of N-phenylbis(trifluoromethanesulfonimide) ($PhNTf_2$, 4.17 g, 11.68 mmol) in 10 mL THF. The mixture was moved to ice bath and stirred for overnight. It was concentrated in vacuo and subjected to silica flash column to isolate compound 257.2 using 20% ethyl acetate in hexane.

[0664] Compound 257.2 (920 mg, 4.0 mmol) was mixed with boronic acid 257.3 (550 mg, 4.0 mmol), $Pd(Ph_3P)_2Cl_2$ (562 mg, 0.8 mmol), K_2CO_3 (1.1 g, 8.0 mmol) in 30 mL dioxane and 15 mL water. The mixture was degassed using argon stream for 3 min and stirred under argon at 85°C for 3.5 h. The mixture was diluted with ethyl acetate, washed with brine x2, dried, concentrated and subjected to flash column to isolate aniline 257.4 (300 mg) as white solid.

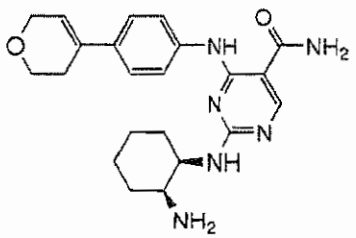
[0665] The title compound was prepared with aniline 257.4 using the same synthetic scheme demonstrated in Example 120. MS found for $C_{22}H_{28}N_6O_2$ as $(M+H)^+$ 409.4. UV λ=246 nm.

Example 176. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(tetrahydro-2H-pyran-4-yl)phenylamino)pyrimidine-5-carboxamide



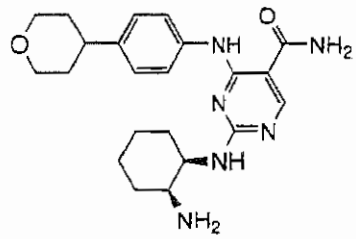
[0666] The title compound was prepared from Example 175 using standard catalysis hydrogenation by treating the solution of Example 175 in methanol with 10% Pd/C under H_2 balloon for overnight. MS found for $C_{22}H_{30}N_6O_2$ as $(M+H)^+$ 411.4. UV λ=241, 290 nm.

Example 177. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(3,6-dihydro-2H-pyran-4-yl)phenylamino)pyrimidine-5-carboxamide



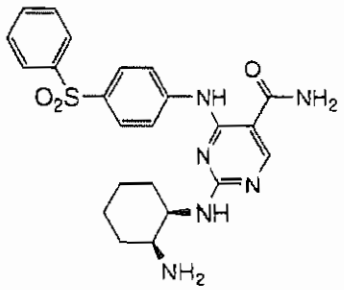
[0667] The title compound was made using the similar chemistry shown for Example 175. MS found for $C_{22}H_{28}N_6O_2$ as $(M+H)^+$ 409.4. UV λ=239, 309 nm. NMR (CD_3OD): δ 8.51 (s, 1H), 7.60 (d, J=7.2 Hz, 2H), 7.50 (d, J=8.0 Hz, 2H), 6.23 (s, 1H), 4.36-4.30 (m, 3H), 3.94 (t, 2H), 3.72 (m, 1H), 2.53 (m, 2H), 1.90-1.58 (m, 8H) ppm.

Example 178. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(tetrahydro-2H-pyran-4-yl)phenylamino)pyrimidine-5-carboxamide



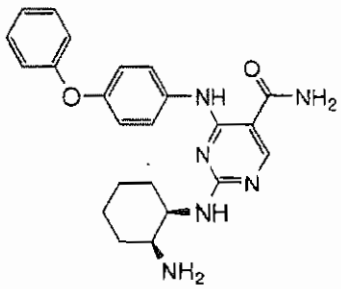
[0668] The title compound was prepared from Example 175 using standard catalysis hydrogenation by treating the solution of Example 175 in methanol with 10% Pd/C under H_2 balloon for overnight. MS found for $C_{22}H_{30}N_6O_2$ as $(M+H)^+$ 411.4. UV λ=243, 296 nm.

Example 179. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(phenylsulfonyl)phenylamino)pyrimidine-5-carboxamide



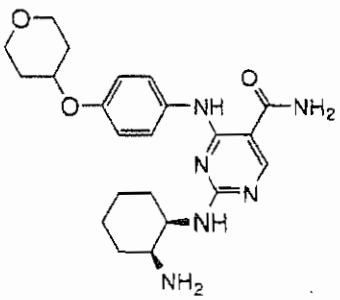
[0669] The title compound was prepared using the same synthetic scheme demonstrated in Example 120 with the corresponding aniline which was commercially available. MS found for $C_{23}H_{26}N_6O_3S$ as $(M+H)^+$ 467.3. UV λ=232, 306 nm.

Example 180. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-phenoxyphenylamino)pyrimidine-5-carboxamide



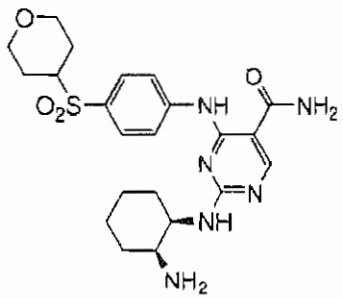
[0670] The title compound was prepared using the same synthetic scheme demonstrated in Example 120 with the corresponding aniline which was commercially available. MS found for $C_{23}H_{26}N_6O_2$ as $(M+H)^+$ 419.3. UV λ=238, 290 nm.

Example 181a. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(tetrahydro-2H-pyran-4-yloxy)phenylamino)pyrimidine-5-carboxamide

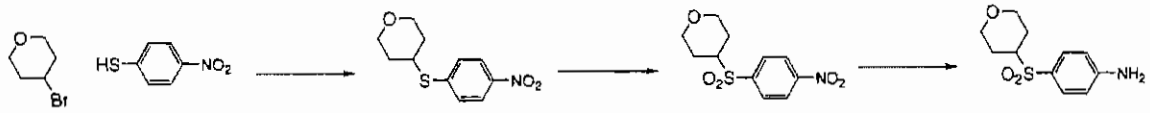


[0671] The title compound was prepared using the same synthetic scheme demonstrated in Example 120 with the corresponding aniline which was commercially available. MS found for $C_{22}H_{30}N_6O_3$ as $(M+H)^+$ 427.3. UV λ=241, 291 nm.

Example 181b. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(tetrahydro-2H-pyran-4-ylsulfonyl)phenylamino)pyrimidine-5-carboxamide



Scheme:



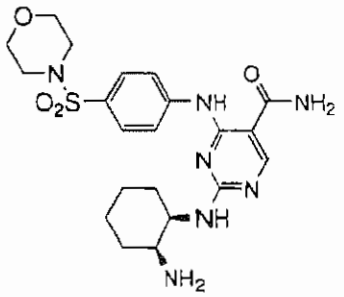
266.1 266.2 266.3

[0672] 4-Nitrothiophenol (400 mg, 2.55 mmol) was dissolved in 10 mL DMF. To it were added cesium carbonate (1.67 g, 5.1 mmol) and 4-bromotetrahydropyran (0.84 g, 5.1 mmol). The mixture was stirred at 50°C for 90 min. It was diluted in ethyl acetate and washed with brine x3. The organic phase was dried, concentrated in vacuo to afford crude compound 266.1. It was dissolved in 100 mL DCM. To it was adde MCPBA (1.98 g, 7.5 mmol) in small portions. The mixture was stirred for 30 min, diluted with ethyl acetate, washed with sat sodium carbonate solution and brine. The organic phase was dried, concentrated and subjected to silica flash column to isolate compound 266.2 (320 mg, 47% for 2 steps) using 1:1 ethyl acetate and hexane.

[0673] Compound 266.2 (320 mg, 1.18 mmol) was dissolved in 150 mL ethyl acetate. To it was added 200 mg 10% Pd/C. The mixture was stirred under H_2 balloon for overnight. The mixture was filtered through celite. The celite was thoroughly washed. The filtrate was concentrated in vacuo to afford aniline 266.3 (260 mg, 91%) as white solid.

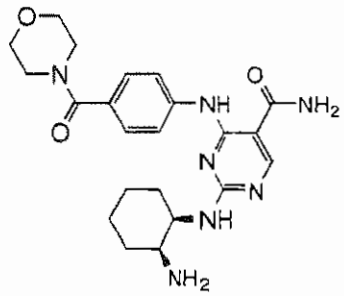
[0674] The title compound was prepared using the same synthetic scheme demonstrated in Example 120 with aniline 266.3. MS found for $C_{22}H_{30}N_6O_4S$ as $(M+H)^+$ 475.3. UV λ=250, 301 nm.

Example 182. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(morpholinosulfonyl)phenylamino)pyrimidine-5-carboxamide



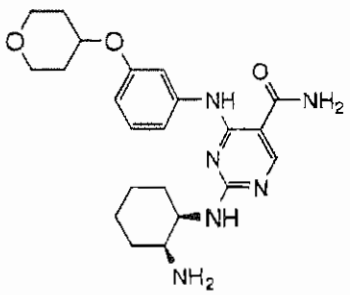
[0675] The title compound was prepared using the same synthetic scheme demonstrated in Example 120 with the corresponding aniline which was commercially available. MS found for $C_{21}H_{29}N_7O_4S$ as $(M+H)^+$ 476.4. UV λ=249, 300 nm.

Example 183. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(morpholine-4-carbonyl)phenylamino)pyrimidine-5-carboxamide

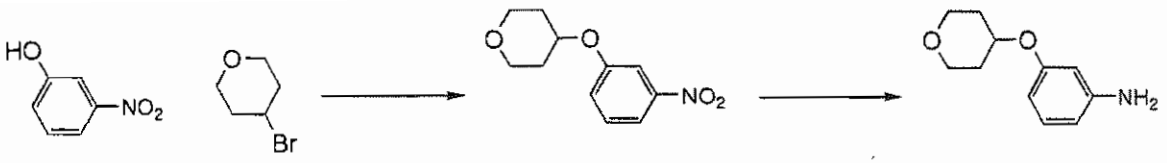


[0676] The title compound was prepared using the same synthetic scheme demonstrated in Example 120 with the corresponding aniline which was commercially available. MS found for $C_{22}H_{29}N_7O_3$ as $(M+H)^+$ 400.4. UV λ=244, 297 nm.

Example 184. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(tetrahydro-2H-pyran-4-yloxy)phenylamino)pyrimidine-5-carboxamide



Scheme:

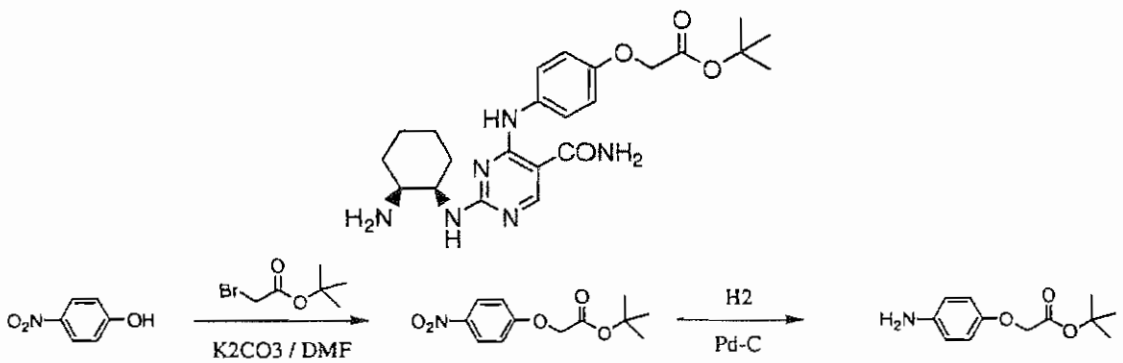


269.1 269.2

[0677] 3-Nitrophenol (500 mg, 3.6 mmol) was dissolved in 15 mL DMF. To it were added cesium carbonate (2.35 g, 7.2 mmol) and then 4-bromotetrahydropyran (2.4 g, 14.4 mmol). The mixture was stirred at 70°C for overnight. The reaction was only 30% completion. It was diluted with ethyl acetate, washed with water, sat sodium carbonate and brine, dried over $MgSO_4$, filtered. To the filtrate containing crude compound 269.1 was added 10% Pd/C 1.0 g. The mixture was stirred under H_2 balloon for overnight. The mixture was filtered, concentrated and purified using silica flash column to afford aniline 269.2 (102 mg, 15% overall yield) as solid.

[0678] The title compound was prepared using the same synthetic scheme demonstrated in Example 120 with aniline 269.2. MS found for $C_{22}H_{30}N_6O_3$ as $(M+H)^+$ 427.4. UV λ=244, 287 nm.

Example 185 tert-butyl 2-(4-(2-((1R,2S)-2-aminocyclohexylamino)-5-carbamoylpyrimidin-4-ylamino)phenoxy)acetate (racemate)

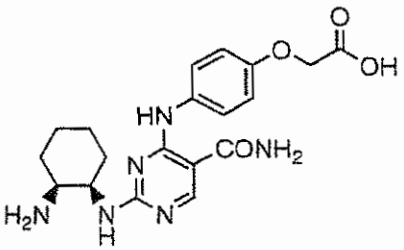


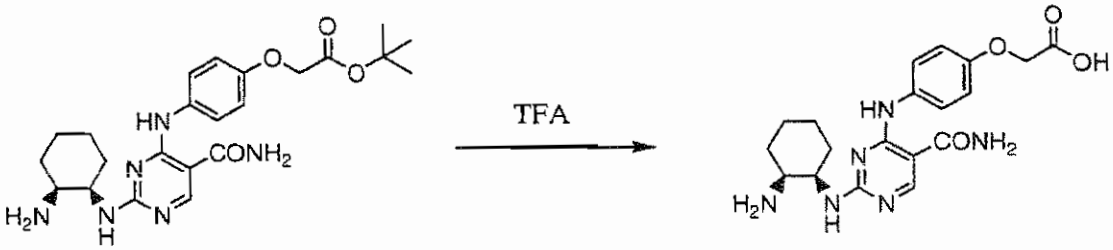
[0679] To a solution of 4-nitrophenol (3.00 g, 21.6 mmol) and K_2CO_3 (6.00 g, 43.4 mmol) in DMF (50 mL), t-butyl bromoacetate (2.90 mL, 19.6 mmol) was added. The mixture was stirred at room temperature for 5 h. Water and EtOAc were added. The organic phase was separated, washed with water, then with aq. 1N NaOH and brine. It was dried over Na_2SO_4, concentrated in vacuo to give tert-butyl 2-(4-nitrophenoxy)acetate as a solid.

[0680] To the solution of the solid in MeOH (40 mL), Pd-C (10%, 410 mg) was added. The mixture was hydrogenated under balloon hydrogen for 20 h. It was then filtered through celite. The filtrate was concentrated in vacuo to give tert-butyl 2-(4-aminophenoxy)acetate.

[0681] The titled compound was synthesized analogously by using tert-butyl 2-(4-aminophenoxy)acetate and cis-1,2-diaminocyclohexane. MS 457.2 (M+H); UV 243.8, 290.0.

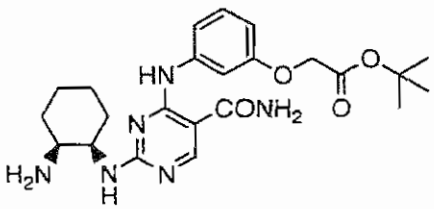
Example 186 2-(4-(2-((1R,2S)-2-aminocyclohexylamino)-5-carbamoylpyrimidin-4-ylamino)phenoxy)acetic acid (racemate)





[0682] A solution of tert-butyl 2-(4-(2-((1R,2S)-2-aminocyclohexylamino)-5-carbamoylpyrimidin-4-ylamino)phenoxy)acetate racemate (180 mg, 0.395 mmol) in TFA (4 mL) was stirred at room temperature for 2 h. It was then concentrated in vacuo. The residue was purified by HPLC to give the titled compound (60 mg). MS 401.2 (M+H).

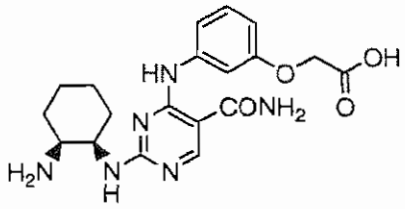
Example 187 tert-butyl 2-(3-(2-((1R,2S)-2-aminocyclohexylamino)-5-carbamoylpyrimidin-4-ylamino)phenoxy)acetate (racemate)



[0683] The titled compound was synthesized analogously as compound tert-butyl 2-(4-(2-((1R,2S)-2-aminocyclohexylamino)-5-carbamoylpyrimidin-4-ylamino)phenoxy)acetate

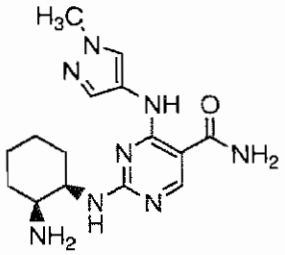
(racemate), by using 3-nitrophenol in place of 4-nitrophenol. MS 457.2 (M+H); UV 242.6, 290.0.

Example 188 2-(3-(2-((1R,2S)-2-aminocyclohexylamino)-5-carbamoylpyrimidin-4-ylamino)phenoxy)acetic acid (racemate)



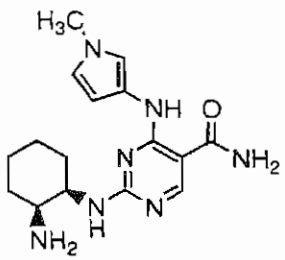
[0684] The titled compound was synthesized analogously as compound 2-(4-(2-((1R,2S)-2-aminocyclohexylamino)-5-carbamoylpyrimidin-4-ylamino)phenoxy)acetic acid (racemate). MS 401.2 (M+H); UV 242.6, 290 nM.

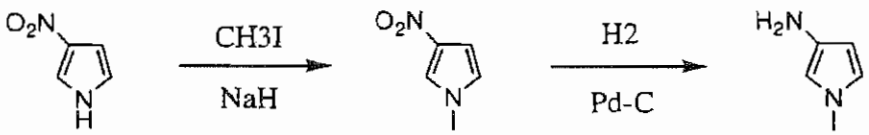
Example 189 2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-1H-pyrazol-4-ylamino)pyrimidine-5-carboxamide



[0685] The titled compound was synthesized analogously by using 1-methyl-1H-pyrazol-4-amine. MS 331.4 (M+H). UV 241.2, 292.1 nm

Example 190 2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-1H-pyrrol-3-ylamino)pyrimidine-5-carboxamide



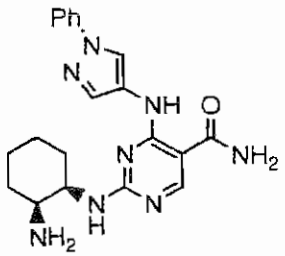


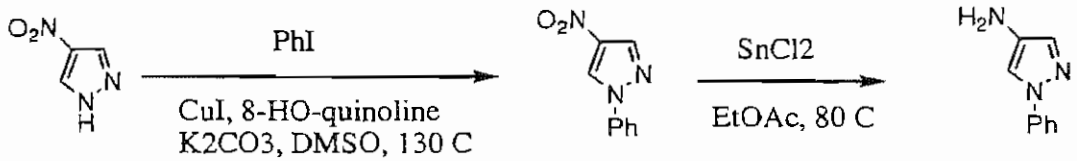
[0686] To sodium hydride (300 mg, 60% in mineral oil, 7.50 mmol) in a flask, which was washed with hexane twice, a solution of 3-nitropyrrole (500 mg, 4.46 mmol) and iodomethane (0.560 mL, 8.97 mmol) in DMF (4 mL) was added. Hydrogen gas evolved. The mixture was then stirred at room temperature for 20 h. Water and EtOAc were added. Organic phase was separated, washed with water, dried over Na_2SO_4, concentrated in vacuo to give 1-methyl-3-nitro-1H-pyrrole (494 mg).

[0687] A mixture of 1-methyl-3-nitro-1H-pyrrole (488 mg, 3.87 mmol) and Pd-C (10%, 110 mg) in MeOH (15 mL) (containing 8 drops 0f 6N HCl) was hydrogenated under ballon hydrogen for 20 h. The mixture was filtered through celite. To the filtrate, 4N HCl in dioxane (2 mL) was added. The solution was concentrated in vacuo to give 1-methyl-1H-pyrrol-3-amine hydrochloride as a solid (514 mg).

[0688] The titled compound was then synthesized analogously by using 1-methyl-1H-pyrrol-3-amine hydrochloride. MS 330.3 (M+H); UV 237.6, 313.1 nm.

Example 191 2-((1R,2S)-2-aminocyclohexylamino)-4-(1-phenyl-1H-pyrazol-4-ylamino)pyrimidine-5-carboxamide





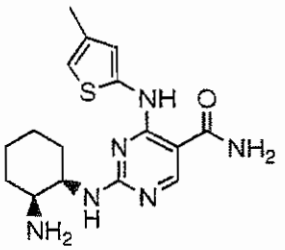
[0689] A mixture of 4-nitropyrazole (270 mg, 2.38 mmol), iodobenzene (485 mg, 2.38 mmol), 8-hydroxyquinoline (60 mg, 0.41 mmol) and K2CO3 (600 mg, 4.34 mmol) in DMSO (3 mL) was degassed with argon before being charged with CuI (45 mg, 0.23 mmol). The mixture in a sealed tube was heated at 130 C for 20 h. Water was added to induce precipitation. The precipitate was collected to give 4-nitro-1-phenyl-1H-pyrazole (454 mg).

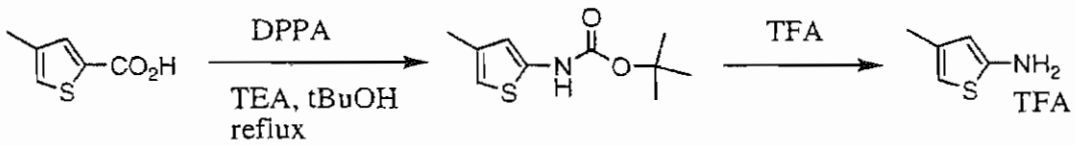
[0690] A mixture of 4-nitro-1-phenyl-1H-pyrazole (440 mg, 2.32 mmol) and SnCl2 dihydrate (2.18 g, 9.66 mmol) in EtOAc (15 mL) was stirred at 80 C for 3 h. Aqueous 1N

NaOH was added to bring pH to 12. The mixture was filtered through celite. The organic phase was separated, dried over Na_2SO_4, concentrated in vacuo. The residue was purified by HPLC to give 1-phenyl-1H-pyrazol-4-amine as a solid (173 mg).

[0691] The titled compound was then synthesized analogously by using 1-phenyl-1H-pyrazol-4-amine. MS 393.4 (M+H); UV 240.0, 303.2.

Example 192 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-methylthiophen-2-ylamino)pyrimidine-5-carboxamide



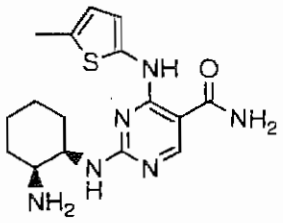


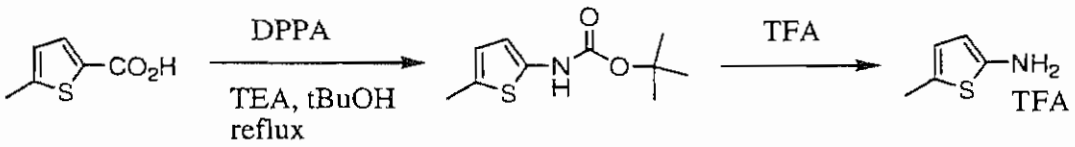
[0692] A solution of 4-methyl thiophene-2-carboxylic acid (1.42 g, 10.0 mmol), triethylamine (1.50 mL, 10.8 mmol) and diphenyl phosporyl azide (2.15 mL, 10.0 mmol) in tBuOH (20 mL) was stirred at reflux for 5 h. tBuOH was removed in vacuo. Et2O and water were added. The organic phase was washed with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo. The residue was purified by a silica gel column, which was eluted with 0-10% EtOAc in hexane to give tert-butyl 4-methylthiophen-2-ylcarbamate as a solid (0.880 g).

[0693] A solution of tert-butyl 4-methylthiophen-2-ylcarbamate (0.880 g, 4.13 mmol) in CH_2Cl_2 (8 mL) and TFA (6 mL) wad stirred at room temperature for 3 h. Solvents was removed in vacuo to give 4-methylthiophen-2-amine as trifluoroacetic acid salt (0.920 g).

[0694] The titled compound was then synthesized analogously by using 4-methylthiophen-2-amine. MS 347.3 (M+H); UV 244.9, 326.1 nm.

Example 193 2-((1R,2S)-2-aminocyclohexylamino)-4-(5-methylthiophen-2-ylamino)pyrimidine-5-carboxamide



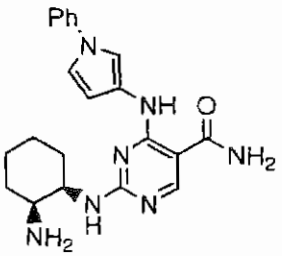


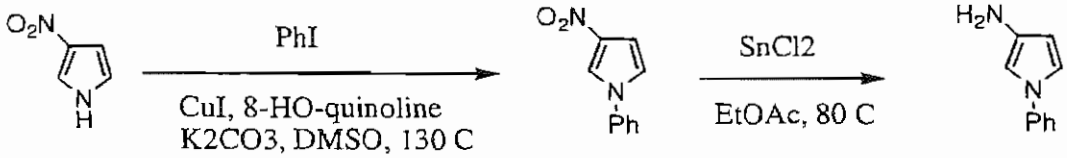
[0695] A solution of 5-methyl thiophene-2-carboxylic acid (1.42 g, 10.0 mmol), triethylamine (1.50 mL, 10.8 mmol) and diphenyl phosporyl azide (2.15 mL, 10.0 mmol) in tBuOH (20 mL) was stirred at reflux for 5 h. tBuOH was removed in vacuo. Et2O and water were added. The organic phase was washed with 5% $NaHCO_3$, then with 1N NaOH, and filtered. The filtrate was dried over Na_2SO_4, concentrated in vacuo to give tert-butyl 5-methylthiophen-2-ylcarbamate as a solid (0.825 g).

[0696] A solution of tert-butyl 5-methylthiophen-2-ylcarbamate (0.825 g, 3.87 mmol) in CH_2Cl_2 (10 mL) and TFA (6 mL) wad stirred at room temperature for 20 h. Solvents was removed in vacuo to give 5-methylthiophen-2-amine as trifluoroacetic acid salt (0.870 g).

[0697] The titled compound was then synthesized analogously by using 5-methylthiophen-2-amine. MS 347.3 (M+H); UV 247.3, 325.6 nm.

Example 194 2-((1R,2S)-2-aminocyclohexylamino)-4-(1-phenyl-1H-pyrrol-3-ylamino)pyrimidine-5-carboxamide



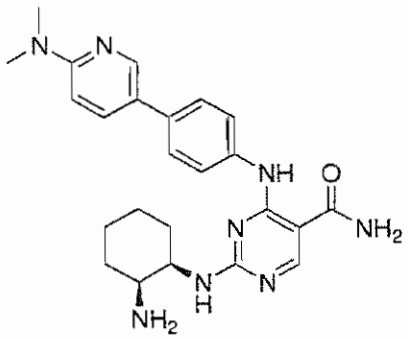


[0698] A mixture of 3-nitropyrrole (270 mg, 2.41 mmol), iodobenzene (0.267 mL, 2.39 mmol), 8-hydroxyquinoline (60 mg, 0.41 mmol) and K2CO3 (600 mg, 4.34 mmol) in DMSO (3 mL) was degassed with argon before being charged with CuI (45 mg, 0.23 mmol). The mixture in a sealed tube was heated at 130 C for 20 h. Water and EtOAc were added. The organic phase was separated, washed with 1N HCl, then with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo to give 3-nitro-1-phenyl-1H-pyrrole (410 mg).

[0699] A mixture of 3-nitro-1-phenyl-1H-pyrrole (410 mg, 2.18 mmol) and SnCl2 dihydrate (2.00 g, 8.86 mmol) in EtOAc (15 mL) was stirred at 80 C for 3 h. Aqueous 1N NaOH was added to bring pH to 12. The mixture was filtered through celite. The organic phase was separated, washed with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo to give 1-phenyl-1H-pyrrol-3-amine as a solid (323 mg).

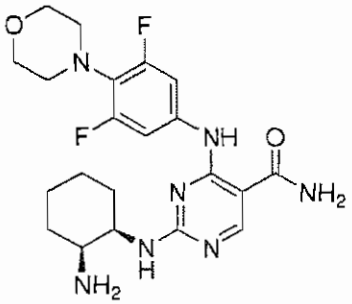
[0700] The titled compound was then synthesized analogously by using 1-phenyl-1H-pyrrol-3-amine. MS 392.4 (M+H); UV 240.0, 314.3 nM.

Example 195 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(6-(dimethylamino)pyridine-3-yl)phenylamino)pyrimidine-5-carboxamide



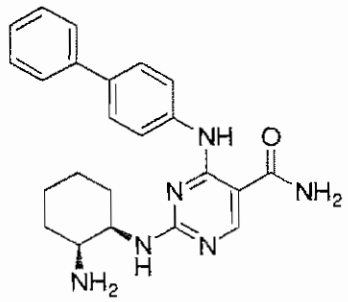
[0701] The title compound was prepared using the same synthetic scheme demonstrated in Example 45 with 6-(dimethylamino)pyridin-3-ylboronic acid to replace boronic acid **116.1**. MS found for $C_{24}H_{30}N_8O$ as $(M+H)^+$ 447.3. UV: λ = 244.0, 316.4

Example 196 2-((1R,2S)-2-aminocyclohexylamino)-4-(3,5-difluoro-4-morpholinophenylamino)pyrimidine-5-carboxamide



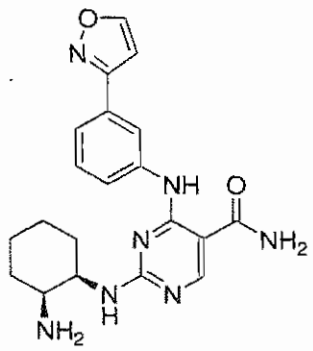
[0702] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with 3,5-difluoro-4-morpholinoaniline to replace aniline **72.4**. MS found for $C_{21}H_{27}F_2N_7O_2$ as $(M+H)^+$ 448.1. UV: λ = 240.4, 304.5.

Example 197 2-((1R,2S)-2-aminocyclohexylamino)-4-(biphenyl-4-ylamino)pyrimidine-5-carboxamide



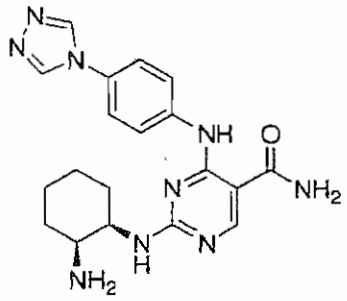
[0703] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with biphenyl-4-amine to replace aniline **72.4**. MS found for $C_{23}H_{26}N_6O$ as $(M+H)^+$ 403.4. UV: λ = 239.3, 308.7.

Example 198 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(isoxazol-3-yl)phenylamino)pyrimidine-5-carboxamide



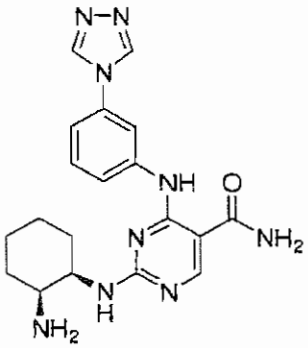
[0704] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with 3-(isoxazol-3-yl)aniline to replace aniline **72.4**. MS found for $C_{20}H_{23}N_7O_2$ as $(M+H)^+$ 394.4. UV: λ = 243.6, 286.5.

Example 199 4-(4-(4*H*-1,2,4-triazol-4-ylphenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



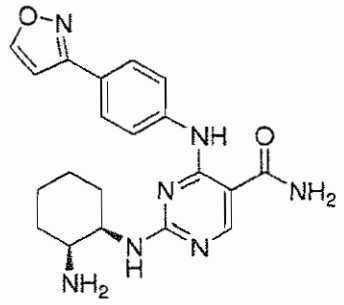
[0705] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with 4-(4*H*-1,2,4-triazol-4-yl)aniline to replace aniline **74.1**. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV: λ = 245.2, 293.8.

Example 200 4-(3-(4*H*-1,2,4-triazol-4-ylphenylamino)-2-((1R,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



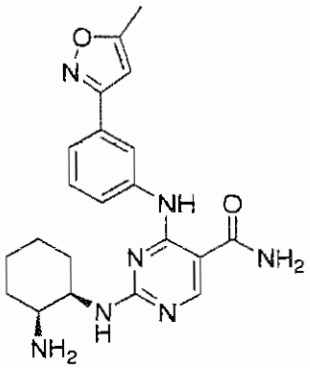
[0706] The title compound was prepared using the same synthetic scheme demonstrated in Example 3 with 3-(4*H*-1,2,4-triazol-4-yl)aniline to replace aniline **74.1**. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV: λ = 239.9.

Example 201 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(isoxazol-3-yl)phenylamino)pyrimidine-5-carboxamide



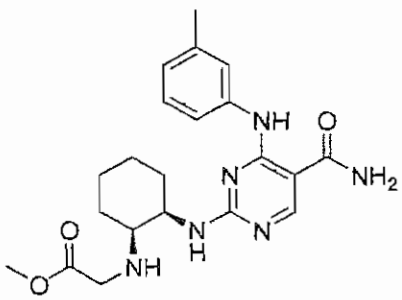
[0707] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with 4-(isoxazol-3-yl)aniline to replace aniline **74.1**. MS found for $C_{20}H_{23}N_7O_2$ as $(M+H)^+$ 394.4. UV: λ = 244.0, 303.3

Example 202 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(5-methylisoxazol-3-yl)phenylamino)pyrimidine-5-carboxamide



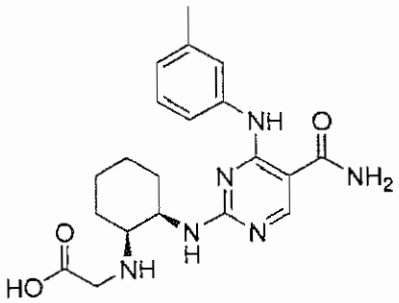
[0708] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with 3-(5-methylisoxazol-3-yl)aniline to replace aniline **74.1**. MS found for $C_{21}H_{25}N_7O_2$ as $(M+H)^+$ 408.4. UV: λ = 243.6, 287.1.

Example 203. Methyl 2-((1S, 2R)-2-(5-carbamoyl-4-(m-tolylamino)pyrimidin-2-ylamino)cyclohexylamino)acetate



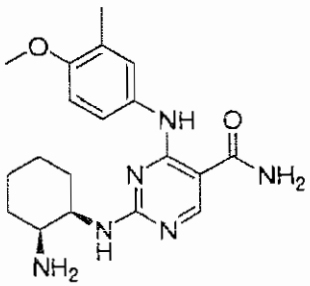
[0709] MS found for $C_{21}H_{28}N_6O_3$ as $(M+H)^+$ 413.1. UV: λ = 241.4, 288.8.

Example 204. 2-((1S, 2R)-2-(5-carbamoyl-4-(m-tolylamino)pyrimidin-2-ylamino)cyclohexylamino)acetic acid



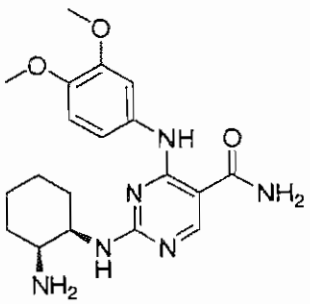
[0710] MS found for $C_{20}H_{26}N_6O_3$ as $(M+H)^+$ 399.2. UV: λ = 240.5, 287.8.

Example 205 2-((1S, 2R)-2-aminocyclohexylamino)-4-(4-methoxy-3-methylphenylamino)pyrimidin-5-carboxamide



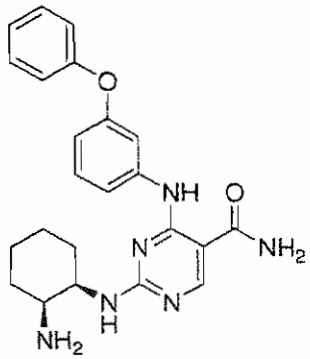
[0711] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with 4-methoxy-3-methylaniline to replace aniline **72.4**. MS found for $C_{19}H_{26}N_6O_2$ as $(M+H)^+$ 371.2. UV: λ = 238.1, 292.6.

Example 206 2-((1S, 2R)-2-aminocyclohexylamino)-4-(3,4-dimethoxyphenylamino)pyrimidin-5-carboxamide



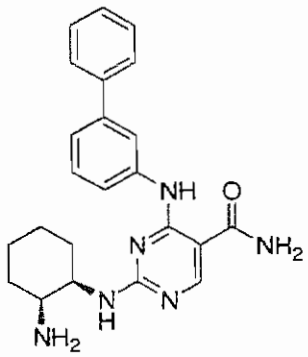
[0712] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with 3,4-dimethoxyaniline to replace aniline **72.4**. MS found for $C_{19}H_{26}N_6O_3$ as $(M+H)^+$ 387.1. UV: λ = 236.9, 286.6.

Example 207 2-((1S, 2R)-2-aminocyclohexylamino)-4-(3-phenoxyphenylamino)pyrimidin-5-carboxamide



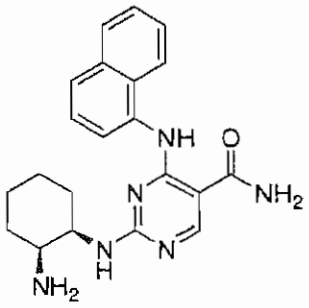
[0713] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with 3-phenoxyaniline to replace aniline **72.4**. MS found for $C_{23}H_{26}N_6O_2$ as $(M+H)^+$ 419.3. UV: λ = 240.4, 292.6.

Example 208. 2-((1R,2S)-2-aminocyclohexylamino)-4-(biphenyl-3-ylamino)pyrimidine-5-carboxamide



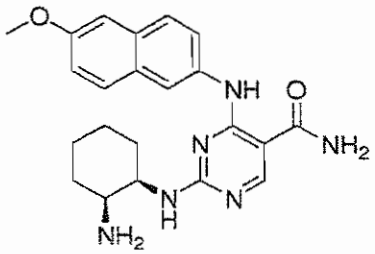
[0714] The title compound was prepared using the same synthetic scheme demonstrated in Example 1 with biphenyl-3-amine to replace aniline **72.4**. MS found for $C_{23}H_{26}N_6O$ as $(M+H)^+$ 403.4. UV: λ = 246.3

Example 209 2-((1R,2S)-2-aminocyclohexylamino)-4-(naphthalen-1-ylamino)pyrimidine-5-carboxamide



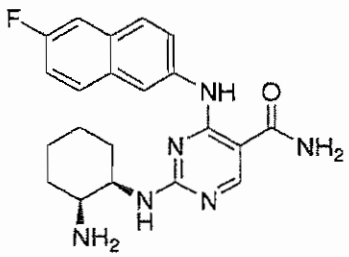
[0715] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with naphthalen-1-amine to replace aniline **208.1**. MS found for $C_{21}H_{24}N_6O$ as $(M+H)^+$ 377.1.

Example 210. 2-((1R,2S)-2-aminocyclohexylamino)-4-(6-methoxynaphthalen-2-ylamino)pyrimidine-5-carboxamide



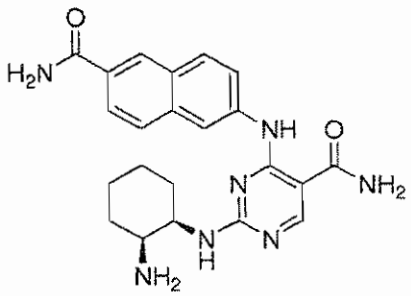
[0716] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with 6-methoxynaphthalen-2-amine to replace aniline **208.1**. MS found for $C_{22}H_{26}N_6O_2$ as $(M+H)^+$ 407.2. UV: λ = 227.5, 319.9.

Example 211a. 2-((1R,2S)-2-aminocyclohexylamino)-4-(6-fluoronaphthalen-2-ylamino)pyrimidine-5-carboxamide



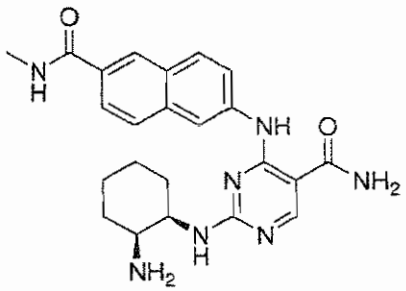
[0717] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with 6-fluoronaphthalen-2-amine to replace aniline **208.1**. MS found for $C_{21}H_{23}FN_6O$ as $(M+H)^+$ 395.1. UV: λ = 212.2, 244.0, 306.8.

Example 211b: 2-((1R,2S)-2-aminocyclohexylamino)-4-(6-carbamoylnaphthalen-2-ylamino)pyrimidine-5-carboxamide



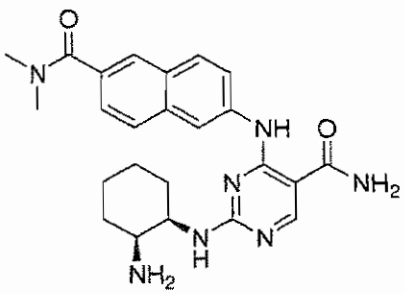
[0718] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with 6-carbamoylnaphthalen-2-amine to replace aniline **208.1**. MS found for $C_{22}H_{25}N_7O_2$ as $(M+H)^+$ 420.2. UV: λ = 223.9, 318.8.

Example 212. 2-((1R,2S)-2-aminocyclohexylamino)-4-(6-(methylcarbamoyl)naphthalen-2-ylamino)pyrimidine-5-carboxamide



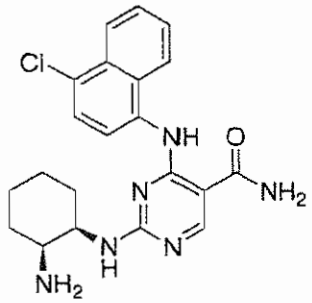
[0719] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with 6-(methylcarbamoyl)naphthalen-2-amine to replace aniline **208.1**. MS found for $C_{23}H_{27}N_7O_2$ as $(M+H)^+$ 434.3. UV: λ = 219.2, 235.7, 318.8.

Example 213. 2-((1R,2S)-2-aminocyclohexylamino)-4-(6-(dimethylcarbamoyl)naphthalen-2-ylamino)pyrimidine-5-carboxamide



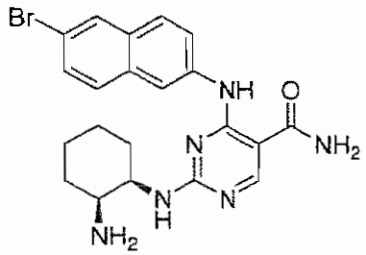
[0720] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with 6-(dimethylcarbamoyl)naphthalen-2-amine to replace aniline **208.1**. MS found for $C_{24}H_{29}N_7O_2$ as $(M+H)^+$ 448.2. UV: λ = 218.0, 314.0.

Example 214. 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-chloronaphthalen-1-ylamino)pyrimidine-5-carboxamide



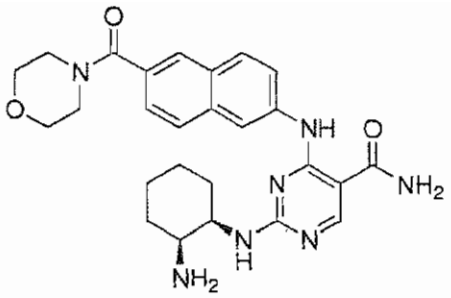
[0721] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with 4-chloronaphthalenyl-1-amine to replace aniline **208.1**. MS found for $C_{21}H_{23}ClN_6O$ as $(M+H)^+$ 411.2,413.1 (Cl pattern). UV: λ = 223.9, 293.8.

Example 215. 2-((1R,2S)-2-aminocyclohexylamino)-4-(6-bromonaphthalen-2-ylamino)pyrimidine-5-carboxamide



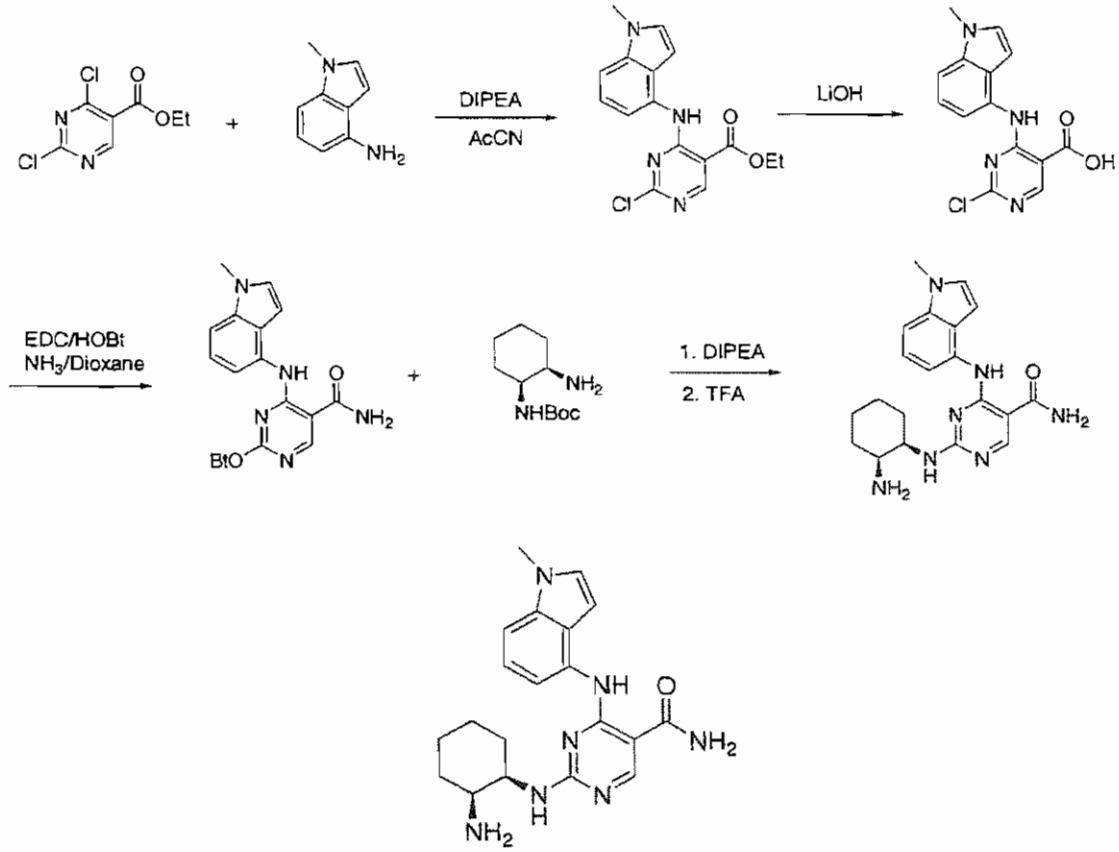
[0722] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with 4-bromonaphthalenyl-2-amine to replace aniline **208.1**. MS found for $C_{21}H_{23}BrN_6O$ as $(M+H)^+$ 455.1, 457.1 (Br pattern).

Example 217. 2-((1R,2S)-2-aminocyclohexylamino)-4-(6-(morpholine-4-carbonyl)naphthalen-2-ylamino)pyrimidine-5-carboxamide



[0723] The title compound was prepared using the same synthetic scheme demonstrated in Example 152 with 6-(morpholine-4-carbonyl)naphthalenyl-2-amine to replace aniline **208.1**. MS found for $C_{26}H_{31}N_7O_3$ as $(M+H)^+$ 490.4. UV: λ = 220.4, 315.2.

Example 218. 2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-1H-indol-4-ylamino)pyrimidine-5-carboxamide



[0724] Step 1: To a solution of ethyl 2,4-dichloropyrimidine-5-carboxylate (328 mg, 1.48 mmol) and 1-methyl-1*H*-indol-4-amine (260 mg, 1.78 mmol) in CH_3CN (6 mL) at room temperature, DIEA (0.4 mL, 2.22 mmol) was added. The mixture was stirred at room temperature for 24 h. Water (15 mL) was added to induce precipitation. The precipitate was

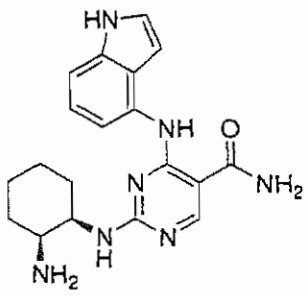
collected, dried on vacuum to give ethyl 2-chloro-4-(1-methyl-1*H*-indol-4-ylamino) pyrimidine-5-carboxylate as a solid.

[**0725**] Step 2: To a solution of ethyl 2-chloro-4-(1-methyl-1*H*-indol-4-ylamino) pyrimidine-5-carboxylate (crude from step 1) in THF (4 mL), aq. 1N LiOH (2.25 mL, 2.25 mmol) was added. The mixture was stirred at room temperature overnight. Upon acidification of the mixture with 1N HCl, white solids precipitated out, which were collected, and dried on vacuum to give 2-chloro-4-(1-methyl-1*H*-indol-4-ylamino) pyrimidine- 5-carboxylic acid (325 mg). MS 303.3, 305.3 (M+H, Cl pattern)

[**0726**] Step 3: To a solution of 2-chloro-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxylic acid (325 mg, 1.08 mmol) and HOBt (198 mg, 1.29 mmol) in DMF (4 mL), EDC (248 mg, 1.29 mmol) was added. The mixture was stirred at room temperature for 1.5 h. Ammonia (0.5 M in dioxane, 8.00 mL, and 4.00 mmol) was added. It was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with 1 N HCl, then with 5% $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo to give 2-(1*H*-benzo[d][1,2,3]triazol-1-yloxy)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide (378 mg). MS 401.4 (M+H)

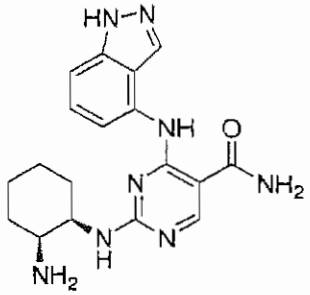
[**0727**] Step 4: To a solid of 2-(1*H*-benzo[d][1,2,3]triazol-1-yloxy)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide (100 mg, 0.25 mmol) in vial was added *tert* butyl (1S, 2R)-2-aminocyclohexylcarbamate (0.3 M solution in NMP, 1.25 mL, 0.375 mmol) and DIPEA (0.09 mL, 0.5 mmol). It was heated at 80 °C for 2 h, cooled and purified by preparative HPLC to give 2-((1R,2S)-2-aminocyclohexylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide (21 mg). MS found for $C_{20}H_{25}N_7O$ as $(M+H)^+$ 380.4. UV: λ = 219.2, 241.6, 336.7.

Example 219a. 4-(1*H*-indol-4-ylamino)-2-((1*R*,2*S*)-2-aminocyclohexylamino) pyrimidine-5-carboxamide



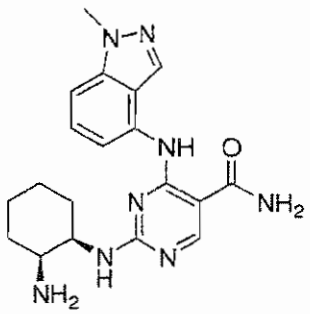
[0728] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 1*H*-indol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{19}H_{23}N_7O$ as $(M+H)^+$ 366.3. UV: λ = 216.7, 239.9, 330.3.

Example 219b. 4-(1*H*-indazol-4-ylamino)-2-((1*R*,2*S*)-2-aminocyclohexylamino) pyrimidine-5-carboxamide



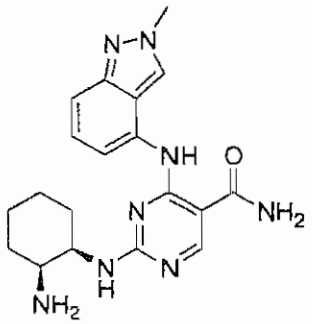
[0729] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 1*H*-indazol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{18}H_{22}N_8O$ as $(M+H)^+$ 367.4. UV: λ = 205.8, 240.5, 314.3

Example 219c. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(1-methyl-1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



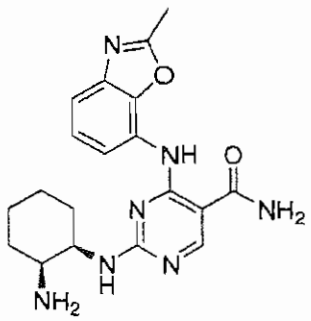
[0730] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 1-methyl-1*H*-indazol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{19}H_{24}N_8O$ as $(M+H)^+$ 381.4. UV: λ = .

Example 220. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(2-methyl-2*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



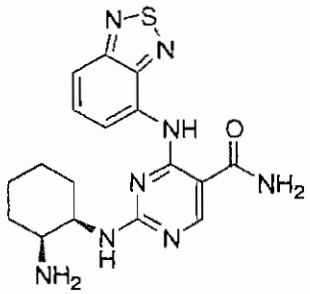
[0731] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 2-methyl-2*H*-indazol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{19}H_{24}N_8O$ as $(M+H)^+$ 381.5. UV: λ = 210.6, 243.0, 329.1.

Example 221. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(2-methylbenzo[d]oxazol-7-ylamino)pyrimidine-5-carboxamide



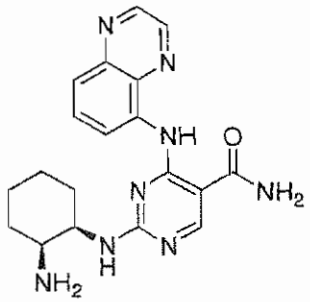
[0732] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 2-methylbenzo[d]oxazol-7-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{19}H_{23}N_7O_2$ as $(M+H)^+$ 382.4. UV: λ = 238.1.

Example 222. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(benzo[c][1,2,5]thiadiazol-4-ylamino)pyrimidine-5-carboxamide



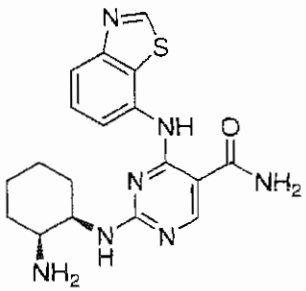
[0733] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with benzo[c][1,2,5]thiadiazol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{17}H_{20}N_8OS$ as $(M+H)^+$ 385.3. UV: λ = 234.5, 298.5, 315.2.

Example 223. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(quinoxalin-5-ylamino)pyrimidine-5-carboxamide



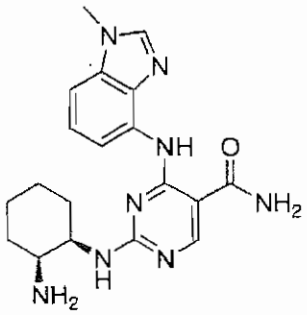
[0734] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with quinoxalinyl-5-amine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{19}H_{22}N_8OS$ as $(M+H)^+$ 379.3. UV: λ = 203.4, 245.4.

Example 224. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(benzo[d]thiazol-7-ylamino)pyrimidine-5-carboxamide



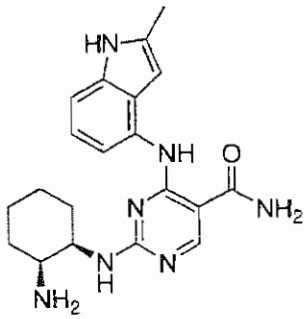
[0735] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with benzo[d]thiazol-7-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{18}H_{21}N_7OS$ as $(M+H)^+$ 384.3. UV: λ = 205.1, 242.8, 290.2.

Example 225. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(1-methyl-1H-benzo[d]imidazol-4-ylamino)pyrimidine-5-carboxamide



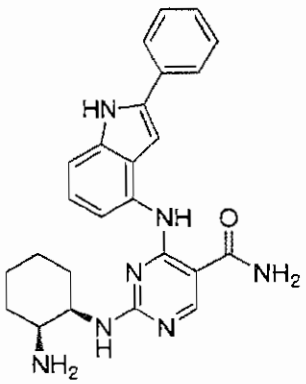
[0736] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 1-methyl-1*H*-benzo[d]imidazol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{19}H_{24}N_8O$ as $(M+H)^+$ 381.4. UV: λ = 202.8, 239.3.

Example 226. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(2-methyl-1H-indol-4-ylamino)pyrimidine-5-carboxamide



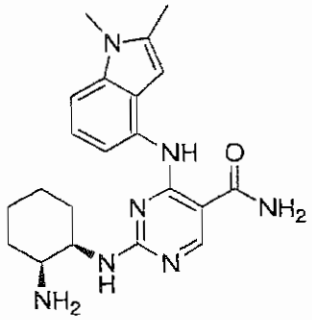
[0737] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 2-methyl-1H-indol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{20}H_{25}N_7O$ as $(M+H)^+$ 380.4. UV: λ = 220.4, 239.3, 336.7.

Example 227. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(2-phenyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



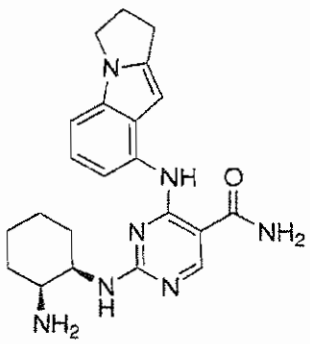
[0738] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 2-phenyl-1*H*-indol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{25}H_{27}N_7O$ as $(M+H)^+$ 442.5. UV: λ = 241.6, 293.8.

Example 228. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(1,2-dimethyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



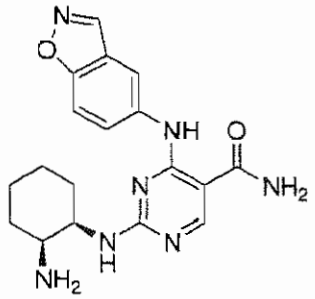
[0739] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 1,2-dimethyl-1*H*-indol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{21}H_{27}N_7O$ as $(M+H)^+$ 394.4. UV: λ = 222.8, 242.8.

Example 229. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



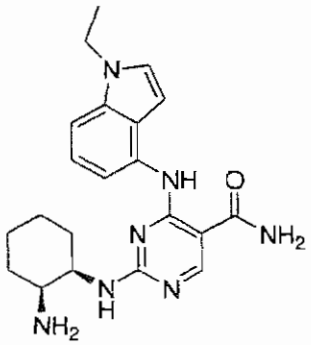
[0740] The title compound was prepared using the same synthetic scheme demonstrated in Example 120 with 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-8-amine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{22}H_{27}N_7O$ as $(M+H)^+$ 406.5. UV: λ = 222.8, 241.6.

Example 230. 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(benzo-[*d*]isoxazol-5-ylamino)pyrimidine-5-carboxamide



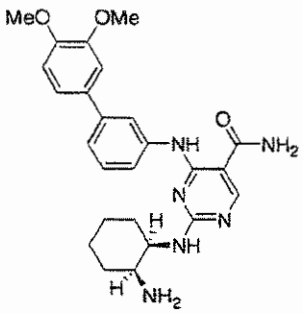
[0741] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with benzo-[*d*]isoxazol-5-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{18}H_{21}N_7O_2$ as $(M+H)^+$ 368.4. UV: λ = 203.9, 236.9, 294.9.

Example 231. 2-((1R,2S)-2-aminocyclohexylamino)-4-(1-ethyl-1H-indol-4-ylamino)pyrimidine-5-carboxamide

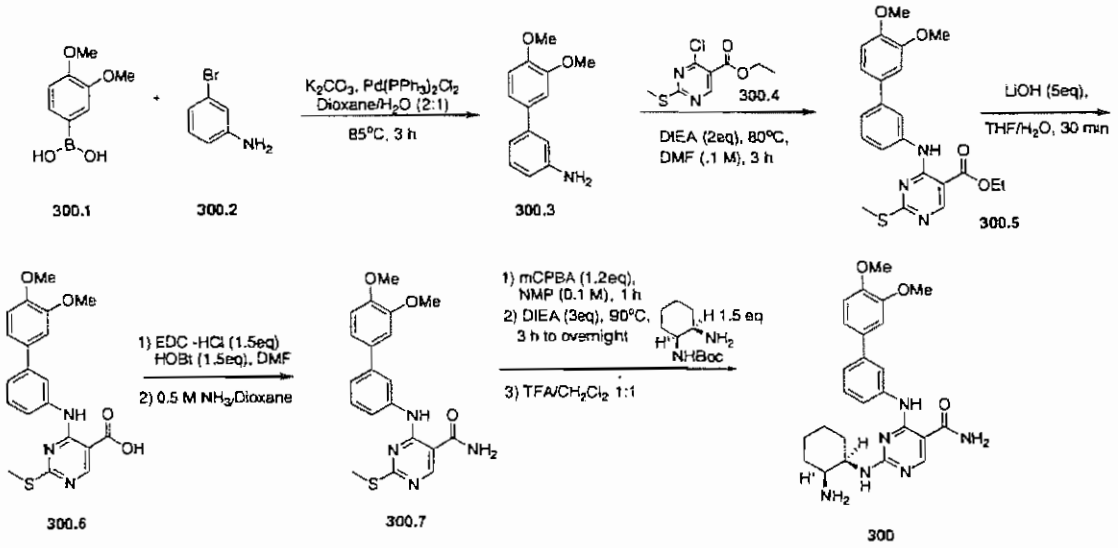


[0742] The title compound was prepared using the same synthetic scheme demonstrated in Example 218 with 1-ethyl-1*H*-indol-4-ylamine to replace 1-methyl-1*H*-indol-4-ylamine. MS found for $C_{21}H_{27}N_7O$ as $(M+H)^+$ 394.4. UV: λ = 220.2, 242.6.

Example 232. 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(3,4-dimethoxyphenyl)phenylamino)pyrimidine-5-carboxamide



Scheme:



[0743] Potassium carbonate (1.81 g, 13.1 mmol) was dissolved in a 2:1 mixture of dioxane/water (45 mL). This solution was added to 3,4-dimethoxyphenylboronic acid (**300.1**; 799 mg, 4.39 mmol) [CAS 122775-35-3] and 3-bromoaniline (**300.2**; 756 mg, 4.39 mmol) [CAS 591-19-5]. The resulting solution was degassed with argon for 5 minutes. Bis(triphenylphosphine) palladium(II) dichloride (598 mg, 0.85 mmol) [CAS 13965-03-2] was added and the reaction was stirred for 3 h at 85°C in a sealed tube. The reaction was cooled and diluted with EtOAc (300 mL), washed with brine (3x100 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting residue was subjected to flash chromatography (gradient of 20% to 70% EtOAc in hexanes) which resulted in 360 mg of **300.3** (36%).

[0744] To **300.3** (360 mg, 1.57 mmol) in DMF (15 mL) was added 4-chloro-2-(methylthio)-5-pyrimidinecarboxylic acid ethyl ester (365 mg, 1.57 mmol) [CAS 5909-24-0] and DIEA (562 µL, 3.14 mmol). The reaction mixture was stirred for 3 h at 80°C in a sealed tube. The reaction was cooled, water was added, and a precipitate formed. The precipitate was filtered, washed with cold water, and dried to give **300.4** in quantitative yield.

[0745] The resulting solid (667 mg, 1.57 mmol) was dissolved in THF (10 mL). To this was added LiOH (188 mg, 7.85 mmol) in H_2O (5 mL). The reaction was stirred for 30 min and was acidified to pH~3 with 1 M HCl. The THF was removed in vacuo and ice-cold water was added to the reaction mixture. The resulting solid was filtered, washed with water, and dried to give 497 mg (88%) of **300.5**.

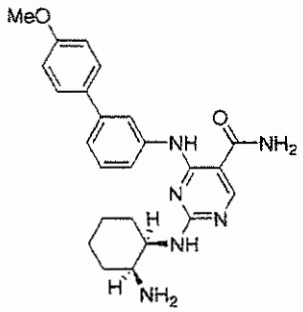
[0746] Carboxylic acid **300.5** (460 mg, 1.15 mmol) was dissolved in 10 mL DMF. To it were added EDC hydrochloride (328 mg, 1.72 mmol) and HOBt hydrate (232 mg, 1.72

mmol). The mixture was stirred at RT for 2 h. Ammonia (commercial 0.5N solution in dioxane, 7 mL, 3.5 mmol) was added and the mixture and was stirred for 1 h. The dioxane was removed by in vacuo and ice-cold water was added to the reaction mixture. The resulting solid was filtered, washed with water, and dried to give 445 mg (97%) of **300.6**.

[0747] Compound **300.6** (70 mg, 0.18 mmol) was dissolved in 4 mL NMP. To it was added mCPBA (70% minimum purity, 50 mg, 0.21 mmol) which was stirred at RT for 30 minutes.

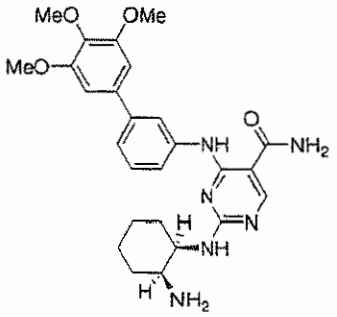
[0748] To it were then added a solution of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate (0.3 M, 0.9 mL, 0.27 mmol) and DIEA (94 μL, 0.54 mmol). The mixture was stirred for 3 h at 90°C in a sealed tube. The mixture was cooled, diluted with EtOAc, washed with a saturated Na_2CO_3 aqueous solution, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated afford a crude intermediate which was stirred in a 1:1 mixture of TFA and DCM at RT for 30 min. The reaction mixture was concentrated in vacuo and subjected to reverse phase preparative HPLC to isolate title compound. MS found for $C_{25}H_{30}N_6O_3$ as $(M+H)^+$ 463.3. UV λ=210, 243 nm. δ 1.40-1.83 (m, 8H), 3.60-3.68 (m, 1H), 3.88 (s, 3H), 3.92 (s, 3H), 4.43-4.51 (m, 1H), 7.60-7.66 (m, 1H), 7.90 (d, 1H), 8.04 (s, 2H), 8.52-8.58 (m, 1H), 8.62 (s, 1H).

Example 233: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-methoxyphenyl)phenylamino)pyrimidine-5-carboxamide



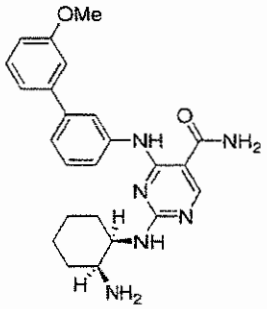
[0749] This compound was prepared utilizing the same chemistry as shown for example 232. However, 4-methoxyphenylboronic acid [CAS 5720-07-0] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{24}H_{28}N_6O_2$ as $(M+H)^+$ 433.4. UV λ=248 nm. δ 1.25-1.80 (m, 8H), 3.58-3.64 (m, 1H), 3.83 (s, 3H), 4.20-4.28 (m, 1H), 7.02 (d, 2H), 7.36-7.48 (m, 3H), 7.59 (d, 2H), 8.03 (br s, 1H), 8.55 (s, 1H)

Example 234: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2,3,4-trimethoxyphenyl)phenylamino)pyrimidine-5-carboxamide



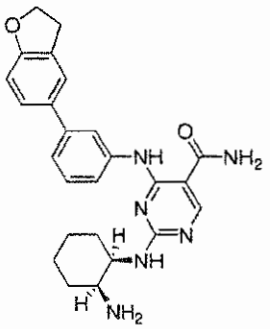
[0750] This compound was prepared utilizing the same chemistry as example 232. However, 3,4,5-trimethoxyphenylboronic acid [CAS 182163-96-8] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{26}H_{32}N_6O_4$ as $(M+H)^+$ 493.4. UV λ=245 nm. δ 1.20-1.80 (m, 8H), 3.61-3.68 (m, 1H), 3.80 (s, 3H), 3.92 (s, 6H), 4.15-4.22 (m, 1H), 6.92 (s, 2H), 7.45 (br s, 3H), 8.05 (br s, 1H), 8.55 (s, 1H).

Example 235: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(3-methoxyphenyl)phenylamino)pyrimidine-5-carboxamide



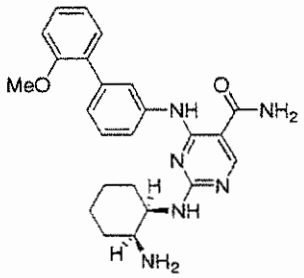
[0751] This compound was prepared utilizing the same chemistry as example 232. However, 3-methoxyphenylboronic acid [CAS 10365-98-7] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{24}H_{28}N_6O_2$ as $(M+H)^+$ 433.3. UV λ=241 nm.

Example 236: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2,3-dihydrobenzofuran-5-yl)phenylamino)pyrimidine-5-carboxamide



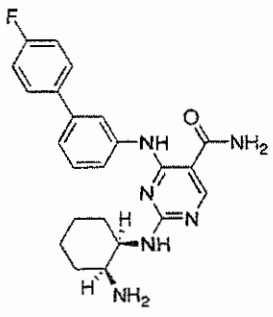
[0752] This compound was prepared utilizing the same chemistry as example 232. However, (2,3-dihydrobenzo[b]furan-5-yl)boronic acid [CAS 227305-69-3] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{25}H_{28}N_6O_2$ as $(M+H)^+$ 445.3. UV λ=245, 276 nm.

Example 237: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2-methoxyphenyl)phenylamino)pyrimidine-5-carboxamide



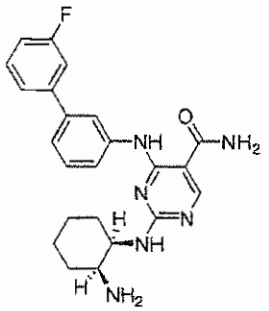
[0753] This compound was prepared utilizing the same chemistry as example 232. However, 2-methoxyphenylboronic acid [CAS 5720-06-9] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{24}H_{28}N_6O_2$ as $(M+H)^+$ 433.3. UV λ=244, 288 nm.

Example 238: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-fluorophenyl)phenylamino)pyrimidine-5-carboxamide



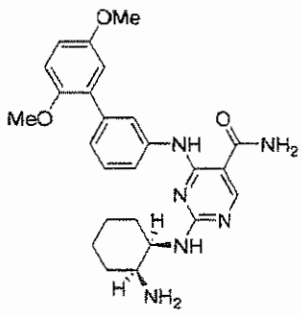
[0754] This compound was prepared utilizing the same chemistry as Example 232. However, 4-fluorophenylboronic acid [CAS 1765-93-1] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{23}H_{25}FN_6O$ as $(M+H)^+$ 421.3. UV λ=245 nm. δ 1.35-1.85 (m, 8H), 3.58-3.65 (m, 1H), 4.25-4.31 (m, 1H), 7.09-7.18 (m, 1H), 7.40-7.54 (m, 6H), 8.11 (br s, 1H), 8.53 (s, 1H).

Example 239: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(3-fluorophenyl)phenylamino)pyrimidine-5-carboxamide



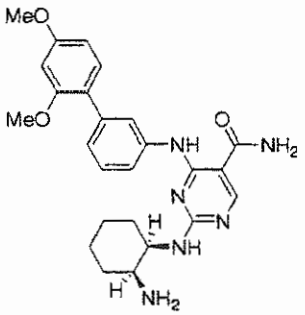
[0755] This compound was prepared utilizing the same chemistry as Example 232. However, 3-fluorophenylboronic acid [CAS 768-35-4] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{23}H_{25}FN_6O$ as $(M+H)^+$ 421.3. UV λ=242 nm.

Example 240: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2,5-dimethoxyphenyl)phenylamino)pyrimidine-5-carboxamide



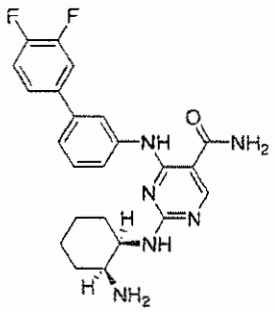
[0756] This compound was prepared utilizing the same chemistry as Example 232. However, 2,5-dimethoxyphenylboronic acid [CAS 107099-99-0] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{25}H_{30}N_6O_3$ as $(M+H)^+$ 463.3. UV λ=246 nm.

Example 241: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2,4-dimethoxyphenyl)phenylamino)pyrimidine-5-carboxamide



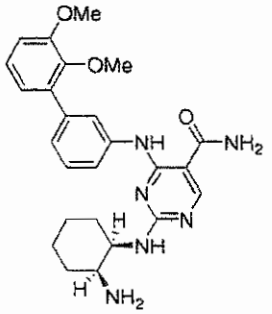
[0757] This compound was prepared utilizing the same chemistry as Example 232. However, 2,4-dimethoxyphenylboronic acid [CAS 133730-34-4] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{25}H_{30}N_6O_3$ as $(M+H)^+$ 463.3. UV λ=245, 288 nm.

Example 242: : 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(3,4-difluorophenyl)phenylamino)pyrimidine-5-carboxamide



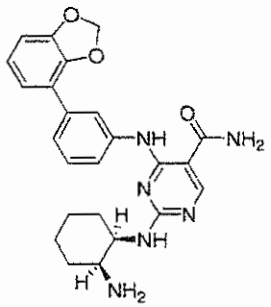
[0758] This compound was prepared utilizing the same chemistry as Example 232. However, 3,4-difluorophenylboronic acid [CAS 168267-41-2] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{23}H_{24}F_2N_6O$ as $(M+H)^+$ 439.3. UV λ=245 nm.

Example 243: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2,3-dimethoxyphenyl)phenylamino)pyrimidine-5-carboxamide



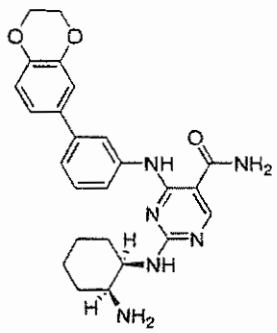
[0759] This compound was prepared utilizing the same chemistry as Example 232. However, 2,3-dimethoxyphenylboronic acid [CAS 40972-86-9] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{25}H_{30}N_6O_3$ as $(M+H)^+$ 463.3. UV λ=244, 288 nm.

Example 244: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(benzo[d][1,3]dioxol-4-yl)phenylamino)pyrimidine-5-carboxamide



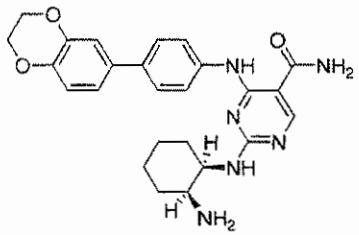
[0760] This compound was prepared utilizing the same chemistry as Example 232. However, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and 4-bromo-1,3-benzodioxole [CAS 6698-13-1] were used as coupling partners. MS found for $C_{24}H_{26}N_6O_3$ as $(M+H)^+$ 447.4. UV λ=242 nm.

Example 245: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenylamino)pyrimidine-5-carboxamide



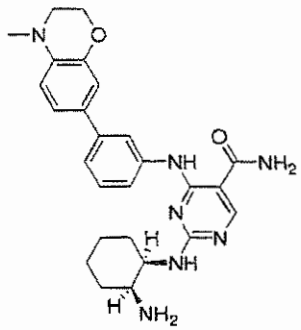
[0761] This compound was prepared utilizing the same chemistry as Example 232. However, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and 6-iodobenzodioxane [CAS 57744-67-9] were used as coupling partners. MS found for $C_{25}H_{28}N_6O_3$ as $(M+H)^+$ 461.4. UV λ=211, 243 nm. δ 1.35-1.85 (m, 8H), 3.58-3.65 (m, 1H), 4.30-4.38 (m, 5H), 6.95 (d, 1H), 7.10-7.18 (m, 2H), 7.30-7.36 (m, 1H), 7.38-7.45 (m, 2H), 8.14 (br s, 1H), 8.50 (s, 1H)

Example 246: 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenylamino)pyrimidine-5-carboxamide



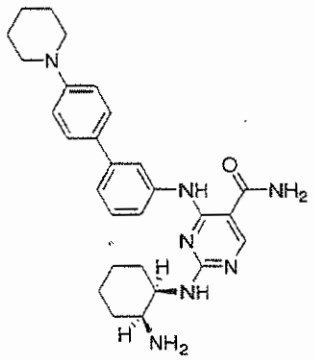
[0762] This compound was prepared utilizing the same chemistry as Example 232. However, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 214360-73-3] and 6-iodobenzodioxane [CAS 57744-67-9] were used as coupling partners. MS found for $C_{25}H_{28}N_6O_3$ as $(M+H)^+$ 461.4. UV λ=242, 316 nm. δ 1.50-1.95 (m, 8H), 3.70-3.78 (m, 1H), 4.25 (s, 4H), 4.34-4.41 (m, 1H), 6.90 (d, 1H), 7.08-7.15 (m, 2H), 7.58-7.68 (m, 4H), 8.50 (s, 1H).

Example 247: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)phenylamino)pyrimidine-5-carboxamide



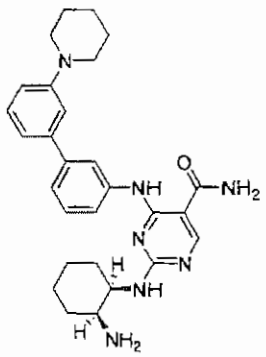
[0763] This compound was prepared utilizing the same chemistry as Example 232. However, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and 7-bromo-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine [CAS 154264-95-6] were used as coupling partners. MS found for $C_{26}H_{31}N_7O_2$ as $(M+H)^+$ 474.4. UV λ=216, 238, 303 nm.

Example 248: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-piperidinylphenyl)phenylamino)pyrimidine-5-carboxamide.



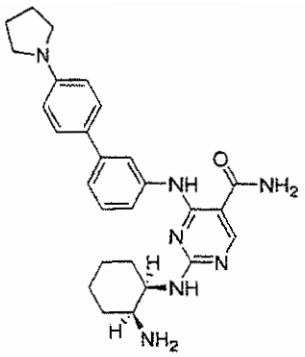
[0764] The initial biarylaniline was prepared utilizing the same chemistry as Example 232 using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and N-(4-bromophenyl)piperidine [CAS 22148-20-5] as coupling partners. The resulting aniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 13 to yield the title compound. MS found for $C_{28}H_{35}N_7O$ as $(M+H)^+$ 486.5. UV λ=252 nm.

Example 249: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(3-piperidinylphenyl)phenylamino)pyrimidine-5-carboxamide



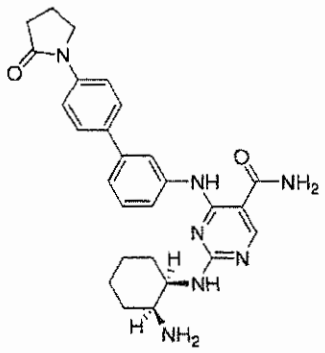
[0765] The initial biarylaniline was prepared utilizing the same chemistry as Example 232 using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and N-(3-bromophenyl)piperidine [CAS 84964-24-9] as coupling partners. The resulting aniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 13 to yield the title compound. MS found for $C_{28}H_{35}N_7O$ as $(M+H)^+$ 486.5. UV λ=247 nm.

Example 250: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-pyrrolidinylphenyl)phenylamino)pyrimidine-5-carboxamide



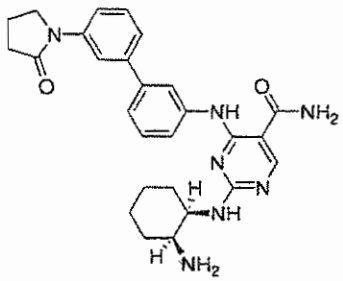
[**0766**] The initial biarylaniline was prepared utilizing the same chemistry as Example 232 using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and N-(4-bromophenyl)pyrrolidine [CAS 22090-26-2] as coupling partners. The resulting aniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 13 to yield the title compound. MS found for $C_{27}H_{33}N_7O$ as $(M+H)^+$ 472.5. UV λ=246 nm.

Example 251: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-pyrrolidin-2-oxo-ylphenyl)phenylamino)pyrimidine-5-carboxamide



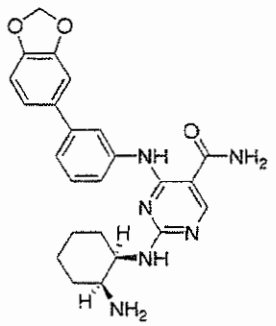
[**0767**] This example was a byproduct in the formation of example 250. MS found for $C_{27}H_{31}N_7O_2$ as $(M+H)^+$ 486.5. UV λ=248, 282 nm.

Example 252 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(3-pyrrolidin-2-oxo-ylphenyl)phenylamino)pyrimidine-5-carboxamide



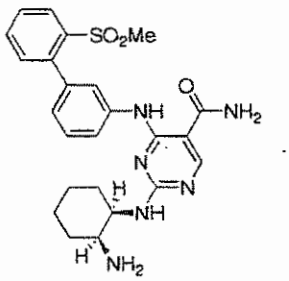
[0768] The initial biarylaniline was prepared utilizing the same chemistry as Example 232 using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and N-(3-bromophenyl)pyrrolidine [CAS 219928-13-9] as coupling partners. The resulting aniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 13 to yield the title compound. MS found for $C_{27}H_{31}N_7O_2$ as $(M+H)^+$ 486.5. UV λ=245 nm.

Example 253: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(benzo[d][1,3]dioxol-5-yl)phenylamino)pyrimidine-5-carboxamide



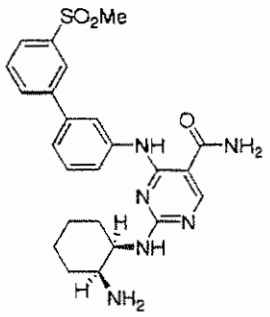
[0769] This compound was prepared utilizing the same chemistry as Example 232. However, 1,3-benzodioxole-5-boronic acid [CAS 94839-07-3] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{24}H_{26}N_6O_3$ as $(M+H)^+$ 447.3. UV λ= 239, 274, 296 nm. δ 1.35-1.85 (m, 8H), 3.58-3.65 (m, 1H), 4.25-4.31 (m, 1H), 6.00 (s, 2H) 6.93 (d, 1H), 7.10-7.18 (m, 2H), 7.37-7.50 (m, 3H), 8.08 (br s, 1H), 8.53 (s, 1H)

Example 254: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2-methylsulfonylphenyl)phenylamino)pyrimidine-5-carboxamide.



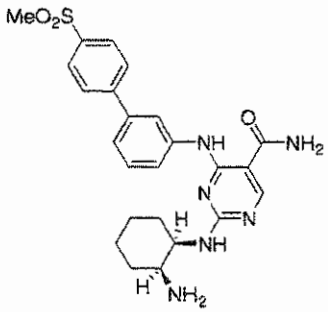
[0770] This compound was prepared utilizing the same chemistry as Example 232. However, 2-methylsulfonylphenylboronic acid [CAS 330804-03-0] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{24}H_{28}N_6O_3S$ as $(M+H)^+$ 481.4. UV λ= 240, 285 nm.

Example 255: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(3-methylsulfonylphenyl)phenylamino)pyrimidine-5-carboxamide



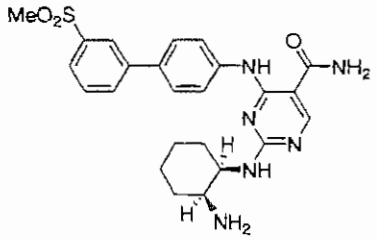
[0771] This compound was prepared utilizing the same chemistry as Example 232. However, 3-methylsulfonylphenylboronic acid [373384-18-0] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{24}H_{28}N_6O_3S$ as $(M+H)^+$ 481.4. UV λ= 246 nm.

Example 256: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(4-methylsulfonylphenyl)phenylamino)pyrimidine-5-carboxamide



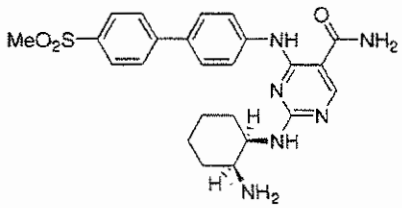
[0772] This compound was prepared utilizing the same chemistry as Example 232. However, 4-methylsulfonylphenylboronic acid [149104-88-1] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. MS found for $C_{24}H_{28}N_6O_3S$ as $(M+H)^+$ 481.4. UV λ= 250 nm. δ 1.25-1.85 (m, 8H), 3.18 (s, 3H), 3.58-3.65 (m, 1H), 4.21-4.28 (m, 1H), 7.52-7.62 (m, 3H) 7.93 (d, 2H), 8.07 (d, 2H), 8.17 (br s, 1H), 8.57 (s, 1H)

Example 257: 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(3-methylsulfonylphenyl)phenylamino)pyrimidine-5-carboxamide



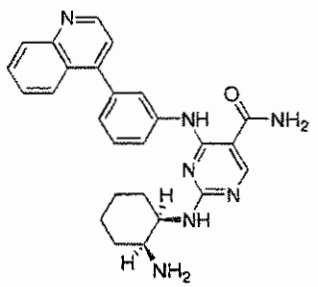
[0773] This compound was prepared utilizing the same chemistry as Example 232. However, 3-methylsulfonylphenylboronic acid [373384-18-0] and 4-iodoaniline [CAS 540-37-4] were used as coupling partners. MS found for $C_{24}H_{28}N_6O_3S$ as $(M+H)^+$ 481.4. UV λ= 235, 308 nm.

Example 259: 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-(4-methylsulfonylphenyl)phenylamino)pyrimidine-5-carboxamide



[0774] This compound was prepared utilizing the same chemistry as Example 232. However, 4-methylsulfonylphenylboronic acid [149104-88-1] and 4-iodoaniline [CAS 540-37-4] were used as coupling partners. MS found for $C_{24}H_{28}N_6O_3S$ as $(M+H)^+$ 481.3. UV λ= 239, 313 nm.

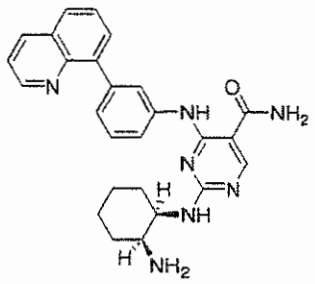
Example 260: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(quinolin-4-yl)phenylamino)pyrimidine-5-carboxamide



The initial biarylaniline was prepared utilizing the same chemistry as Example 232 using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and 4-bromoquinoline [CAS 3964-04-3] as coupling partners. The resulting aniline was reacted

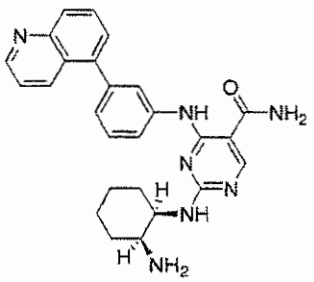
with **72.3** and subjected to the subsequent chemistry shown in example 13 to yield the title compound. MS found for $C_{26}H_{27}N_7O$ as $(M+H)^+$ 454.4. UV λ=239, 302 nm.

Example 261: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(quinolin-8-yl)phenylamino)pyrimidine-5-carboxamide



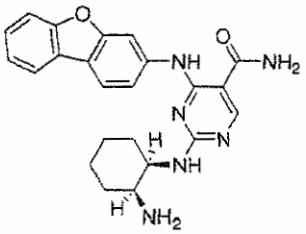
[0775] The initial biarylaniline was prepared utilizing the same chemistry as Example 232 using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline [CAS 210907-84-9] and 8-bromoquinoline [CAS 16567-18-3] as coupling partners. The resulting aniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 13 to yield the title compound. MS found for $C_{26}H_{27}N_7O$ as $(M+H)^+$ 454.4. UV λ=240, 301 nm.

Example 262: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(quinolin-5-yl)phenylamino)pyrimidine-5-carboxamide



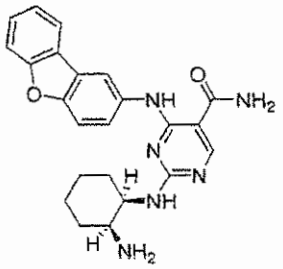
[0776] This compound was prepared utilizing the same chemistry as Example 232. However, 5-quinolinylboronic acid [CAS 355386-94-6] was used instead of 3,4-dimethoxyphenylboronic acid [CAS 122775-35-3]. The resulting aniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 13 to yield the title compound. MS found for $C_{26}H_{27}N_7O$ as $(M+H)^+$ 454.5. UV λ=241, 302 nm.

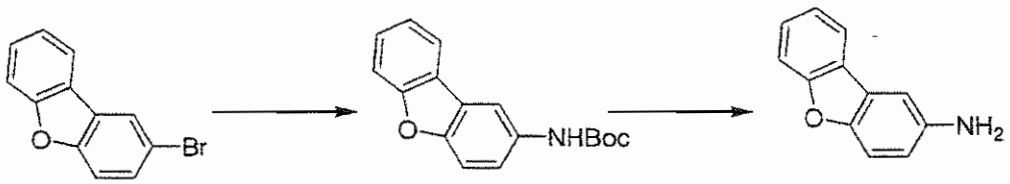
Example 264: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-dibenzofuranamino)pyrimidine-5-carboxamide



[0777] This compound was prepared reacting commercially available 3-aminodibenzofuran [CAS 4106-66-5] with **300.4** and DIEA. Subsequent reactions utilizing chemistry shown in Example 232 provided the title compound. MS found for $C_{23}H_{24}N_6O_2$ as $(M+H)^+$ 417.4. UV λ=212, 236, 322 nm.

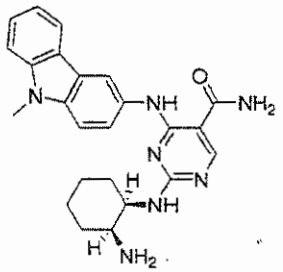
Example 265: 2-((1R,2S)-2-aminocyclohexylamino)-4-(2-dibenzofuranamino)pyrimidine-5-carboxamide

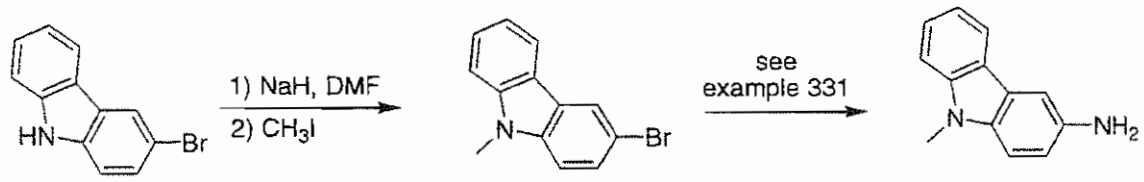




[0778] 2-Bromodibenzofuran (**331.1**; 942 mg, 3.81 mmol) [CAS 86-76-0], *tert*-butyl carbamate (670 mg, 5.72 mmol) [CAS 4248-19-5], and Cs_2CO_3 were added to degassed dioxane. Xantphos (330 mg, 0.51 mmol) [CAS 161265-03-8] and $Pd_2(dba)_3$ (175 mg, 0.19 mmol) [CAS 51364-51-3] were subsequently added. The reaction was heated under argon at 85°C for 18 h. The reaction was cooled and subjected to flash chromatography to give **331.2** which was dissolved in 4 N HCl/dioxane. Reaction stirred for 12 h and then was concentrated in vacuo to yield 331.3 (200 mg). This aniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 120 to yield the title compound to yield the title compound. MS found for $C_{23}H_{24}N_6O_2$ as $(M+H)^+$ 417.4. UV λ=210, 244, 289 nm.

Example 266: 2-((1R,2S)-2-aminocyclohexylamino)-4-(9-methyl-9H-carbazol-3-ylamino)pyrimidine-5-carboxamide



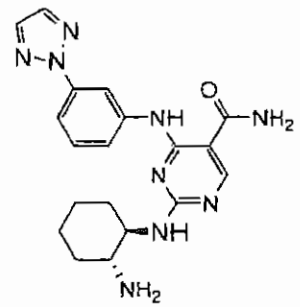


332.1 **332.2** **332.3**

[0779] To 3-bromocarbazole (**332.1**) (530 mg, 2.15 mmol) [CAS 1592-95-6] in DMF (~20 mL) at 0°C was added NaH in DMF(~5 mL). The reaction was warmed to RT and then heated at 60°C for 1 h. The solution was allowed to cool to RT and iodomethane was added dropwise. The reaction was heated at 12 h 60°C in a sealed tube. The reaction mixture was cooled diluted with EtOAc and washed with water (4 times), brine, dried over MgSO4 and concentrated to yield **332.2** (550 mg).

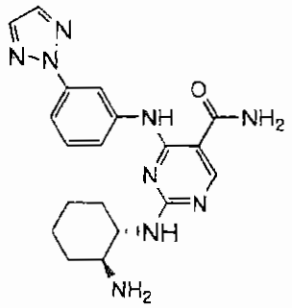
[0780] Intermediate **332.2** was subjected to chemistry seen in example 265 to yield **332.3**. This aniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 13 to yield the title compound to yield the title compound. MS found for $C_{23}H_{24}N_6O_2$ as $(M+H)^+$ 430.4. UV λ=238, 296 nm.

Example 267. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,2R)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



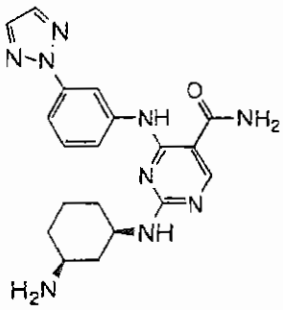
[0781] The title compound was prepared using the same chemistry shown for Example 87 with commercially available (1R,2R)-cyclohexane-1,2-diamine and DIEA. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV λ=250 nm.

Example 268. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1S,2S)-2-aminocyclohexylamino)pyrimidine-5-carboxamide



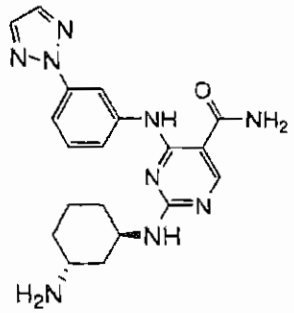
[0782] The title compound was prepared using the same chemistry shown for Example 87 with commercially available (1S,2S)-cyclohexane-1,2-diamine and DIEA. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV λ=250 nm.

Example 269. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,3S)-3-aminocyclohexylamino)pyrimidine-5-carboxamide (racemic)



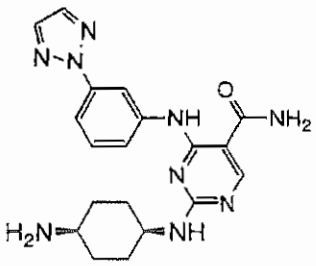
[0783] The title racemic compound was prepared using the same chemistry shown for Example 87 with commercially available cis-cyclohexane-1,3-diamine and DIEA. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV λ=252 nm.

Example 270. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,3R)-3-aminocyclohexylamino)pyrimidine-5-carboxamide (racemic)



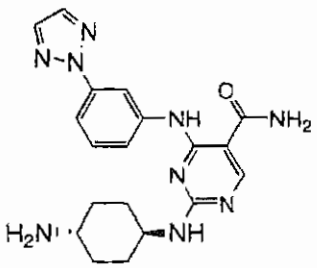
[0784] The title racemic compound was prepared using the same chemistry shown for Example 87 with commercially available trans-cyclohexane-1,3-diamine and DIEA. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV λ=252 nm.

Example 271. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1S,4S)-4-aminocyclohexylamino)pyrimidine-5-carboxamide



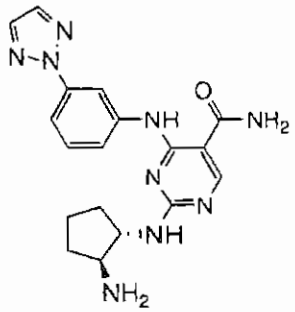
[0785] The title compound was prepared using the same chemistry shown for Example 87 with commercially available cis-cyclohexane-1,4-diamine and DIEA. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV λ=252 nm.

Example 272. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,4R)-4-aminocyclohexylamino)pyrimidine-5-carboxamide



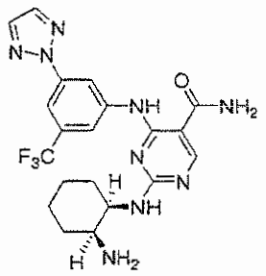
[0786] The title compound was prepared using the same chemistry shown for Example 417 with commercially available trans-cyclohexane-1,4-diamine and DIEA. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV λ=252 nm.

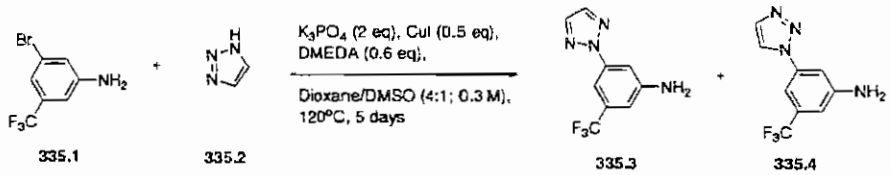
Example 273. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1S,2S)-2-aminocyclopentylamino)pyrimidine-5-carboxamide (racemic)



[0787] The title racemic compound was prepared using the same chemistry shown for Example 417 with commercially available trans-cyclopentane-1,2-diamine and DIEA. MS found for $C_{18}H_{21}N_9O$ as $(M+H)^+$ 380.4. UV λ=251 nm.

Example 274: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)phenylamino)pyrimidine-5-carboxamide

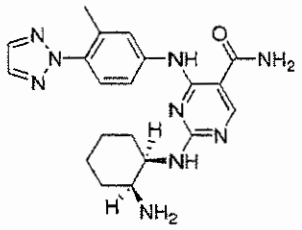


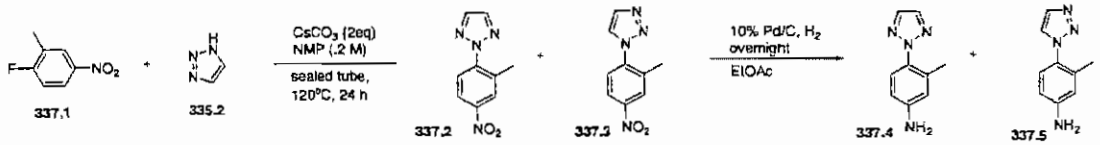


[0788] A mixture of 3-bromo-5-(trifluoromethyl)aniline **335.1** (1.08 g, 4.50 mmol) [CAS 54962-75-3, 1H-1,2,3-triazole **335.2** (1.04 mL, 18.0 mmol), K_3PO_4 (1.91 g, 9.00 mmol), CuI (428 mg, 2.25 mmol), N,N'-dimethylethylenediamine (0.29 mL, 2.70 mmol) in 12 mL dioxane and 3mL DMSO was stirred in a sealed tube at 120°C for 5 days. A mixture of **335.3** and **335.4** (in ~1.4:1 ratio) was obtained. The mixture was diluted with EtOAc (250 mL), washed with water, brine, dried over $MgSO_4$, filtered, and was concentrated in vacuo. The crude mixture was subjected to flash column chromatography to isolate **335.3**.

[0789] Aniline **335.3** was reacted with **300.4** according to reaction conditions outlined in Example 232. The chemistry of the scheme was completed to yield the title compound. MS found for $C_{20}H_{22}F_3N_9O$ as $(M+H)^+$ 462.3. UV λ=259 nm. δ 1.50-2.00 (m, 8H), 3.61-3.68 (m, 1H), 4.80-4.88 (m, 1H), 7.80 (s, 1H), 8.05 (s, 2H), 8.15 (s, 1H), 8.60 (s, 1H), 9.05 (s, 1H)

Example 275: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-methyl-4-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide

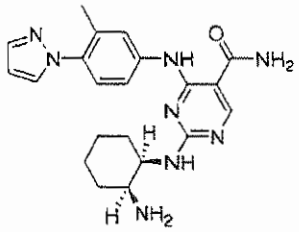




[0790] A mixture of 4-fluoro-3-methylnitrobenzene **337.1** (819 mg, 5.28 mmoL) [CAS 455-88-9], 1H-1,2,3-triazole **335.2** (1.23 mL 21.1 mmol) [CAS 288-36-8], and cesium carbonate (3.44 g, 10.6 mmol) in 25 mL dry NMP was stirred in a sealed tube at 120°C for 24 h. It was cooled, diluted with 400 mL ethyl acetate and washed with water. The aqueous phase was further extracted with EtOAc (2x200 mL). The combined organic phase was washed with water and brine, dried over $MgSO_4$ and filtered to yield a solution of crude products **337.2 and 337.3** in ~1:1 ratio. This solution was concentrated to 100 mL and a catalytic amount of 10% Pd/C was added. To this suspension was mounted a hydrogen balloon for overnight stirring. The mixture was filtered through celite and concentrated in vacuo to afford crude anilines **337.4** and **337.5**. MS found for $C_9H_{10}N_4$ as $(M+H)^+$ 175.1. The two anilines were purified using flash column.

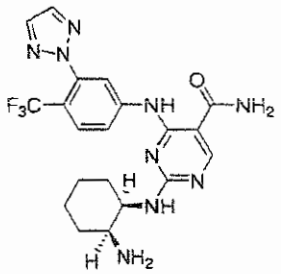
[0791] Aniline **337.4** was reacted with **300.4** and was subjected to the chemistry shown in Example 232 to yield the title compound. MS found for $C_{20}H_{25}N_9O$ as $(M+H)^+$ 408.4. UV λ=239, 296 nm. δ 1.5-2.0 (m, 8H), 2.38 (s, 3H), 3.65-3.75 (m, 1H), 4.35-4.45 (m, 1H), 7.52-7.62 (m, 1H), 7.65-7.75 (m, 2H), 7.95 (s, 2H), 8.55 (s, 1H).

Example 276: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-methyl-4-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide



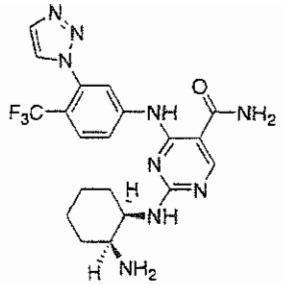
[0792] This compound was prepared utilizing the chemistry in example 275. Specifically, pyrazole [CAS 288-13-1] and **337.1** were reacted to form 3-methyl-4-(1H-pyrazol-1-yl)benzenamine. This aniline was then reacted with **300.4** according to conditions outlined in Example 232. The chemistry of the scheme was completed to yield the title compound. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 407.5. UV λ=238, 296 nm. δ 1.5-2.0 (m, 8H), 2.25 (s, 3H), 3.60-3.70 (m, 1H), 4.35-4.45 (m, 1H), 6.55 (s, 1H), 7.40 (d,1H), 7.60-7.68 (m, 2H), 7.75 (br s, 1H), 7.82 (br s, 1H), 8.55 (s, 1H).

Example 277: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(2H-1,2,3-triazol-2-yl)-4-(trifluoromethyl)phenylamino)pyrimidine-5-carboxamide



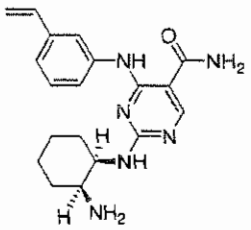
[0793] This compound was prepared utilizing a modified procedure from the chemistry in example 275. Notably, 2-Fluoro-4-nitro-1-trifluoromethylbenzene [CAS 69411-67-2] was used instead of 2-Fluoro-1-methyl-4-nitrobenzene [CAS 1427-07-2], and the initial displacement reaction was stirred at 45°C for 3 h. After hydrogenation, the resulting aniline was reacted with **300.4** according to conditions outlined in Example 232. The chemistry of the scheme was completed to yield the title compound. MS found for $C_{17}H_{18}F_3N_9O$ as $(M+H)^+$ 462.3. UV λ= 245, 295 nm. δ 1.50-1.95 (m, 8H), 3.58-3.64 (m, 1H), 4.43-4.51 (m, 1H), 7.60-7.66 (m, 1H), 7.90 (d, 1H), 8.04 (s, 2H), 8.52-8.58 (m, 1H), 8.62 (s, 1H).

Example 278: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(1H-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenylamino)pyrimidine-5-carboxamide



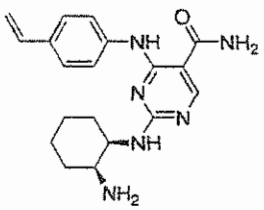
[0794] The 1-substituted triazole precursor of the title compound was formed in the reaction described in example 277. After hydrogenation, the resulting aniline was reacted with **300.4** according to conditions outlined in Example 232. The chemistry of the scheme was completed to yield the title compound. MS found for $C_{17}H_{18}F_3N_9O$ as $(M+H)^+$ 462.3. UV λ= 245, 295 nm. δ 1.45-1.85 (m, 8H), 3.58-3.64 (m, 1H), 4.38-4.46 (m, 1H), 7.63-7.71 (m, 1H), 7.89-7.97 (m, 2H), 8.34 (br s, 1H), 8.49-8.56 (m, 1H), 8.62 (s, 1H).

Example 279: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-vinylphenylamino)pyrimidine-5-carboxamide



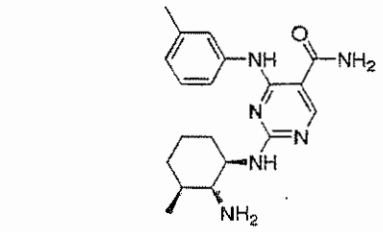
[0795] Commerically available 3-vinylaniline was reacted with **72.3** and subjected to the subsequent chemistry shown in example 87 to yield the title compound. MS found for $C_{19}H_{24}N_6O$ as $(M+H)^+$ 353.4. UV λ= 244 nm.

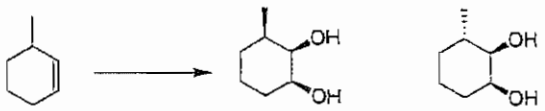
Example 280: 2-(cis-2-aminocyclohexylamino)-4-(4-vinylphenylamino)pyrimidine-5-carboxamide



The title compound was synthesized utilizing the chemistry in Example 11. However, instead of aniline **72.4**, 4-vinylaniline [CAS 1520-21-4] was utilized. MS found for $C_{19}H_{24}N_6O$ as $(M+H)^+$ 353.4. UV λ= 236, 310 nm.

Example 281: 2-(cis-2-amino-cis-3-methylcyclohexylamino)-4-(3-methylphenylamino)pyrimidine-5-carboxamide

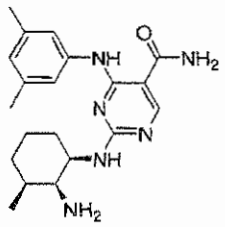




This compound was synthesized utilizing the same chemistry shown in Example 302.

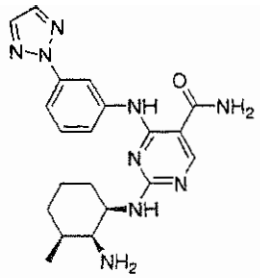
MS found for $C_{19}H_{26}N_6O$ as $(M+H)^+$ 355.4. UV λ=242, 289 nm. δ 1.00 (d, 3H), 1.20-1.95 (m, 7H), 2.40 (s, 3H), 3.18 (s, 3H), 3.72-3.80 (m, 1H), 4.02-4.10 (m, 1H), 7.07-7.14 (m, 1H) 7.25-7.35 (m, 2H), 7.41-7.48 (m, 1H), 8.54 (s, 1H).

Example 282: 2-(cis-2-amino-cis-3-methylcyclohexylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



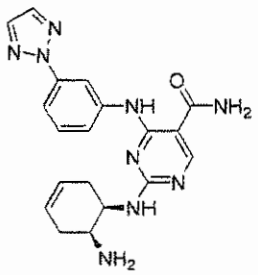
[0796] This compound was synthesized utilizing the same chemistry shown in Example 303. MS found for $C_{20}H_{28}N_6O$ as $(M+H)^+$ 369.4. UV λ=240, 290 nm. δ 1.00 (d, 3H), 1.20-1.95 (m, 7H), 2.38 (s, 6H), 3.70-3.78 (m, 1H), 4.04-4.12 (m, 1H), 6.95 (s, 1H), 7.19-7.25 (m, 2H), 8.50 (s, 1H).

Example 283: 2-(cis-2-amino-cis-3-methylcyclohexylamino)-4-(3-(2H-1,2,3-triazol-2-yl) phenylamino)pyrimidine-5-carboxamide



[0797] This compound was synthesized utilizing the same chemistry shown in Example 298. MS found for $C_{20}H_{25}N_9O$ as $(M+H)^+$ 408.4. UV λ=250 nm. δ 0.75-0.85 (m, 3H), 1.20-1.95 (m, 7H), 3.62-3.70 (m, 1H), 4.20-4.26 (m, 1H), 7.38-7.42 (m, 1H), 7.55 (t, 1H), 7.89-7.94 (m, 1H), 7.97 (s, 2H), 8.56 (s, 1H), 8.66-8.70 (m, 1H).

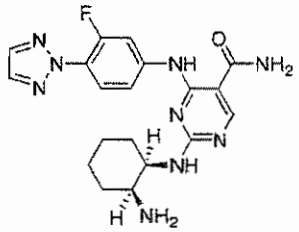
Example 284: 2-(cis-6-aminocyclohex-3-enylamino)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



This compound was synthesized utilizing the same chemistry shown in Example 298.

[0798] MS found for $C_{19}H_{21}N_9O$ as $(M+H)^+$ 392.3. UV λ=250 nm.

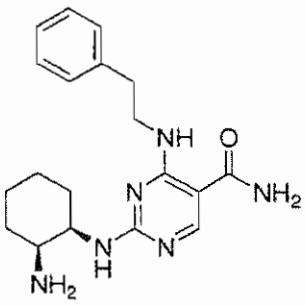
Example 285: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-fluoro-4-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



[0799] The 3-fluoro-4-(2H-1,2,3-triazole) aniline intermediate was prepared by reacting 1H-1,2,3-triazole and 4-bromo-3-fluoroaniline [CAS 656-65-5] according to example 92. This intermediate was then reacted with **300.4** according to the reaction conditions outlined in Example 232. The chemistry of the scheme was completed to yield the title compound. MS

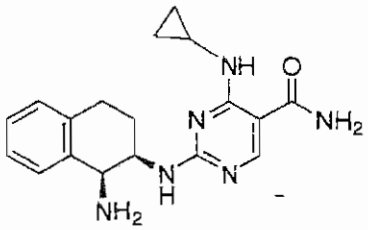
found for $C_{19}H_{22}FN_9O$ as $(M+H)^+$ 412.4. UV λ=242, 305 nm. δ 1.5-2.0 (m, 8H), 3.75-3.85 (m, 1H), 4.40-4.50 (m, 1H), 7.45 (d, 1H), 7.75-7.85 (m, 1H), 7.95-8.1 (m, 3H), 8.60 (s, 1H).

Example 286: 2-((1SR, 2S)-2-aminocyclohexylamino)-4-(phenethylamino)pyrimidine-5-carboxamide



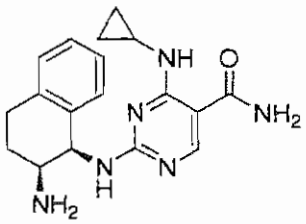
[0800] The title compound was prepared using the same synthetic scheme demonstrated in Example 9. MS found for $C_{19}H_{26}N_6O$ as $(M+H)^+$ 355.4. UV: λ = 232.2.

Example 287 2-((1S,2R)-1-amino-1,2,3,4-tetrahydronaphthalen-2-ylamino)-4-(cyclopropylamino)pyrimidine-5-carboxamide



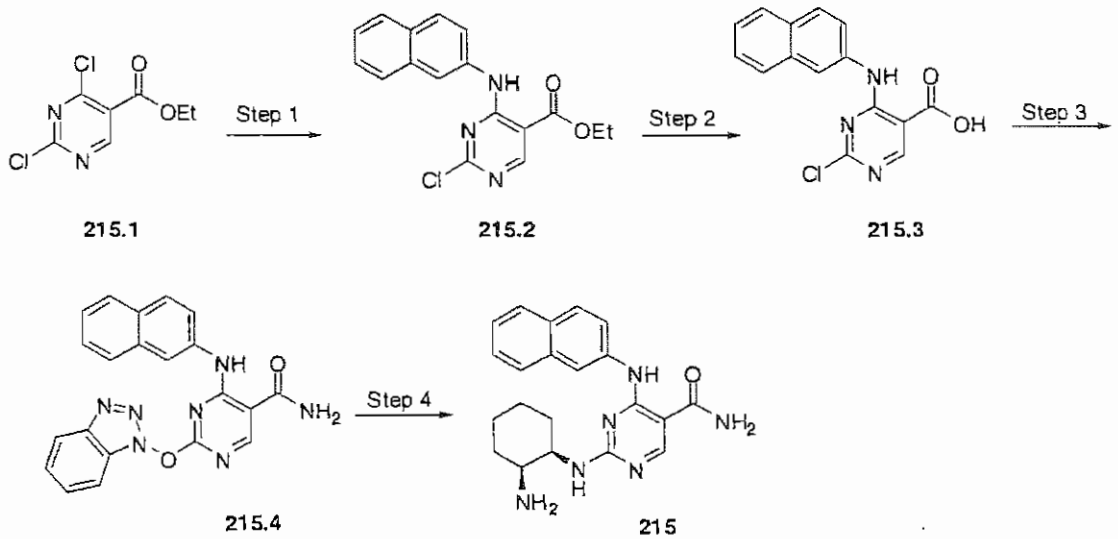
[0801] The above compound was prepared using similar procedure as described. MS found for $C_{18}H_{22}N_6O$ as $(M+H)^+$ 339.2.

Example 288. 2-((1R,2S)-2-amino-1,2,3,4-tetrahydronaphthalen-1-ylamino)-4-(cyclopropylamino)pyrimidine-5-carboxamide



[**0802**] The above compound was prepared using similar procedure as described. MS found for $C_{18}H_{22}N_6O$ as $(M+H)^+$ 339.2.

Example 289. 2-((1R,2S)-2-aminocyclohexylamino)-4-(naphthalen-2-ylamino)pyrimidine-5-carboxamide



[0803] Step 1: To a solution of Dichloropyrimidine **215.1** (700 mgs, 3.16 mmol) in acetonitrile (8 mL) was added a suspension of 6-amino-naphthylene (3.16 mmol), diisopropylamine (0.61 mL, 3.5 mmol) in acetonitrile (10 mL) at 0 °C. Reaction mixture was then slowly warmed to rt and stirred overnight. The reaction mixture was then diluted with water and the precipitate collected by filtration affording the desired product **215.2**.

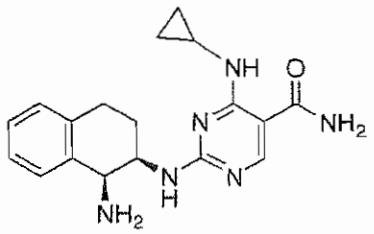
[0804] Step 2: Ethyl ester **215.2** (960 mgs, 2.81 mmol) was diluted with 1,4-dioxane (7.5 mL) and ethanol (2 mL), followed by aqueous lithium hydroxide (1.0 M, 2.8 mL, 2.8 mmol) and stirred at rt until all starting material had been converted to the carboxylic acid. The reaction was then diluted with and acidified with 1N HCl (3.0 mL). The resulting suspension was then filtered, washed with water and dried giving 870 mgs of the carboxylic acid **215.3**.

[0805] Step 3: To carboxylic acid **215.3** (870 mgs, 2.76 mmol), EDC (792 mgs, 4.14 mmol), HOBt (560 mgs, 4.14 mmol) in N,N-dimethylformamide (14 mL) was added ammonia (0.5 M in 1,4-dioxane, 14 mL, 6.9 mmol) and stirred overnight. The reaction mixture was then diluted with water (100 mL) and the precipitate collected by filtration affording the desired product **215.4**.

[0806] Step 4: A mixture of Benzotriazolyl ether **215.4** (75 mgs, 0.182 mmol), cis-1,2-diaminocyclohexane (25 mgs, 0.218 mmol), DIPEA (0.1 mL, 0.546 mmol) in iso-propanol (3 mL) was heated in microwave (Emry's Optimizer) at 130°C for 20 min.

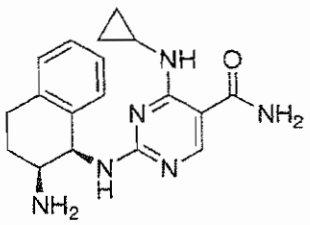
[0807] The reaction mixture was then diluted with water and acetonitrile and directly purified by preparative HPLC affording the desired product, **215**, after lyophilization. MS found for $C_{21}H_{22}N_6O$ as $(M+H)^+$ 377.3.

Example 290 2-((1S,2R)-1-amino-1,2,3,4-tetrahydronaphthalen-2-ylamino)-4-(cyclopropylamino)pyrimidine-5-carboxamide



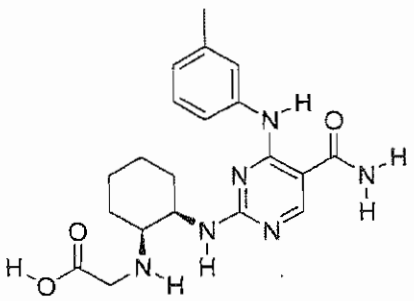
[0808] The above compound was prepared using a similar procedure as described herein. MS found for $C_{18}H_{22}N_6O$ as $(M+H)^+$ 339.2.

Example 291. 2-((1R,2S)-2-amino-1,2,3,4-tetrahydronaphthalen-1-ylamino)-4-(cyclopropylamino)pyrimidine-5-carboxamide



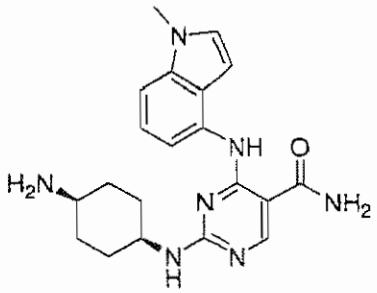
[0809] The above compound was prepared using similar procedure as described. MS found for $C_{18}H_{22}N_6O$ as $(M+H)^+$ 339.2.

Example 293: 2-((1*S*, 2*R*)-2-(5-carbamoyl-4-(*m*-tolylamino)pyrimidin-2-ylamino)cyclohexylamino)acetic acid



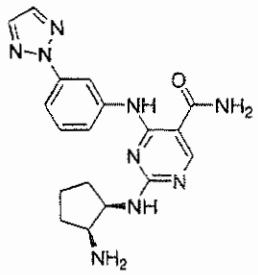
[0810] The above compound was prepared using a similar procedure as described herein. MS found for $C_{20}H_{26}N_6O_3$ as $(M+H)^+$ 399.2. UV: λ = 240.5, 212.2, 287.8.

Example 294: 2-(cis-4-aminocyclohexylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



[0811] The title compound was prepared using the same synthetic scheme demonstrated in Example 271. MS found for $C_{20}H_{25}N_7O$ as $(M+H)^+$ 380.4. UV: $\lambda = 245.4$.

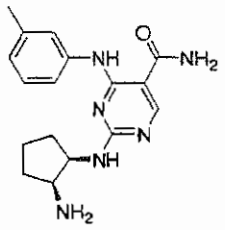
Example 295: 2-(cis-2-aminocyclopentylamino)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide

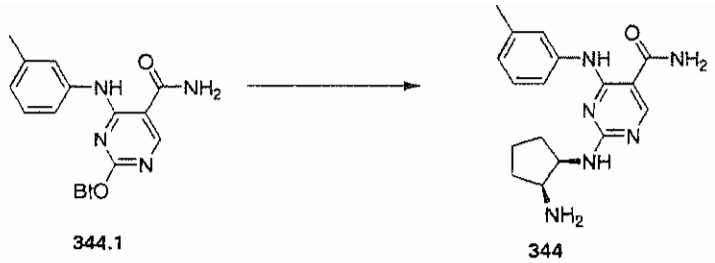


This compound was synthesized utilizing the same chemistry shown in Example 87.

[0812] MS found for $C_{18}H_{21}N_9O$ as $(M+H)^+$ 380.4. UV λ=249 nm.

Example 296: 2-(cis-2-aminocyclopentylamino)-4-(3-methylphenylamino)pyrimidine-5-carboxamide

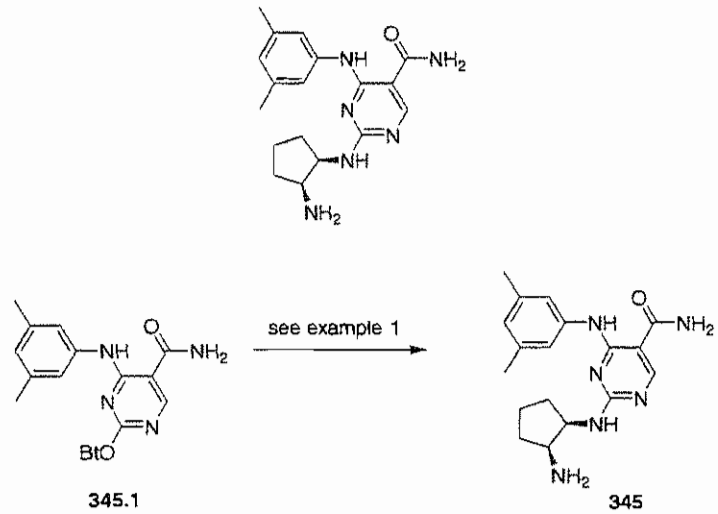




344.1 344

[0813] Compound **344** was synthesized utilizing similar chemistry as that found in example 1. The benzotrizole containing precursor **344.1** was reacted with cis-diamine **343.4** to give the title compound. MS found for $C_{17}H_{22}N_6O$ as $(M+H)^+$ 327.4. UV λ=240, 287 nm.

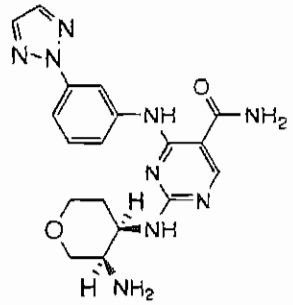
Example 297: 2-(cis-2-aminocyclopentylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



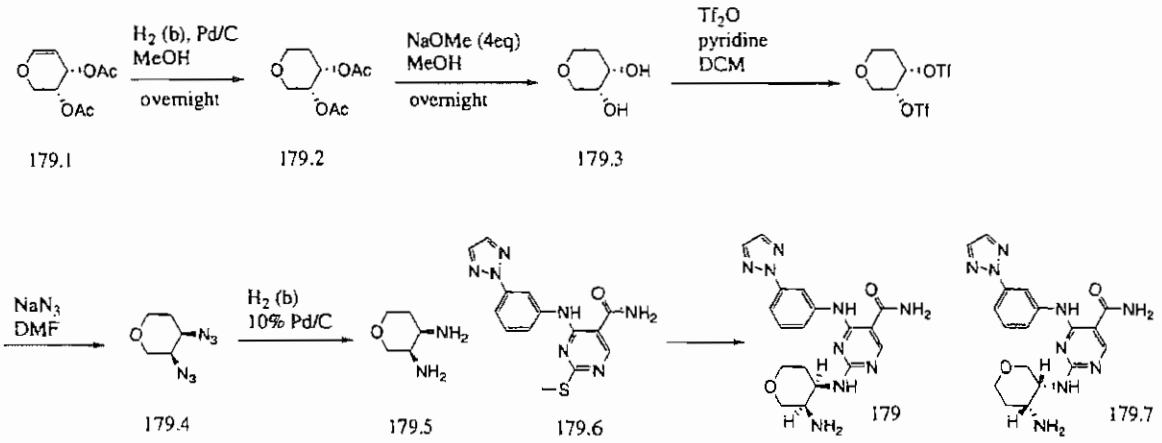
345.1 345

[0814] Compound **345** was synthesized utilizing similar chemistry as that found in example 1. The benzotrizole containing precursor **345.1** was reacted with cis-diamine **343.4** to give the title compound. MS found for $C_{18}H_{24}N_6O$ as $(M+H)^+$ 341.4. UV λ=217, 239, 290 nm.

Example 298. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)pyrimidine-5-carboxamide



Scheme:



[0815] Step 1: 3,4-Di-O-acetyl-D-arabinal [CAS 3945-17-3] (179.1) was made by standard literature method or bought as commercially available chemical reagent. It (5.0 g, 25 mmol) was dissolved in 100 mL methanol. To it was added 1.0 gram of 10% Pd/C and the mixture was stirred under a hydrogen balloon for overnight to give compound 179.2. The mixture was filtered to remove Pd/C. The filtrate was treated with sodium methoxide (5.4 g, 100 mmol) at RT for overnight. It was quenched with 6N HCl (20 mL) in ice bath. The mixture was concentrated in vacuo to dryness. The residue was treated with 500 mL ethyl acetate and vigorously stirred at 45°C for 30 min. The slurry was filtrered using a fine-grade Buchner funnel. The filtrate was concentrated in vacuo and pumped overnight to afford diol 179.3 (2.82 g, 95%).

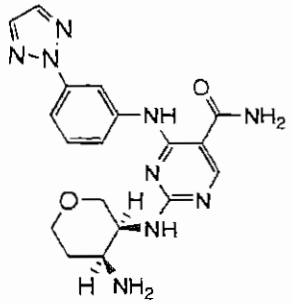
[0816] Step 2: Diol 179.3 (205 mg, 1.74 mmol) was dissolved in 10 mL dry DCM. To it were added pyridine (0.35 mL, 4.34 mmol) and in the ice bath Tf_2O (0.63 mL, 3.74 mmol). The reaction was monitored by TLC (stain: ammonium molybdate (12.5 g), Ce(IV) sulfate (5 g), 10% H_2SO_4 500 mL; heated using strong heat from a hot heat gun after dipping). The reaction was over in 15 min. To the mixture were added 24 mL DMF and 3 mL HMPA. Then sodium azide (2.28 g, 35 mmol) was added. The mixture was then stirred at 50°C for 3 h (reaction was complete in 1.5 h by TLC). The mixture was diluted with ethyl acetate, filtered, washed with brine. The organic phase was dried, concentrated and subjected to silic flash column to isolate diazide 179.4 (220 mg, 75%).

[0817] Step 3: Diazide 179.4 (220 mg, 1.3 mmol) was dissolved in 40 mL ethyl acetate. It was treated with 10% Pd/C under H_2 balloon for overnight. The mixture was filtered through celite and concentrated in vacuo to offer crude diamine 179.5.

[0818] Step 4: Intermediate 179.6 was made using aniline 156.6 (Example 66) using the same chemistry shown in Example 1. MS found for $C_{14}H_{13}N_7OS$ as $(M+H)^+$ 328.2.

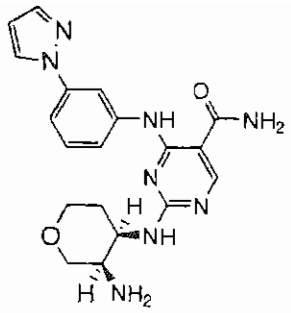
[0819] Step 5: Methylthio pyrimidine 179.6 (105 mg, 0.32 mmol) was dissolved in 2 mL NMP and treated with MCPBA (102 mg, 0.38 mmol) at RT for 45 min. To it were added DIEA (226 μL, 1.3 mmol) and diamine 179.5 made in Step 3. The mixture was stirred 2 h at 90°C for 2h. Two major products found were 179 and 179.7 at 1.58 min and 1.55 min by reverse phase analytical HPLC (5 min run) in ratio of 1.7:1 in favor of 179. Compound 179 was isolated from the mixture using reverse phase prep HPLC. MS found for $C_{18}H_{21}N_9O_2$ as $(M+H)^+$ 396.3. UV λ=249 nm. NMR (CD_3OD): δ 8.66 (s, 1H), 8.52 (s, 1H), 7.93 (s, 2H), 7.82 (m, 1H), 7.47 (m, 1H), 7.27 (m, 1H), 4.40 (m, 1H), 4.00 (m, 1H), 3.78 (m, 1H), 3.72 (m, 1H), 3.55 (m, 1H), 3.42 (m, 1H), 2.00 (m, 1H), 1.86 (m, 1H) ppm.

Example 299. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((3S,4S)-4-aminotetrahydro-2H-pyran-3-ylamino)pyrimidine-5-carboxamide



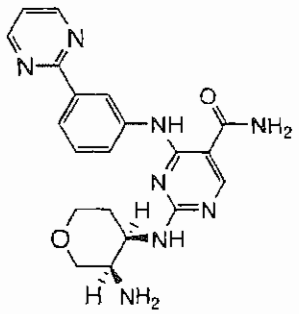
[0820] This compound was prepared using the same chemistry shown for Example 298 using 3,4-Di-O-acetyl-L-arabinal [CAS 3945-18-4], commercially available, to replace 3,4-Di-O-acetyl-D-arabinal [CAS 3945-17-3]. The title compound was the minor product isolated from the reaction mixture in the final step. MS found for $C_{18}H_{21}N_9O_2$ as $(M+H)^+$ 396.3. UV λ=250 nm. NMR (CD_3OD): δ 8.73 (s, 1H), 8.58 (s, 1H), 8.09 (s, 2H), 7.90 (m, 1H), 7.54 (m, 1H), 7.34 (m, 1H), 4.50 (m, 1H), 4.06 (m, 1H), 3.83 (m, 1H), 3.76 (m, 1H), 3.63 (m, 1H), 3.60 (m, 1H), 3.43 (m, 1H), 2.08 (m, 1H), 1.92 (m, 1H) ppm.

Example 300. 4-(3-(1H-pyrazol-1-yl)phenylamino)-2-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)pyrimidine-5-carboxamide



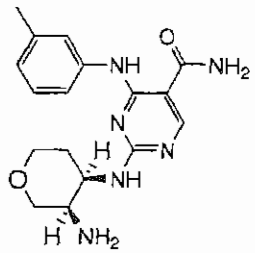
[0821] This compound was prepared using the same chemistry shown for Example 298. MS found for $C_{19}H_{22}N_8O_2$ as $(M+H)^+$ 395.4. UV λ=246 nm.

Example 301. 2-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



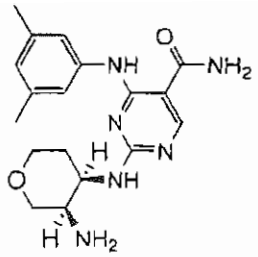
[0822] This compound was prepared using the same chemistry shown for Example 298. MS found for $C_{20}H_{22}N_8O_2$ as $(M+H)^+$ 407.4. UV λ=249 nm.

Example 302. 2-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



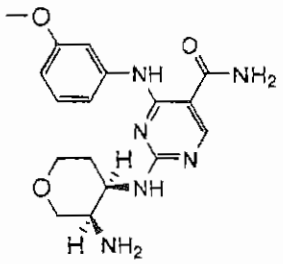
[0823] This compound was prepared using the same chemistry shown for Example 298. MS found for $C_{17}H_{22}N_6O_2$ as $(M+H)^+$ 343.3. UV λ=240, 288 nm.

Example 303. 2-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



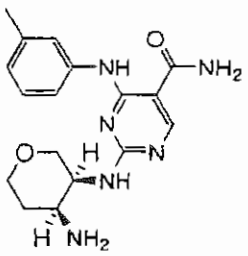
[0824] This compound was prepared using the same chemistry shown for Example 298. MS found for $C_{18}H_{24}N_6O_2$ as $(M+H)^+$ 357.4. UV λ=240, 290 nm.

Example 304. 2-((3R,4R)-3-aminotetrahydro-2H-pyran-4-ylamino)-4-(3-methoxyphenylamino)pyrimidine-5-carboxamide



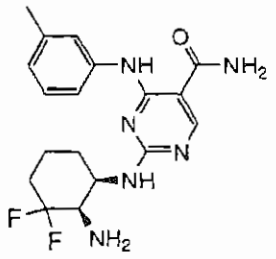
[0825] This compound was prepared using the same chemistry shown for Example 298. MS found for $C_{17}H_{22}N_6O_3$ as $(M+H)^+$ 359.4. UV λ=240, 283 nm. NMR (CD_3OD): δ 8.46 (s, 1H), 7.29 (m, 1H), 7.26 (m, 1H), 6.99 (m, 1H), 6.74 (m, 1H), 4.25 (m, 1H), 4.03 (m, 1H), 3.89 (m, 1H), 3.79 (m, 1H), 3.77 (s, 3H), 3.62 (m, 1H), 3.55 (m, 1H), 2.02 (m, 1H), 1.82 (m, 1H) ppm.

Example 305. 2-((3S,4S)-4-aminotetrahydro-2H-pyran-3-ylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide

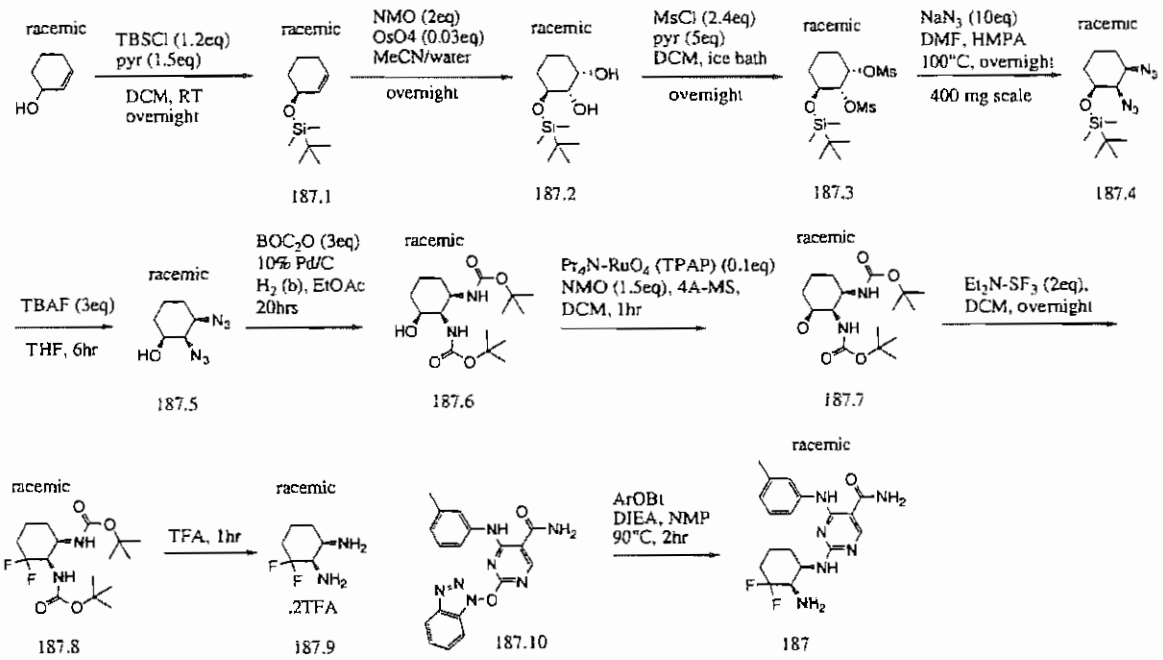


[0826] This compound was prepared using the same chemistry shown for Example 299. MS found for $C_{17}H_{22}N_6O_2$ as $(M+H)^+$ 343.3. UV λ=241, 287 nm. NMR (CD_3OD): δ 8.53 (s, 1H), 7.47 (m, 1H), 7.37 (m, 1H), 7.28(m, 1H), 7.02 (m, 1H), 4.50 (m, 1H), 4.05 (m, 1H), 4.01 (m, 1H), 3.73-3.68 (m, 2H), 3.57 (m, 1H), 2.38 (s, 3H), 2.05 (m, 1H), 1.87 (m, 1H) ppm.

Example 306. 2-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide (racemic)



Scheme:



[0827] Step 1: 2-Cyclohexen-1-ol (5.0 mL, 50 mmol) was dissolved in 100 mL DCM. To it were added pyridine (12.2 mL, 150 mmol) and TBDMSCl (12.1 g, 80 mmol). The mixture was stirred at RT for overnight. The mixture was concentrated in vacuo to remove pyridine. The residue was taken into 300 mL ethyl acetate and 200 mL water. The organic phase was separated, washed with brine, dried, concentrated and purified using silica flash column using 15% ethyl acetate in hexane. Compound 187.1 was thus got as oil (10.1 g, 94%).

[0828] Step 2: Compound 187.1 (10.1 g, 47.7 mmol) was dissolved in 70 mL acetonitrile. To it was added NMO (50% water solution, 22.5 mL, 95.4 mmol) and OsO_4 (4% water solution, 9.1 mL, 1.43 mmol). The mixture was stirred overnight at RT. It was diluted with 600 mL ethyl acetate, washed with brine, sat sodium bicarbonate, dried, concentrated and

purified by silica flash column using 60% ethyl acetate in hexane to give compound 187.2 (10.8 g, 92%) as oil.

[0829] Step 3: Diol 187.2 (10.8 g, 43.9 mmol) was dissolved in 200 mL DCM. In ica bath, to it were added pyridine (17.7 mL, 219 mmol) and dropwise MsCl (8.2 mL, 105 mmol). The mixture was stirred for overnight at RT. It was dilute with 500 mL DCM, washed with brine x3, dried, concentrated, purified using silica flash column with 45% ethyl acetate in hexane to give compound 187.3 (16.8 g, 95%) as oil.

[0830] Step 4: Compound 187.3 (15.7 g, 39 mmol) was dissolved in 80 mL DMF and 20 mL HMPA. To it was added sodium azide (16.5 g, 253 mmol). The mixture was stirred at 100°C for overnight (24 h). The mixture was diluted with 800 mL ethyl acetate, washed with water and brine x2, dried, concentrated and purified by silica flash column using 10% ethyl acetate in hexane to isolate diazide 187.4 (3.16 g, 27%) as oil.

[0831] Step 5: Compound 187.4 (1.21 g, 4.1 mmol) was dissolved in 60 mL dry THF. To it was added TBAF (1.0 M in THF, 8.2 mL, 8.2 mmol). The mixture was stirred for 2 h. It was quenched with methanol, concentrated in vacuo and subjected to silica flash column using 40-50% ethyl acetate in hexane to isolated compound 187.5 (854 mg, 99%) as oil.

[0832] Step 6: Compound 187.5 (450 mg, 2.5 mmol) was dissolved in 100 mL ethyl acetate. 10% Pd/C (500 mg) was added. The mixture was stirred under H_2 balloon for overnight (20 h). It was filtered through celite. The celite was washed thoroughly using ethyl acetate. The filtrate was concentrated and subjected to silica flash column to isolate compound 187.6 (650 mg, 79%) as solid. MS found for $C_{16}H_{30}N_2O_5$ as $(M+H)^+$ 331.3.

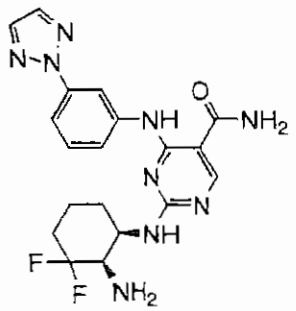
[0833] Step 7: Compound 187.6 (72 mg, 0.22 mmol) was dissolved in 10 mL dry DCM. To it were added 4A molecular sieve (activated) (100 mg), NMO (solid, 39 mg, 0.33 mmol) and at last TPAP (8 mg, 0.022 mmol). The mixture was stirred at RT for 2 h. It was concentrated and directly loaded on silica flash column to isolate compound 187.7 (77 mg, 100%) as solid. MS found for $C_{16}H_{28}N_2O_5$ as $(M+H)^+$ 329.3.

[0834] Step 8: Ketone 187.7 (134 mg, 0.41 mmol) was dissolved in 10 mL DCM. To it was added DAST (110 μL, 0.82 mmol). The mixture was stirred for overnight at RT. It was directly loaded onto silica flash column to isolate compound 187.8 (MS found for $C_{16}H_{28}F_2N_2O_4$ as $(M+H)^+$ 351.2) using 20% ethylacetate in hexane. It was then treated with

neat TFA at RT for 1 h and concentrated to dryness to afford compound 187.9. MS found for $C_6H_{12}F_2N_2$ as $(M+H)^+$ 151.2.

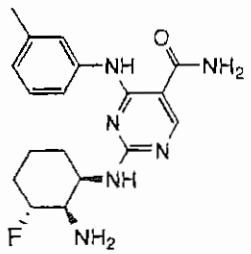
[0835] Step 9: Compound 187.10 (72 mg, 0.2 mmol) was dissolved in 3 mL NMP. To it was added DIEA (350 µL, 2 mmol) and all the crude compound 187.9 made in Step 8. The mixture was stirred at 90°C for 2 h and subjected to reverse phase prep HPLC to isolate the title compound 187 (racemic). MS found for $C_{18}H_{22}F_2N_6O$ as $(M+H)^+$ 377.2. UV λ=239, 292 nm. NMR (CD_3OD): δ 8.51 (s, 1H), 7.45 (m, 1H), 7.34 (m, 1H), 7.25 (m, 1H), 7.02 (m, 1H), 4.61 (m, 1H), 4.10 (m, 1H), 2.36 (s, 3H), 1.8-2.1 (m, 6H) ppm.

Example 307. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,2R)-2-amino-3,3-difluorocyclohexylamino)pyrimidine-5-carboxamide (racemic)

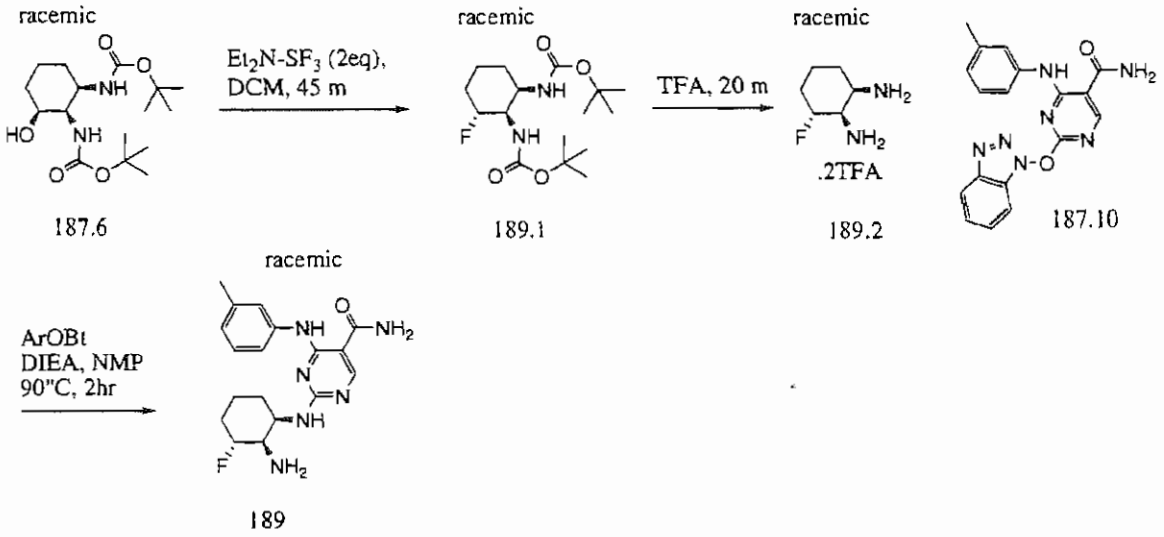


[0836] The title compound was prepared using the same chemistry shown for Example 306. MS found for $C_{19}H_{21}F_2N_9O$ as $(M+H)^+$ 430.4. UV λ=250 nm.

Example 308. 2-((1R,2R,3R)-2-amino-3-fluorocyclohexylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide (racemic)



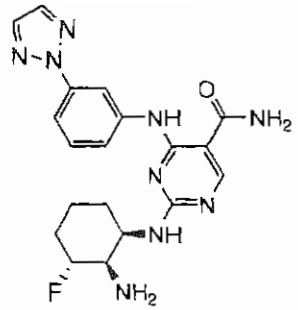
Scheme.



[0837] Step 1: Compound 187.6 (described in Example 306) (350 mg, 1. 06 mmol) was dissolved in 20 mL DCM. At -78°C, to it was added a solution of DAST (280 μL, 2.12 mmol) in 10 mL DCM dropwise. The mixture was stirred in the cold bath for 45 min, diluted with ethyl acetate, washed with brine, concentrated and subjected by flash column to isolate compound 189.1 in 30% yield. MS found for $C_{16}H_{29}FN_2O_4$ as $(M+H)^+$ 333.2. It was treated with 3 mL neat TFA for 20 min. The mixture was concentrated to dryness to afford crude compound 189.2. MS found for $C_6H_{13}FN_2$ as $(M+H)^+$ 133.1.

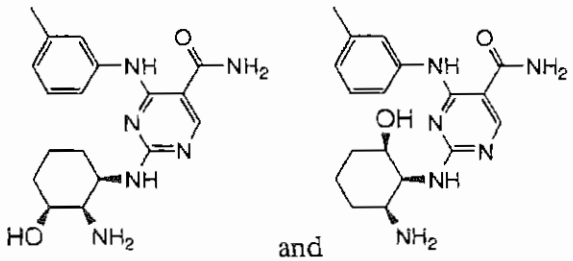
[0838] Step 2: Compound 187.10 (108 mg, 0.3 mmol) was dissolved in 3 mL NMP. To it was added DIEA (260 μL, 1.5 mmol) and all the crude compound 189.2 made in Step 1. The mixture was stirred at 90°C for 2 h and subjected to reverse phase prep HPLC to isolate the title compound 189 (racemic). MS found for $C_{18}H_{23}FN_6O$ as $(M+H)^+$ 359.2. UV λ=240, 292 nm. NMR (CD_3OD): δ 8.51 (s, 1H), 7.45 (m, 1H), 7.38 (m, 1H), 7.24 (m, 1H), 6.97 (m, 1H), 4.83-4.78 (m, 2H), 3.65 (m, 1H), 2.36 (s, 3H), 1.8-2.2 (m, 6H) ppm.

Example 309. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,2R,3R)-2-amino-3-fluorocyclohexylamino)pyrimidine-5-carboxamide (racemic)

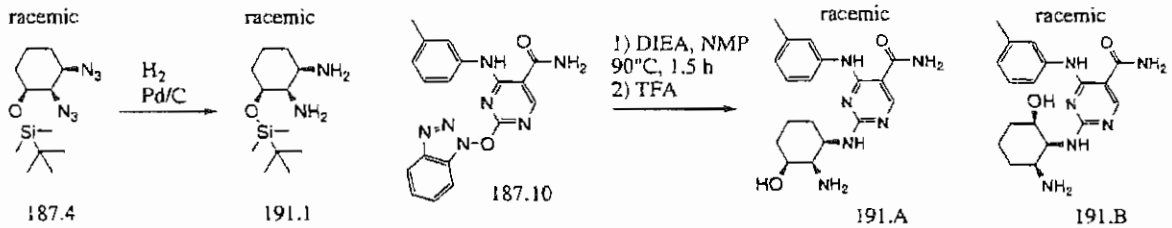


[0839] The title compound was prepared using the same chemistry shown for Example 308. MS found for $C_{19}H_{22}FN_9O$ as $(M+H)^+$ 412.4. UV λ=251 nm.

Example 310. 2-((1R,2R,3S)-2-amino-3-hydroxycyclohexylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide (racemic, 191A) and 2-((1S,2S,6R)-2-amino-6-hydroxycyclohexylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide (racemic, 191B)



Scheme.

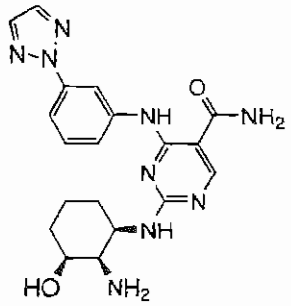


[0840] Step 1: Compound 187.4 (described in Example 306) (180 mg, 0.60 mmol) was dissolved in 50 mL ethyl acetate. To it was added 10% Pd/C (100 mg) and the mixture was stirred for overnight under a hydrogen balloon. The mixture was filtered through celite, which was then thoroughly washed with methanol. The filtrate was concentrated in vacuo to afford compound 191.1 in quantitative yield as oil. MS found for $C_{12}H_{28}N_2OSi$ as $(M+H)^+$ 245.3.

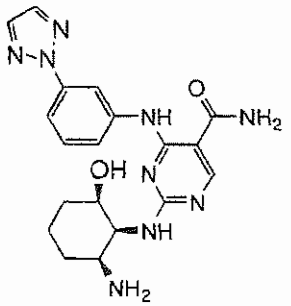
[0841] Step 2: Compound 191.1 from Step 1 was dissolved in 5 mL NMP. To it were added DIEA (313 µL, 1.8 mmol) and compound 187.10 (108 mg, 0.3 mmol). The mixture was stirred at 90°C for 90 min. To it were then added 10 mL methanol, 10 mL TFA and 3 mL

water. The mixture was stirred at 80°C for 2 h. It was concentrated in vacuo and subjected to reverse prep HPLC to isolate racemic title compounds 191.A and 191.B. Ratio of 191.A (less polar) and 191.B was 7:1 by analytical HPLC. Compound 191.A: MS found for $C_{18}H_{24}N_6O_2$ as $(M+H)^+$ 357.3. UV λ=243, 294 nm. Compound 191.B: MS found for $C_{18}H_{24}N_6O_2$ as $(M+H)^+$ 357.3. UV λ=243, 290 nm.

Example 311. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,2R,3S)-2-amino-3-hydroxycyclohexylamino)pyrimidine-5-carboxamide (racemic, 192.A) and 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1S,2S,6R)-2-amino-6-hydroxycyclohexylamino)pyrimidine-5-carboxamide (racemic, 192.B)

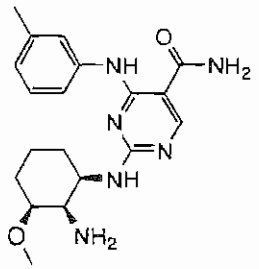


and

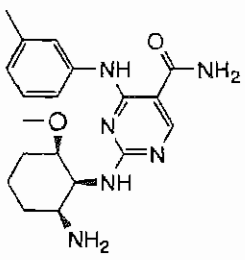


[0842] The two title racemic compounds were prepared using the same chemistry shown for Example 310. Ratio of 192.A (less polar) and 192.B was 1.6:1 by analytical HPLC. Compound 192.A: MS found for $C_{19}H_{23}N_9O_2$ as $(M+H)^+$ 410.4. UV λ=250 nm. Compound 192.B: MS found for $C_{19}H_{23}N_9O_2$ as $(M+H)^+$ 410.4. UV λ=249 nm.

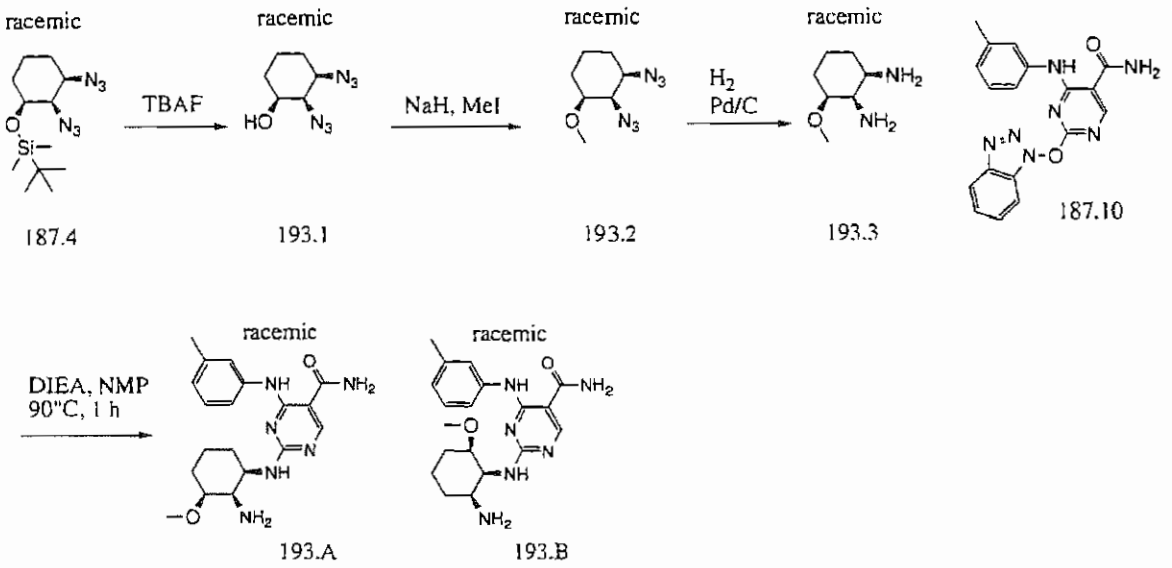
Example 312. 2-((1R,2R,3S)-2-amino-3-methoxycyclohexylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide (racemic, 193.A) and 2-((1S,2S,6R)-2-amino-6-methoxycyclohexylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide (racemic, 193.B)



and



Scheme.



187.4 193.1 193.2 193.3 187.10

193.A 193.B

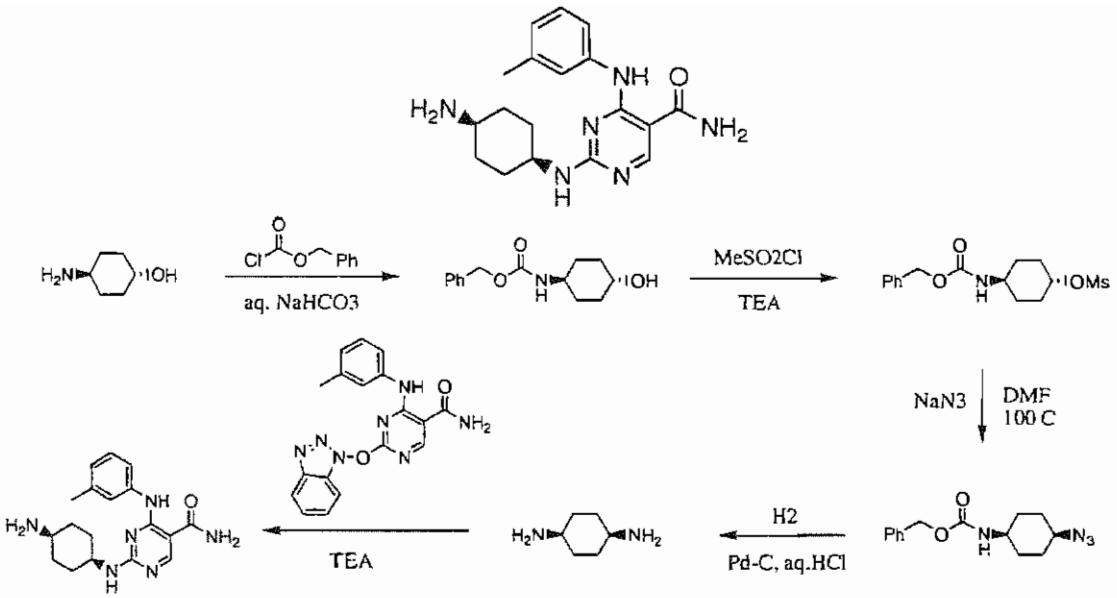
[0843] Step 1: Compound 187.4 (described in Example 306) (1.21 g, 4.1 mmol) was dissolved in 60 mL dry THF. To it was added TBAF (1.0 M in THF, 8.2 mL, 8.2 mmol). The mixture was stirred at RT for 2 h. It was concentrated and loaded onto silica flash column to isolate compound 193.1 (854 mg, 99%) as solid.

[0844] Step 2: Compound 193.1 (124 mg, 0.68 mmol) was dissolved in 10 mL dry THF. To it were added NaH (60 wt% in mineral oil, 55 mg, 1.36 mmol) and 5 min later iodomethane (0.42 mL, 6.8 mmol). The mixture was stirred for 1 h. It was concentrated in vacuo and loaded onto silica flash column to isolate compound 193.2 (115 mg, 85%) as oil.

[0845] Step 3: Compound 193.2 (115 mg, 0.58 mmol) made in Step 2 was dissolved in 80 mL ethyl acetate. To it was added 100 mg 10% Pd/C and the mixture was stirred under H_2 balloon for overnight. It was filtered through celite, and the celite was thoroughly washed with methanol. The filtrate was concentrated in vauo to give compound 193.3.

[0846] Step 4: All the compound 193.3 made in Step 3 was dissolved in 3 mL NMP. To it were added compound 187.10 (180 mg, 0.5 mmol) and DIEA (0.26 mL, 1.5 mmol). The mixture was stirred at 90°C for 1 h to give a mixture of 193.A (less polar) and 193.B in ratio of 6:1. The two racemic title compounds were isolated using reverse phase prep HPLC. Compound 193.A: MS found for $C_{19}H_{26}N_6O_2$ as $(M+H)^+$ 371.3. UV λ=247, 295 nm. Compound 193.B: MS found for $C_{19}H_{26}N_6O_2$ as $(M+H)^+$ 371.3. UV λ=242, 289 nm.

Example 313. 2-((1s,4s)-4-aminocyclohexylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



To a mixture of trans-4-aminocyclohexanol (2.07 g, 13.6 mmol) and $NaHCO_3$ (3.50 g, 41.7 mmol) in H_2O (20 mL) at room temperature, a solution of benzyl chloroformate (1.92 mL, 13.6 mmol) in dioxane (15 mL) was added. The mixture was stirred at room temperature for 20 h. The white precipitate was collected as benzyl (1R,4R)-4-hydroxycyclohexylcarbamate (3.37 g).

[0847] To a suspension of benzyl (1R,4R)-4-hydroxycyclohexylcarbamate (1.14 g, 4.58 mmol) and triethylamine (1.30 mL, 9.34 mmol) in CH_2Cl_2 (15 mL) at room temperature, methanesulfonyl chloride (0.425 mL, 5.49 mmol) was added. The mixture was stirred at room temperature for 20 h. More methanesulfonyl chloride (0.425 mL, 5.49 mmol) and triethylamine (1.00 mL) were added. Stirring was continued for 48 h. The reaction solution was washed with 5% $NaHCO_3$, then with 1 N HCl. The organic phase was separated, dried over Na_2SO_4, concentrated in vacuo to give (1R,4R)-4-(benzyloxycarbonyl)cyclohexyl methanesulfonate as a solid (1.13 g).

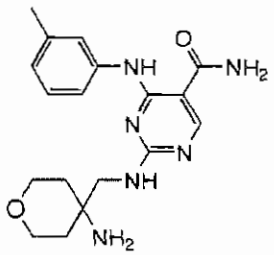
[0848] A mixture of (1R,4R)-4-(benzyloxycarbonyl)cyclohexyl methanesulfonate (1.13 g, 3.46 mmol) and NaN3 (0.674 g, 10.4 mmol) in DMF (10 mL) was stirred at 100 C for 20 h. Water and EtOAc were added. The organic phase was separated, washed with water, dried over Na_2SO_4, concentrated in vacuo to give benzyl (1s,4s)-4-azidocyclohexylcarbamate (0.819 g).

[0849] A mixture of benzyl (1s,4s)-4-azidocyclohexylcarbamate (400 mg, 1.46 mmol) and Pd-C (10%, 70 mg) in MeOH (20 mL) (containing 5 drops of 6N HCl) was hydrogenated

under balloon hydrogen for 20 h. It was filtered through celite. The filtrate was concentrated in vacuo to give (1s,4s)-cyclohexane-1,4-diamine (223 mg).

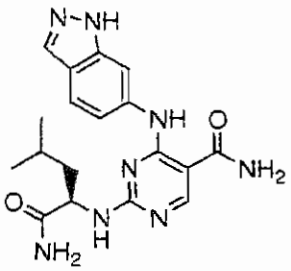
[0850] To a solution of (1s,4s)-cyclohexane-1,4-diamine (60 mg, 0.40 mmol) and TEA (0.208 mL, 1.50 mmol)in DMF (2 mL) and MeOH (1 mL), compound 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(m-tolylamino)pyrimidine-5-carboxamide (65 mg, 0.18 mmol) was added. The mixture was stirred at room temperature for 20 h. It was concentrated in vacuo. The residue was purified by HPLC to give the titled compound (30 mg). MS 341.2 (M+H); UV 247.8, 298.8.

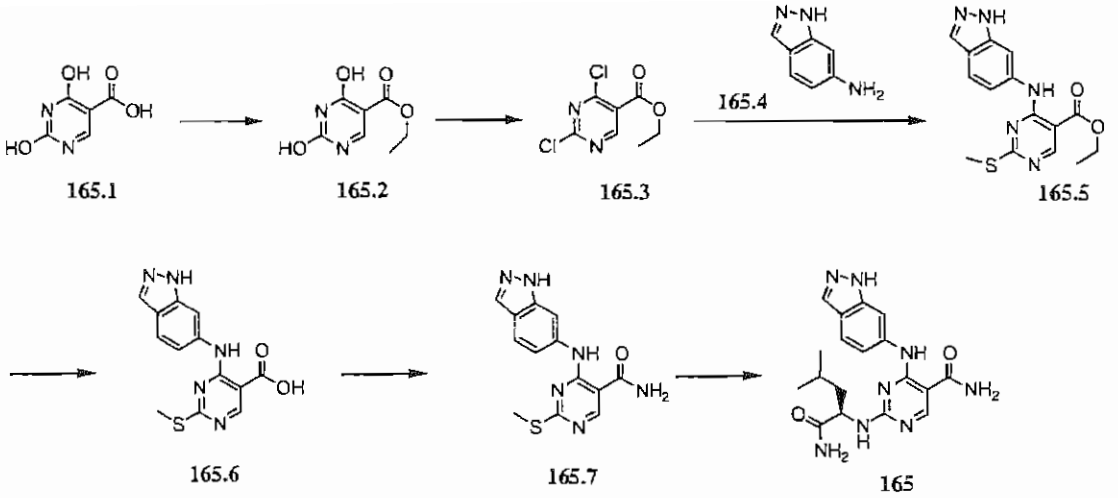
Example 314. 2-((4-aminotetrahydro-2H-pyran-4-yl)methylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



[**0851**] Compound 187.10 (as shown in Example 306) (70 mg, 0.19 mmol) was dissolved in 3 mL NMP. To it were added commercially available 4-(aminomethyl)tetrahydro-2H-pyran-4-amine (78 mg, 0.38 mmol) and DIEA (0.20 mL, 1.14 mmol). The mixture was stirred at 90°C for 2 h. From this mixture the title compound was isolated using reverse phase prep HPLC. MS found for $C_{18}H_{24}N_6O_2$ as $(M+H)^+$ 357.3. UV λ=240 nm.

[0852] Example 315. (R)-4-(1H-indazol-6-ylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide





[0853] Step 1: To a stirring solution of carboxylic acid **165.1**(85 g, 540 mmol) in thionyl chloride (425 mL) was added pyridine (8.5 mL, 0.11 mmol), slowly. The reaction was stirred at 75°C overnight at which time it was concentrated and dried under vacuum to a light yellow powder. This yellow solid was slowly diluted with 750 mL of ethanol and refluxed overnight. The next day the reaction was determined to be complete by HPLC and then cooled in an ice bath and the solid filtered and washed with diethyl ether affording ethyl ester **165.2** as an off-white powder (91 g, 87% for two steps). MS found for $C_7H_8N_2O_4$ as $(M+H)^+$ 185.0.

[0854] Step 2: Ester **165.2** (22 g, 120 mmol) was dissolved in phosphorous oxychloride (60 mL, 600 mmol) and the mixture treated with N,N-diethylaniline (27 mL, 167 mmol) and the mixture heated to 105°C until the reaction was determined to be complete by HPLC. It was then cooled to RT and slowly added to 1 L of crushed ice resulting in the formation of a beige precipitate which was collected by filtration and dried under vacuum affording dichloride **165.3** as a light yellow powder (22.5 g, 85%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.13 (s, 1H), 4.37 (q, 2H), 1.32 (t, 3H).

[0855] Step 3: Dichloropyrimidine **165.3** (1.04 g, 4.7 mmol) was dissolved in NMP (30 mL) and stirred in ice bath. To it were added 6-aminoindazole **165.4** (690 mg, 5.2 mmol) and then dropwise ethyldiisopropylamine (DIEA, 1.64 mL, 9.4 mmol). The mixture was stirred for 40 minutes, and to it was added sodium thiomethoxide (660 mg, 9.4 mmol). The mixture was stirred for overnight, diluted with ethyl acetate, washed with brine three times, and concentrated in vacuo to give crude compound **165.5** as a light brown solid in quantitative yield. MS found for $C_{15}H_{15}N_5O_2S$ as $(M+H)^+$ 330.1.

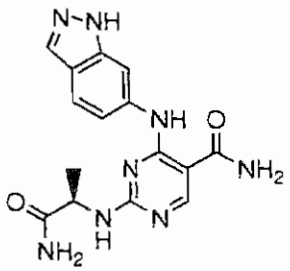
[0856] Step 4: Ethyl ester **165.5** (4.7 mmol) was dissolved in 60 mL THF. To it were added lithium hydroxide hydrate (236 mg, 5.6 mmol) and 20 mL water. The mixture was

stirred for overnight and to it was carefully added 1N HCl solution till pH reaching 2. The mixture was concentrated in vacuo to remove THF. White solid crashed out and was isolated using a Büchner funnel. It was washed with water and dried in vacuum oven to give compound **165.6** (1.14 g, 81%) as a white solid. MS found for $C_{13}H_{11}N_5O_2S$ as $(M+H)^+$ 302.1.

[0857] Step 5: Carboxylic acid **165.6** (1.14 g, 3.8 mmol) was dissolved in 30 mL DMF. To it were added EDC hydrochloride (1.09 g, 5.7 mmol) and HOBt hydrate (770 mg, 5.7 mmol). The mixture was stirred at RT for 1 hour. To it was then added ammonia (commercial 0.5N solution in dioxane, 22 mL, 11.4 mmol). The mixture was stirred for 2 hours. It was then concentrated in vacuo and taken into water and ethyl acetate. The organic phase was separated and washed with brine four times. The organic phase was then dried over $MgSO_4$ and concentrated in vacuo to afford compound **165.7** as a light yellow solid (820 mg, 72%). MS found for $C_{13}H_{12}N_6OS$ as $(M+H)^+$ 301.1.

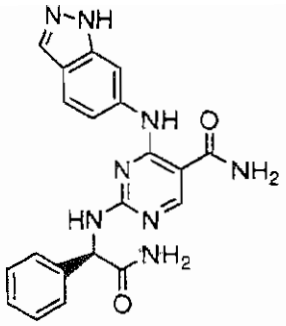
[0858] Step 6: Compound **165.7** (40 mg, 0.13 mmol) was dissolved in 3 mL NMP. To it was added MCPBA (65% pure, 53 mg, 0.18 mmol). It was stirred at RT for 45 minutes. To it then were added H-D-Leu-NH_2 HCl (108 mg, 0.65 mmol) and DIEA (230 µL, 1.3 mmol). The mixture was stirred for 90 minutes at 120°C bath. This mixture was then subjected to preparative HPLC to isolate the title compound **165**. MS found for $C_{18}H_{22}N_8O_2$ as $(M+H)^+$ 383.2. UV λ=246, 303 nm.

[0859] Example 316. (R)-4-(1H-indazol-6-ylamino)-2-(1-amino-1-oxopropan-2-ylamino)pyrimidine-5-carboxamide



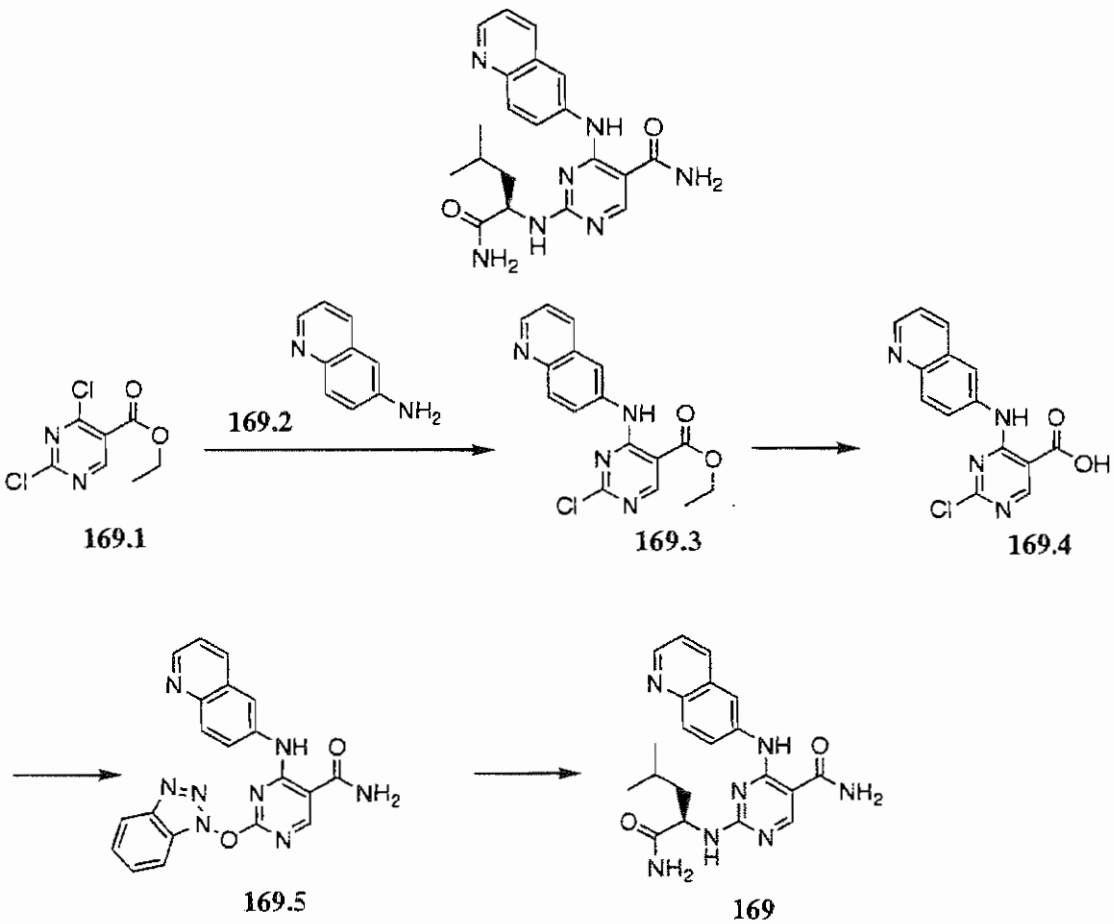
[0860] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with H-D-Ala-NH_2 HCl to replace H-D-Leu-NH_2 HCl. MS found for $C_{15}H_{16}N_8O_2$ as $(M+H)^+$ 341.2. UV λ=245, 302 nm.

[0861] Example 317. (R)-4-(1H-indazol-6-ylamino)-2-(2-amino-2-oxo-1-phenylethylamino)pyrimidine-5-carboxamide



[0862] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with H-D-Phe-NH_2 HCl to replace H-D-Leu-NH_2 HCl. MS found for $C_{20}H_{18}N_8O_2$ as $(M+H)^+$ 403.2. UV λ=249, 298 nm.

[0863] Example 318. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(quinolin-6-ylamino)pyrimidine-5-carboxamide



[0864] Step 1: Dichloropyrimidine **169.1** (500 mg, 2.3 mmol) was dissolved in NMP (20 mL) and stirred in ice bath. To it were added 6-aminoquinoline **169.2** (390 mg, 2.7 mmol) and then dropwise ethyldiisopropylamine (DIEA, 0.72 mL, 4.1 mmol). The mixture was

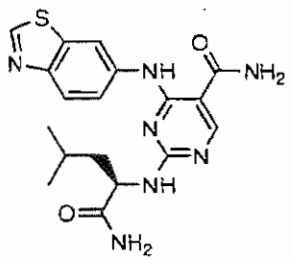
stirred for 2 hours, diluted with ethyl acetate, washed with brine three times, and concentrated in vacuo to give crude compound **169.3** as a light brown solid in quantitative yield. MS found for $C_{16}H_{13}ClN_4O_2$ as $(M+H)^+$ 329.1.

[0865] Step 2: Ethyl ester **169.3** (2.3 mmol) was dissolved in 30 mL THF. To it were added lithium hydroxide hydrate (193 mg, 4.6 mmol) and 6 mL water. The mixture was stirred for 7 hours and to it was carefully added 1N HCl solution till pH reaching 5. The mixture was concentrated in vacuo to remove THF and was extracted with ethyl acetate 5 times. The organic phases were combined, dried and concentrated in vacuo to give crude acid **169.4**. MS found for $C_{14}H_9ClN_4O_2$ as $(M+H)^+$ 301.1.

[0866] Step 3: Carboxylic acid **169.4** (220 mg, 0.73 mmol) was dissolved in 18 mL NMP. To it were added EDC hydrochloride (210 mg, 1.1 mmol) and HOBt hydrate (150 mg, 1.1 mmol). The mixture was stirred at RT for 1 hour. To it was then added ammonia (commercial 0.5N solution in dioxane, 7.3 mL, 3.65 mmol). The mixture was stirred for 2.5 hours. It was then concentrated in vacuo and taken into water and ethyl acetate. The organic phase was separated and washed with brine three times. The organic phase was then dried over $MgSO_4$ and concentrated in vacuo to afford compound **169.5** as a solid (180 mg, 62%). MS found for $C_{20}H_{14}N_8O_2$ as $(M+H)^+$ 399.1.

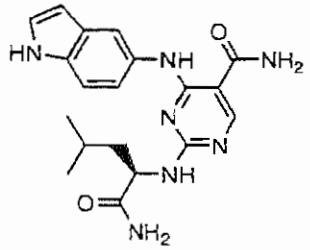
[0867] Step 6: Compound **169.5** (71 mg, 0.18 mmol) was dissolved in 3 mL NMP. To it were added H-D-Leu-NH_2 HCl (150 mg, 0.90 mmol) and DIEA (0.31 mL, 1.8 mmol). The mixture was stirred for 90 minutes at 120°C bath. This mixture was then subjected to preparative HPLC to isolate the racemic title compound **169**. MS found for $C_{20}H_{23}N_7O_2$ as $(M+H)^+$ 394.2. UV λ=241, 283 nm.

[0868] Example 319. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(benzo[d]thiazol-6-ylamino)pyrimidine-5-carboxamide



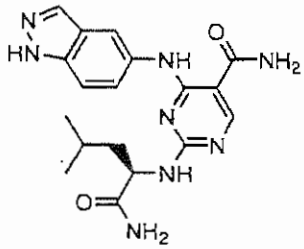
[0869] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 6-aminobenzothiophene to replace 6-aminoindazole **165.4**. MS found for $C_{18}H_{21}N_7O_2S$ as $(M+H)^+$ 400.2. UV λ=243, 303 nm.

[0870] Example 320. (R)-4-(1H-indol-5-ylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



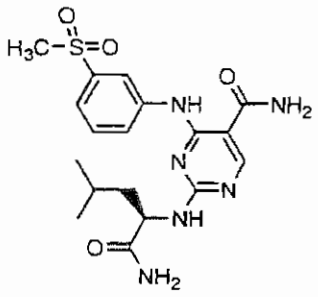
[0871] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 6-aminoindole to replace 6-aminoindazole **165.4**. MS found for $C_{19}H_{23}N_7O_2$ as $(M+H)^+$ 382.2. UV λ=245 nm.

[0872] Example 321. (R)-4-(1H-indazol-5-ylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



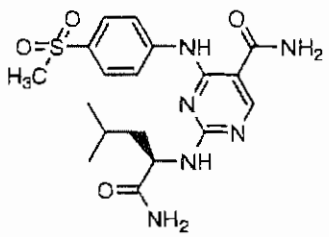
[0873] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 5-aminoindazole to replace 6-aminoindazole **165.4**. MS found for $C_{18}H_{22}N_8O_2$ as $(M+H)^+$ 383.2. UV λ=247, 301 nm.

[0874] Example 322. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(3-(methylsulfonyl)phenylamino)pyrimidine-5-carboxamide



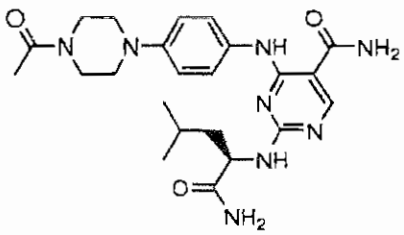
[0875] The above compound was prepared using the same synthetic scheme in Example 315 with 3-(methylsulfonyl)aniline to replace 6-aminoquinoline **169.2**. MS found for $C_{18}H_{24}N_6O_4S$ as $(M+H)^+$ 421.2. UV λ=249, 285 nm.

[0876] Example 323. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(methylsulfonyl)phenylamino)pyrimidine-5-carboxamide



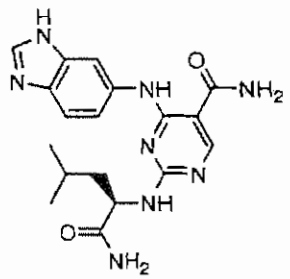
[0877] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(methylsulfonyl)aniline to replace 6-aminoquinoline **169.2**. MS found for $C_{18}H_{24}N_6O_4S$ as $(M+H)^+$ 421.2. UV λ=250, 300 nm.

[0878] Example 324. (R)-4-(4-(4-acetylpiperazin-1-yl)phenylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



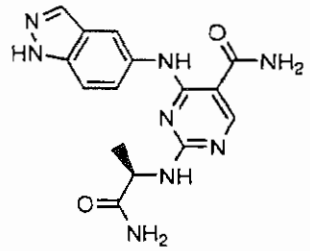
[0879] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone to replace 6-aminoquinoline **169.2**. MS found for $C_{23}H_{32}N_8O_3$ as $(M+H)^+$ 469.3. UV λ=243, 296 nm.

[0880] Example 325. ((R)-4-(1H-benzo[d]imidazol-6-ylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



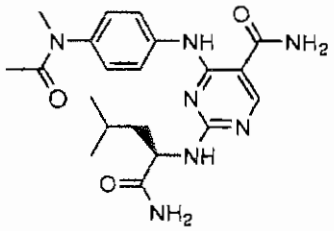
[0881] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 1H-benzo[d]imidazol-6-amine to replace 6-aminoquinoline **169.2**. MS found for $C_{18}H_{22}N_8O_2$ as $(M+H)^+$ 383.2. UV λ=244, 297 nm.

[0882] Example 327. (R)-4-(1H-indazol-5-ylamino)-2-(1-amino-1-oxopropan-2-ylamino)pyrimidine-5-carboxamide



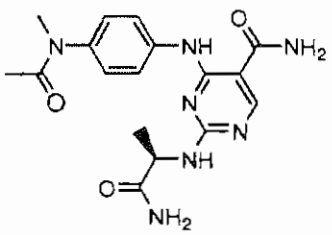
[0883] The above compound was prepared using the same synthetic scheme demonstrated Example 315 with H-D-Ala-NH_2 HCl to replace H-D-Leu-NH_2 HCl. MS found for $C_{15}H_{16}N_8O_2$ as $(M+H)^+$ 341.2. UV λ=245, 299 nm.

[0884] Example 328. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(N-methylacetamido)phenylamino)pyrimidine-5-carboxamide



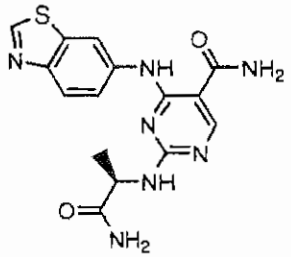
[0885] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with N-(4-aminophenyl)-N-methylacetamide to replace 6-aminoquinoline **169.2**. MS found for $C_{20}H_{27}N_7O_3$ as $(M+H)^+$ 414.2. UV λ=245, 296 nm.

[0886] Example 329. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(4-(N-methylacetamido)phenylamino)pyrimidine-5-carboxamide



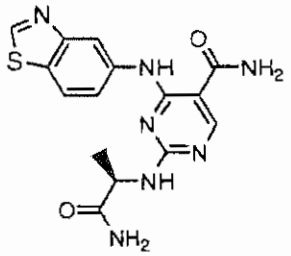
[0887] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with H-D-Ala-NH_2 HCl to replace H-D-Leu-NH_2 HCl. MS found for $C_{17}H_{21}N_7O_3$ as $(M+H)^+$ 372.2. UV λ=244, 295 nm.

[0888] Example 330. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(benzo[d]thiazol-6-ylamino)pyrimidine-5-carboxamide



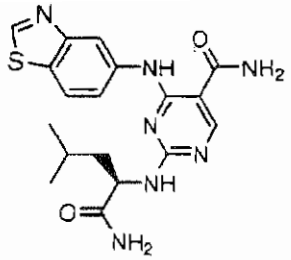
[0889] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with H-D-Ala-NH_2 HCl to replace H-D-Leu-NH_2 HCl. MS found for $C_{15}H_{15}N_7O_2S$ as $(M+H)^+$ 358.1. UV λ=244, 303 nm. NMR (CD_3OD): δ 9.22 (s, 1H), 8.51 (m, 2H), 8.07 (d, J=8.8 Hz, 1H), 7.71 (d, J=8.8 Hz, 1H), 4.44 (m, 1H), 1.55 (d, J=6.8 Hz, 3H) ppm.

Example 331. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(benzo[d]thiazol-5-ylamino)pyrimidine-5-carboxamide



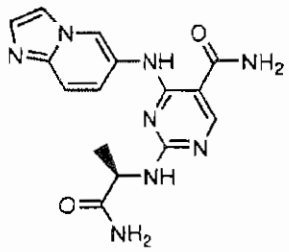
[0890] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 5-aminobenzothiophene to replace 6-aminobenzothiophene. MS found for $C_{15}H_{15}N_7O_2S$ as $(M+H)^+$ 358.1. UV λ=249, 292 nm. NMR (CD_3OD): δ 9.34 (s, 1H), 8.67 (s, 1H), 8.51 (s, 1H), 8.10 (d, J=8.8 Hz, 1H), 7.59 (d, J=8.8 Hz, 1H), 4.64 (m, 1H), 1.55 (d, J=7.2 Hz, 3H) ppm.

[0891] Example 332. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(benzo[d]thiazol-5-ylamino)pyrimidine-5-carboxamide



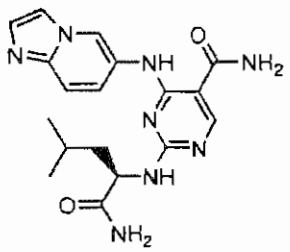
[0892] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 5-aminobenzothiophene to replace 6-aminobenzothiophene. MS found for $C_{18}H_{21}N_7O_2S$ as $(M+H)^+$ 400.2. UV λ=247, 295 nm.

Example 333. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(imidazo[1,2-a]pyridin-6-ylamino)pyrimidine-5-carboxamide



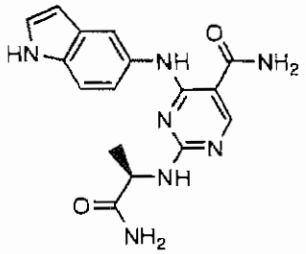
[0893] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with imidazo[1,2-a]pyridin-6-amine to replace 6-aminobenzothiophene. MS found for $C_{15}H_{16}N_8O_2$ as $(M+H)^+$ 341.2. UV λ=250 nm.

Example 334. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(imidazo[1,2-a]pyridin-6-ylamino)pyrimidine-5-carboxamide



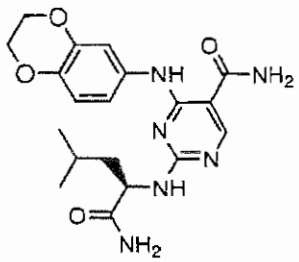
The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with imidazo[1,2-a]pyridin-6-amine to replace 6-aminoindazole **165.4**. MS found for $C_{18}H_{22}N_8O_2$ as $(M+H)^+$ 383.2. UV λ=252 nm.

Example 335. (R)-4-(1H-indol-5-ylamino)-2-(1-amino-1-oxopropan-2-ylamino)pyrimidine-5-carboxamide



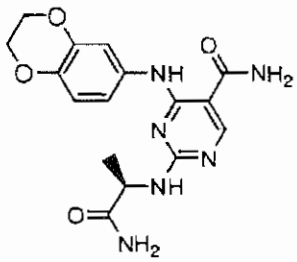
[0894] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with H-D-Ala-NH_2 HCl to replace H-D-Leu-NH_2 HCl. MS found for $C_{16}H_{17}N_7O_2$ as $(M+H)^+$ 340.2. UV λ=224 nm. NMR (CD_3OD): δ 8.38 (s, 1H), 7.84 (m, 1H), 7.40 (m, 1H), 7.26 (m, 2H), 6.51 (s, 1H), 4.44 (m, 1H), 1.50 (d, J=7.6 Hz, 3H) ppm. 8.82 (s, 1H), 8.74 (m, 1H), 8.61 (s, 1H), 8.10 (d, J=8.8 Hz, 1H), 7.87 (d, J=8.4 Hz, 1H), 4.54 (m, 1H), 3.82 (m, 1H), 1.99-1.62 (m, 8H) ppm.

Example 336. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-ylamino)pyrimidine-5-carboxamide



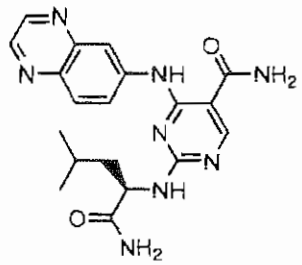
[0895] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 2,3-dihydrobenzo[b][1,4]dioxin-6-amine to replace 6-aminoquinoline **169.2**. MS found for $C_{19}H_{24}N_6O_4$ as $(M+H)^+$ 401.2. UV λ=243, 310 nm.

Example 337. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-ylamino)pyrimidine-5-carboxamide



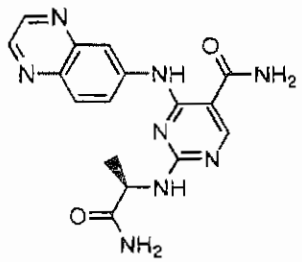
The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with H-D-Ala-NH_2 HCl to replace H-D-Leu-NH_2 HCl. MS found for $C_{16}H_{18}N_6O_4$ as $(M+H)^+$ 359.2. UV λ=243, 312 nm.

Example 338. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(quinoxalin-6-ylamino)pyrimidine-5-carboxamide



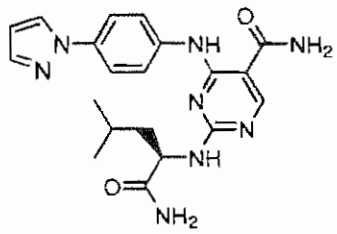
[0896] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with quinoxalin-6-amine to replace 6-aminoindazole **165.4**. MS found for $C_{19}H_{22}N_8O_2$ as $(M+H)^+$ 395.2. UV λ=243 nm.

Example 339. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(quinoxalin-6-ylamino)pyrimidine-5-carboxamide



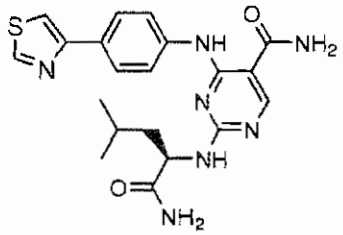
[0897] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with H-D-Ala-NH_2 HCl to replace H-D-Leu-NH_2 HCl. MS found for $C_{16}H_{16}N_8O_2$ as $(M+H)^+$ 353.2. UV λ=242 nm.

Example 340. (R)-4-(4-(1H-pyrazol-1-yl)phenylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



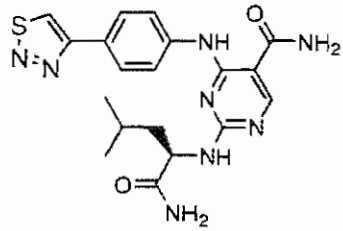
[0898] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(1H-pyrazol-1-yl)aniline to replace 6-aminoindazole **165.4**. MS found for $C_{20}H_{24}N_8O_2$ as $(M+H)^+$ 409.2. UV λ=241, 308 nm.

Example 341. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxamide



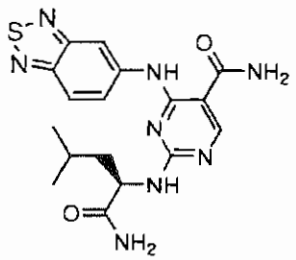
[0899] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(thiazol-4-yl)aniline to replace 6-aminoindazole **165.4**. MS found for $C_{20}H_{23}N_7O_2S$ as $(M+H)^+$ 426.2. UV λ=240, 314 nm.

Example 342. (R)-4-(4-(1,2,3-thiadiazol-4-yl)phenylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



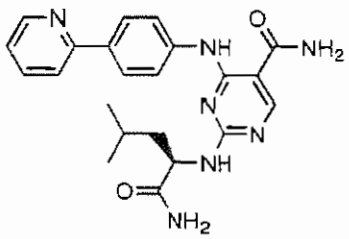
[0900] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(1,2,3-thiadiazol-4-yl)aniline to replace 6-aminoindazole **165.4**. MS found for $C_{19}H_{22}N_8O_2S$ as $(M+H)^+$ 427.2. UV λ=233, 311 nm.

Example 343. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(benzo[c][1,2,5]thiadiazol-5-ylamino)pyrimidine-5-carboxamide



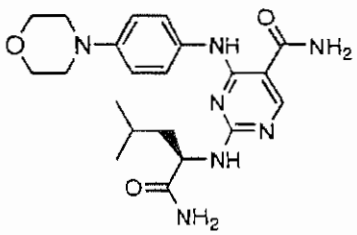
[0901] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with benzo[c][1,2,5]thiadiazol-5-amine to replace 6-aminoquinoline **169.2**. MS found for $C_{17}H_{20}N_8O_2S$ as $(M+H)^+$ 400.2. UV λ=240 nm.

Example 344. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(pyridin-2-yl)phenylamino)pyrimidine-5-carboxamide



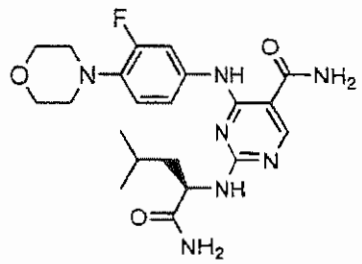
[0902] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(pyridin-2-yl)aniline to replace 6-aminoquinoline **169.2**. MS found for $C_{22}H_{25}N_7O_2$ as $(M+H)^+$ 420.2. UV λ=244, 314 nm.

Example 345. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-morpholinophenylamino)pyrimidine-5-carboxamide



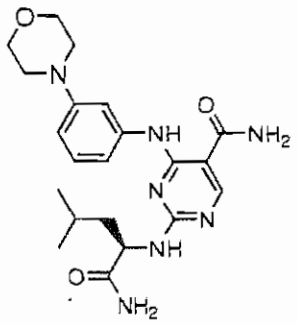
[0903] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-morpholinoaniline to replace 6-aminoquinoline **169.2**. MS found for $C_{21}H_{29}N_7O_3$ as $(M+H)^+$ 428.2. UV λ=244, 294 nm.

Example 346. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(3-fluoro-4-morpholinophenylamino)pyrimidine-5-carboxamide



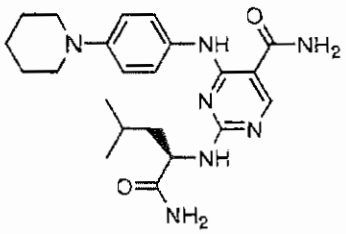
[0904] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 3-fluoro-4-morpholinoaniline to replace 6-aminoquinoline **169.2**. MS found for $C_{21}H_{28}FN_7O_3$ as $(M+H)^+$ 446.2. UV λ=240, 310 nm.

Example 347 (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(3-morpholinophenylamino)pyrimidine-5-carboxamide



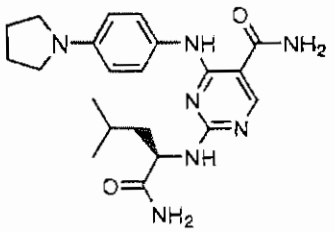
[0905] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 3-morpholinoaniline to replace 6-aminoquinoline **169.2**. MS found for $C_{21}H_{29}N_7O_3$ as $(M+H)^+$ 428.2. UV λ=246 nm.

Example 348a. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(piperidin-1-yl)phenylamino)pyrimidine-5-carboxamide



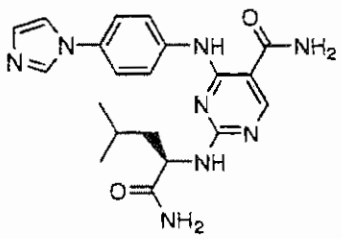
[0906] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(piperidin-1-yl)aniline to replace 6-aminoquinoline **169.2**. MS found for $C_{22}H_{31}N_7O_2$ as $(M+H)^+$ 426.2. UV λ=247, 291 nm.

Example 348b. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(pyrrolidin-1-yl)phenylamino)pyrimidine-5-carboxamide



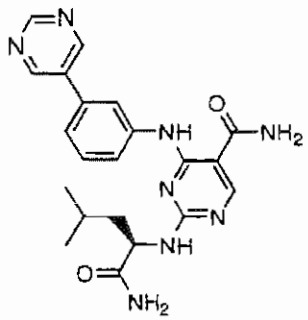
[0907] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(pyrrolidin-1-yl)aniline to replace 6-aminoquinoline **169.2**. MS found for $C_{21}H_{29}N_7O_2$ as $(M+H)^+$ 412.2. UV λ=247, 292 nm.

Example 349a. (R)-4-(4-(1H-imidazol-1-yl)phenylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



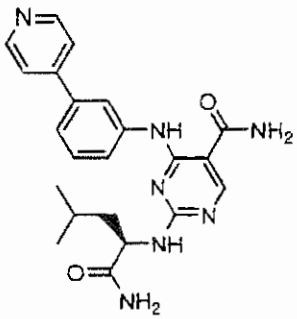
[0908] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(1H-imidazol-1-yl)aniline to replace 6-aminoquinoline **169.2**. MS found for $C_{20}H_{24}N_8O_2$ as $(M+H)^+$ 409.2. UV λ=247, 297 nm.

Example 349b. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(3-(pyrimidin-5-yl)phenylamino)pyrimidine-5-carboxamide



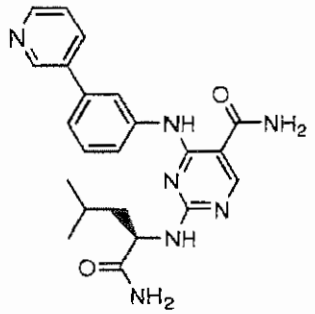
[0909] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 3-(pyrimidin-5-yl)aniline to replace 6-aminoquinoline **169.2**. MS found for $C_{21}H_{24}N_8O_2$ as $(M+H)^+$ 421.2. UV λ=247 nm.

Example 350. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(3-(pyridin-4-yl)phenylamino)pyrimidine-5-carboxamide



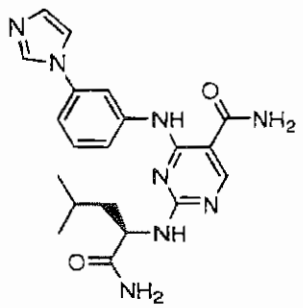
[0910] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 3-(pyridin-4-yl)aniline to replace 6-aminoindazole **165.4**. MS found for $C_{22}H_{25}N_7O_2$ as $(M+H)^+$ 420.2. UV λ=241, 314 nm.

[0911] Example 351. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(3-(pyridin-3-yl)phenylamino)pyrimidine-5-carboxamide



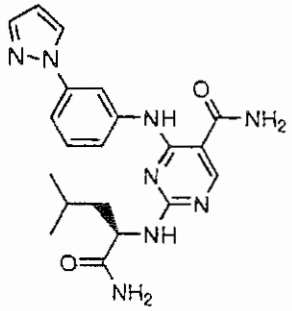
[0912] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 3-(pyridin-3-yl)aniline to replace 6-aminoindazole **165.4**. MS found for $C_{22}H_{25}N_7O_2$ as $(M+H)^+$ 420.2. UV λ=250 nm.

Example 352. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(3-(pyridin-3-yl)phenylamino)pyrimidine-5-carboxamide



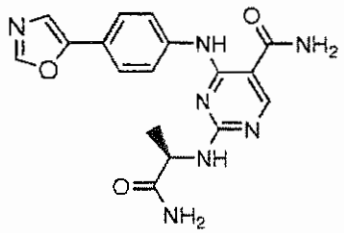
[0913] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 3-(1H-imidazol-1-yl)aniline to replace 6-aminoindazole **165.4**. MS found for $C_{20}H_{24}N_8O_2$ as $(M+H)^+$ 409.2. UV λ=243, 284 nm.

Example 353. (R)-4-(3-(1H-pyrazol-1-yl)phenylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



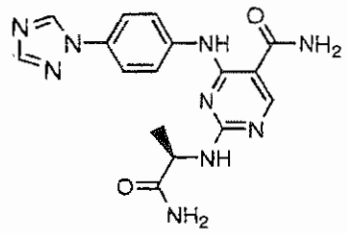
[0914] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 3-(1H-pyrazol-1-yl)aniline to replace 6-aminoindazole **165.4**. MS found for $C_{20}H_{24}N_8O_2$ as $(M+H)^+$ 409.2. UV λ=250 nm.

Example 354. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(4-(oxazol-5-yl)phenylamino)pyrimidine-5-carboxamide



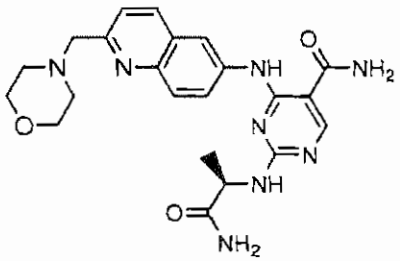
[0915] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(oxazol-5-yl)aniline to replace 6-aminobenzothiophene. MS found for $C_{17}H_{17}N_7O_3$ as $(M+H)^+$ 368.2.

Example 355. (R)-4-(4-(1H-1,2,4-triazol-1-yl)phenylamino)-2-(1-amino-1-oxopropan-2-ylamino)pyrimidine-5-carboxamide



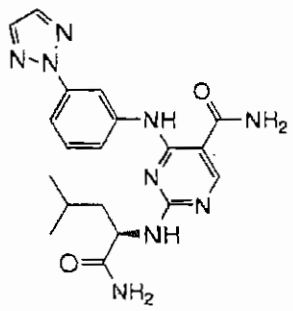
[0916] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 4-(1H-1,2,4-triazol-1-yl)aniline to replace 6-aminobenzothiophene. MS found for $C_{16}H_{17}N_9O_2$ as $(M+H)^+$ 368.2.

Example 356. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(2-(morpholinomethyl)quinolin-6-ylamino)pyrimidine-5-carboxamide

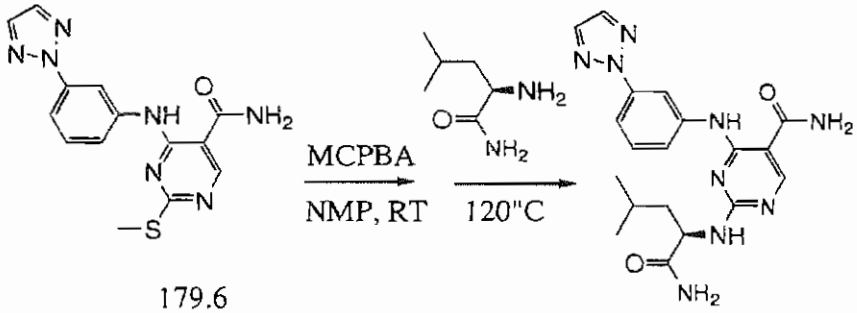


[0917] The above compound was prepared using the same synthetic scheme demonstrated in Example 315 with 2-(morpholinomethyl)quinolin-6-amine to replace 6-aminobenzothiophene. MS found for $C_{22}H_{26}N_8O_3$ as $(M+H)^+$ 451.2.

Example 357. (R)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)pyrimidine-5-carboxamide



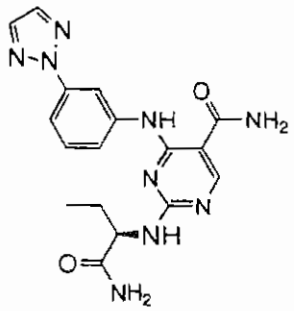
Scheme:



179.6

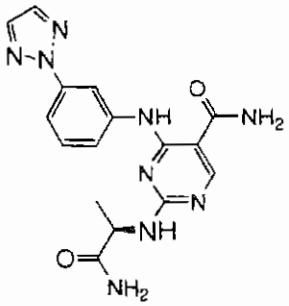
[0918] Compound 179.6 (100 mg, 0.31 mmol) was dissolved in 5 mL NMP. To it was added MCPBA (97 mg, 0.37 mmol) and the mixture was stirred for 30 min. To it was added DIEA (0.32 mL, 1.86 mmol) and then commercially available H-D-Leu-NH_2.HCl (155 mg, 0.93 mmol). The mixture was stirred at 120°C for 3 h. From this mixture the title compound was isolated using reverse phase prep HPLC. MS found for $C_{19}H_{23}N_9O_2$ as $(M+H)^+$ 410.3. UV λ=251 nm.

Example 358. (R)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(1-amino-1-oxobutan-2-ylamino)pyrimidine-5-carboxamide



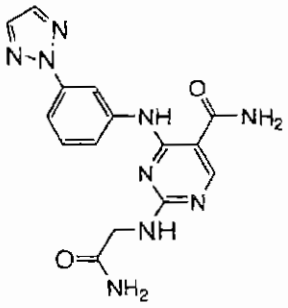
[0919] The title compound was made using the similar chemistry scheme shown for Example 357. MS found for $C_{17}H_{19}N_9O_2$ as $(M+H)^+$ 382.3. UV λ=250 nm.

Example 359. (R)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(1-amino-1-oxopropan-2-ylamino)pyrimidine-5-carboxamide



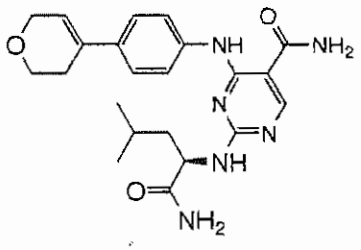
[0920] The title compound was made using the similar chemistry scheme shown for Example 357. MS found for $C_{16}H_{17}N_9O_2$ as $(M+H)^+$ 368.3. UV λ=251 nm.

Example 360. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(2-amino-2-oxoethylamino)pyrimidine-5-carboxamide



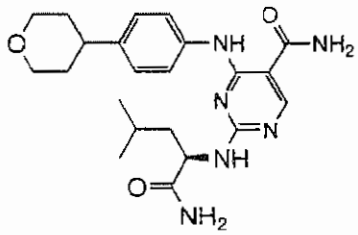
The title compound was made using the similar chemistry scheme shown for Example 357. MS found for $C_{15}H_{15}N_9O_2$ as $(M+H)^+$ 354.3. UV λ=250 nm.

Example 361. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(3,6-dihydro-2H-pyran-4-yl)phenylamino)pyrimidine-5-carboxamide



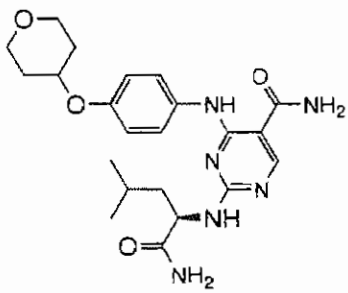
[0921] The title compound was made using the similar chemistry shown for Example 357. MS found for $C_{22}H_{28}N_6O_3$ as $(M+H)^+$ 425.4. UV λ=240, 313 nm.

Example 362. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(tetrahydro-2H-pyran-4-yl)phenylamino)pyrimidine-5-carboxamide



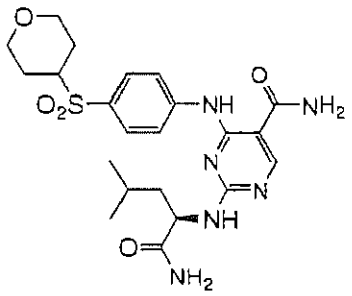
[0922] The title compound was prepared from Example 361 using standard catalysis hydrogenation by treating the solution of Example 261 in methanol with 10% Pd/C under H_2 balloon for overnight. MS found for $C_{22}H_{30}N_6O_3$ as $(M+H)^+$ 427.4. UV λ=244, 298 nm.

Example 363. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(tetrahydro-2H-pyran-4-yloxy)phenylamino)pyrimidine-5-carboxamide



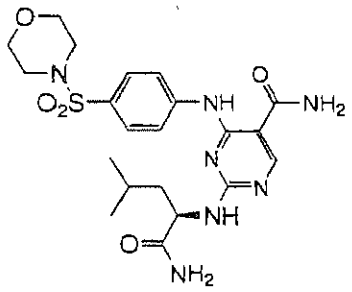
[0923] The title compound was prepared using the same synthetic scheme demonstrated in Example 315 with the corresponding aniline which was commercially available. MS found for $C_{22}H_{30}N_6O_4$ as $(M+H)^+$ 443.4. UV λ=244, 295 nm.

Example 364. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(tetrahydro-2H-pyran-4-ylsulfonyl)phenylamino)pyrimidine-5-carboxamide

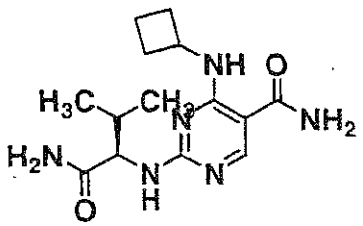


[0924] The title compound was prepared using the same synthetic scheme demonstrated in Example 315 with the corresponding aniline (synthesis shown in for compound 266). MS found for $C_{22}H_{30}N_6O_5S$ as $(M+H)^+$ 491.4. UV λ=251, 302 nm.

Example 365. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-(morpholinosulfonyl)phenylamino)pyrimidine-5-carboxamide

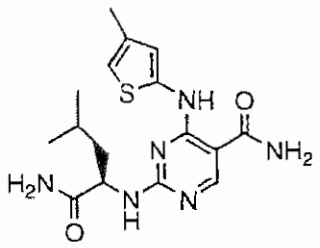


Example 366 (R)-2-(1-amino-3-methyl-1-oxobutan-2-ylamino)-4-(cyclobutylamino)pyrimidine-5-carboxamide



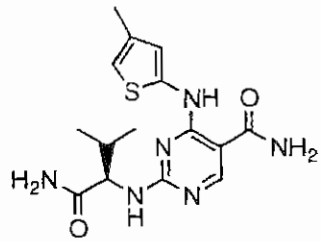
[0925] Benzotriazolyl ether **1.7** (509 mg, 0.17 mmol), (R)-valine hydrochloride (30 mg, 0.26 mmol), diisopropylethylamine (89 uL, 0.51 mmol) and 5 mL of 1,4-dioxane were combined and heated to 120°C overnight. The reaction mixture was then cooled, diluted with water and purified by preparative HPLC to give the desired compound. MS found for $C_{14}H_{22}N_6O_2$ as $(M+H)^+$ 307.3.

Example 367. (R)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(4-methylthiophen-2-ylamino)pyrimidine-5-carboxamide



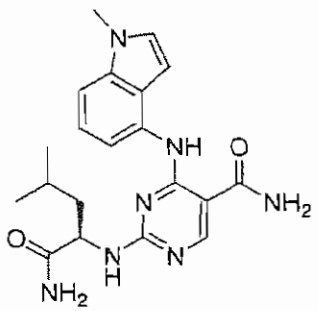
[0926] The titled compound was then synthesized analogously by using 4-methylthiophen-2-amine. MS 363.3 (M+H); UV 201.6, 244.3, 326.1 nm.

Example 368. (R)-2-(1-amino-3-methyl-1-oxobutan-2-ylamino)-4-(4-methylthiophen-2-ylamino)pyrimidine-5-carboxamide



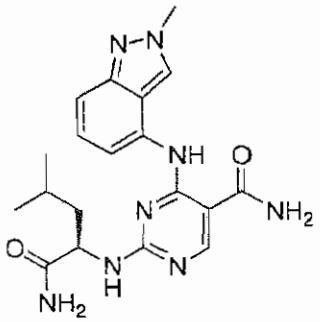
[0927] The titled compound was then synthesized analogously by using 4-methylthiophen-2-amine. MS 349.3 (M+H); UV 202.9, 251.0, 324.8 nm.

Example 369. (*R*)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(1-methyl-1H-indol-4-ylamino)pyrimidine-5-carboxamide



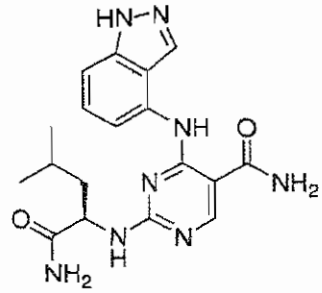
[0928] The title compound was prepared using the same synthetic scheme demonstrated in Example 318. MS found for $C_{20}H_{25}N_7O_2$ as $(M+H)^+$ 396.3. UV: λ = 216.9, 244.0.

Example 370. (*R*)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(2-methyl-2*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



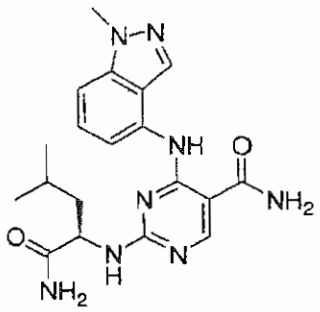
[0929] The title compound was prepared using the same synthetic scheme demonstrated in Example 318. MS found for $C_{19}H_{24}N_8O_2$ as $(M+H)^+$ 397.4. UV: λ = 213.3, 244.0, 333.1.

Example 371. (*R*)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



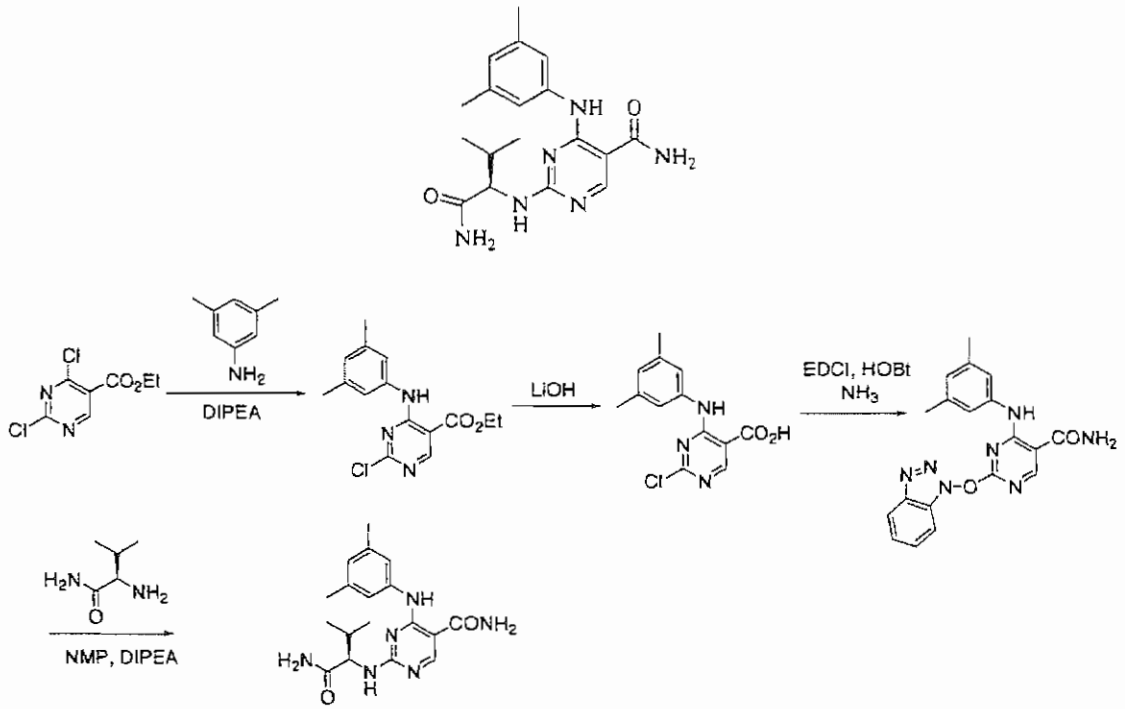
[0930] The title compound was prepared using the same synthetic scheme demonstrated in Example 318. MS found for $C_{18}H_{22}N_8O_2$ as $(M+H)^+$ 383.4. UV: λ = 241.6, 318.8.

Example 372. (*R*)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(1-methyl-1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



[0931] The title compound was prepared using the same synthetic scheme demonstrated in Example 318. MS found for $C_{19}H_{24}N_8O_2$ as $(M+H)^+$ 397.4. UV: λ = 207.5, 244.0, 325.9.

Example 373. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



[0932] Step 1 & 2 are same as described for Example 100.

[0933] Step 3: Dichloropyrimidine **165.3** (5.09 g, 22.6 mmol) was dissolved in acetonitrile (50 mL) and stirred in ice bath. To it were added 3,5-dimethylaniline (2.19g, 18.2 mmol) and then dropwise ethyldiisopropylamine (DIEA, 5.74 mL, 33.9 mmol). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, washed with brine three times, and concentrated in vacuo to give crude compound 4 as a light brown solid 2.4gm (88% yield). MS found for $C_{15}H_{16}ClN_3O_2$ as $(M+H)^+$ 306.09.

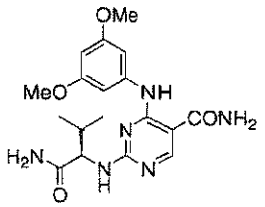
[0934] Step 4: Ethyl ester **4** (9.8 mmol) was dissolved in 20 mL THF. To it were added lithium hydroxide hydrate (530 mg, 10.2 mmol) and 15 mL water. The mixture was stirred for overnight and to it was carefully added 1N HCl solution till pH reaching 2. The mixture was concentrated in vacuo to remove THF. White solid crashed out and was isolated using a Büchner funnel. It was washed with water and dried in vacuum oven to give compound **5** (2.14 g, 81%) as a white solid. MS found for $C_{13}H_{12}ClN_3O_2$ as $(M+H)^+$ 278.1.

[0935] Step 5: Carboxylic acid **5** (1.09 g, 3.6 mmol) was dissolved in 30 mL DMF. To it were added EDC hydrochloride (1.24 g, 6.4 mmol) and HOBt hydrate (870 mg, 6.4 mmol). The mixture was stirred at RT for 1 hour. The reaction mixture was cooled to 0°C to it was then added ammonia (commercial 0.4M solution in dioxane, 16 mL, 8.3 mmol). The mixture was stirred for 2 hours. It was then concentrated in vacuo and taken into water and ethyl

acetate. The organic phase was separated and washed with brine four times. The organic phase was then dried over $MgSO_4$ and concentrated in vacuo to afford compound **6** as a solid (150 mg, 55%). MS found for $C_{19}H_{17}N_7O_2$ as $(M+H)^+$ 376.1.

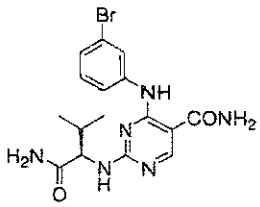
[0936] Step 6: Compound **6** (188 mg, 0.5 mmol) was dissolved in 3 mL NMP. To it were added H-D-Val-NH_2 HCl (174 mg, 1.5 mmol) and DIEA (0.200 mL, 1.0mmol). The mixture was stirred for 90 minutes at 120°C bath. This mixture was then subjected to preparative HPLC to isolate the title compound **7**. MS found for $C_{18}H_{24}N_6O_2$ as $(M+H)^+$ 357.20.

Example 374. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3,5-dimethoxyphenylamino)pyrimidine-5-carboxamide



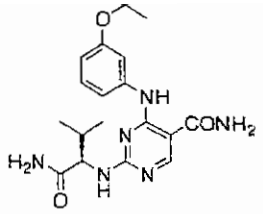
[0937] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with 3,5-dimethoxyaniline to replace 3,5-dimethylaniline. MS found for $C_{18}H_{24}N_6O_4$ as $(M+H)^+$ 388.

Example 375. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3-bromophenylamino)pyrimidine-5-carboxamide.



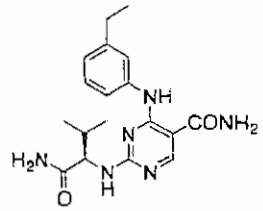
[0938] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with 3-bromoaniline to replace 3,5-dimethylaniline. MS found for $C_{16}H_{19}BrN_6O_2$ as $(M+H)^+$ 407.

Example 376. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3-ethoxyphenylamino)pyrimidine-5-carboxamide



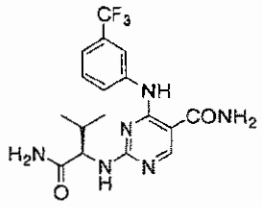
[0939] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with 3-ethoxyaniline to replace 3,5-dimethylaniline. MS found for $C_{18}H_{24}N_6O_3$ as $(M+H)^+$ 373

Example 377. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3-ethylphenylamino)pyrimidine-5-carboxamide



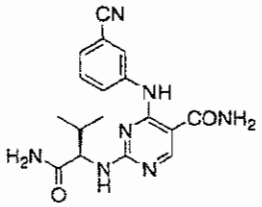
The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with 3-ethylaniline to replace 3,5-dimethylaniline. MS found for $C_{18}H_{24}N_6O_2$ as $(M+H)^+$ 356.3

Example 378. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxamide



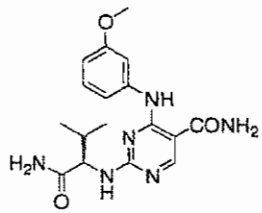
[0940] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with 3-trifluoromethylaniline to replace 3,5-dimethylaniline. MS found for $C_{17}H_{19}F_3N_6O_2$ as $(M+H)^+$ 396.3

Example 379. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3-cyanophenylamino)pyrimidine-5-carboxamide



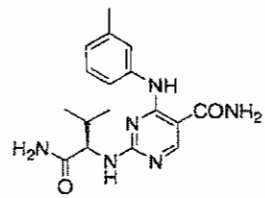
[0941] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with 3-aminobenzonitrile to replace 3,5-dimethylaniline. MS found for $C_{17}H_{19}N_7O_2$ as $(M+H)^+$ 353.38

Example 380. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3-methoxyphenylamino)pyrimidine-5-carboxamide



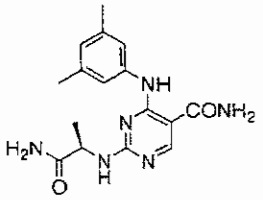
[0942] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with 3-methoxyaniline to replace 3,5-dimethylaniline. MS found for $C_{17}H_{22}N_6O_3$ as $(M+H)^+$ 358.4

Example 381. (R)-2-(-amino-3-methyl-1oxobutan-2-ylamino)-4-(3-(m-tolylamino)pyrimidine-5-carboxamide



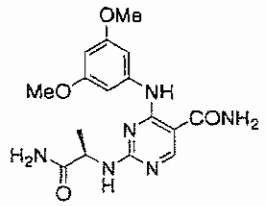
[0943] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with m-toluidine to replace 3,5-dimethylaniline. MS found for $C_{17}H_{22}N_6O_2$ as $(M+H)^+$ 343

Example 382. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



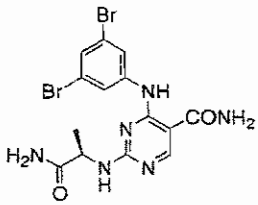
[0944] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Ala-NH_2 HCl to replace H-D-Val-NH_2 HCl. MS found for $C_{16}H_{20}N_6O_2$ as $(M+H)^+$ 328.2.

Example 383. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(3,5-dimethoxyphenylamino)pyrimidine-5-carboxamide



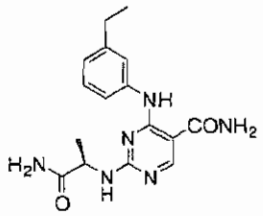
[0945] The above compound was prepared using the same synthetic scheme demonstrated in Example 382 with 3,5-dimethoxyaniline to replace 3,5-dimethylaniline. MS found for $C_{16}H_{20}N_6O_4$ as $(M+H)^+$ 360.3.

Example 384. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(3-bromophenylamino)pyrimidine-5-carboxamide



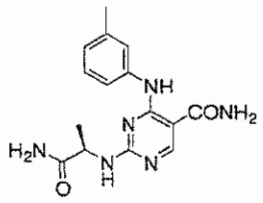
[0946] The above compound was prepared using the same synthetic scheme demonstrated in Example 382 with 3-bromoaniline to replace 3,5-dimethylaniline. MS found for $C_{14}H_{15}BrN_6O_4$ as $(M+H)^+$ 360.3.

Example 385. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(3-ethylphenylamino)pyrimidine-5-carboxamide



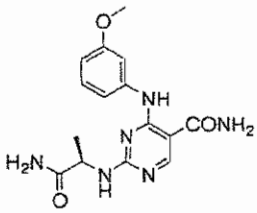
[0947] The above compound was prepared using the same synthetic scheme demonstrated in Example 382 with 3-ethylaniline to replace 3,5-dimethylaniline. MS found for $C_{16}H_{20}N_6O_2$ as $(M+H)^+$ 328.3.

Example 386. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



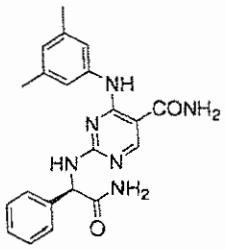
[0948] The above compound was prepared using the same synthetic scheme demonstrated in Example 382 with m-toluidine to replace 3,5-dimethylaniline. MS found for $C_{15}H_{18}N_6O_2$ as $(M+H)^+$ 314.34.

Example 387. (R)-2-(1-amino-1-oxopropan-2-ylamino)-4-(3-methoxyphenylamino)pyrimidine-5-carboxamide



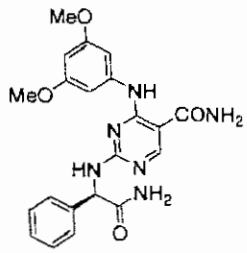
[0949] The above compound was prepared using the same synthetic scheme demonstrated in Example 382 with 3-methoxyaniline to replace 3,5-dimethylaniline. MS found for $C_{15}H_{18}N_6O_3$ as $(M+H)^+$ 330.34.

Example 388. (R)-2-(2-amino-2-oxo-1-phenylethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



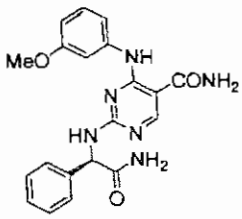
[0950] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Phe-NH_2 HCl to replace H-D-Val-NH_2 HCl. MS found for $C_{21}H_{22}N_6O_2$ as $(M+H)^+$ 328.2.

Example 389. (R)-2-(2-amino-2-oxo-1-phenylethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



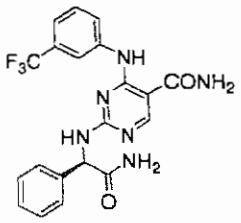
[0951] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Phe-NH_2 HCl to replace H-D-Val-NH_2 HCl and 3,5-dimethoxyaniline to replace 3,5-dimethylaniline. MS found for $C_{21}H_{22}N_6O_4$ as $(M+H)^+$ 423.

Example 390. (R)-2-(2-amino-2-oxo-1-phenylethylamino)-4-(3-methoxyphenylamino)pyrimidine-5-carboxamide



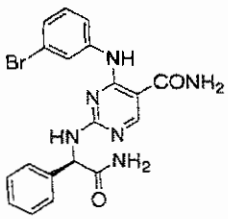
[0952] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Phe-NH_2 HCl to replace H-D-Val-NH_2 HCl and 3-methoxyaniline to replace 3,5-dimethylaniline. MS found for $C_{20}H_{20}N_6O_3$as $(M+H)^+$ 392.4.

Example 391. (R)-2-(2-amino-2-oxo-1-phenylethylamino)-4-(3-trifluoromethylphenylamino)pyrimidine-5-carboxamide



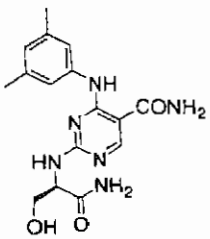
[0953] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Phe-NH_2 HCl to replace H-D-Val-NH_2 HCl and 3-trifluoromethylaniline to replace 3,5-dimethylaniline. MS found for $C_{20}H_{17}F_3N_6O_2$ as $(M+H)^+$ 430.39.

Example 392. (R)-2-(2-amino-2-oxo-1-phenylethylamino)-4-(3-bromophenylamino)pyrimidine-5-carboxamide



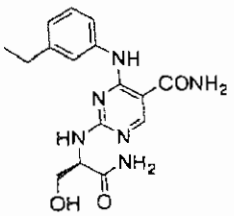
[0954] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Phe-NH_2 HCl to replace H-D-Val-NH_2 HCl and 3-bromoaniline to replace 3,5-dimethylaniline. MS found for $C_{19}H_{17}BrN_6O_2$ as $(M+H)^+$ 441.29.

Example 393. (R)-2-(1-amino-3-hydroxy-1-oxo-2-ylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



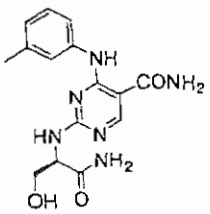
[0955] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Ser-NH_2 HCl to replace H-D-Val-NH_2 HCl. MS found for $C_{16}H_{20}N_6O_3$ as $(M+H)^+$ 344.37.

Example 394. (R)-2-(1-amino-3-hydroxy-1-oxo-2-ylamino)-4-(3-ethylphenylamino)pyrimidine-5-carboxamide



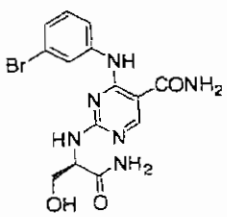
[0956] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Ser-NH_2 HCl to replace H-D-Val-NH_2 HCl and 3-ethylaniline to replace 3,5-dimethylaniline. MS found for $C_{16}H_{20}N_6O_3$ as $(M+H)^+$ 344.37.

Example 396. (R)-2-(1-amino-3-hydroxy-1-oxo-2-ylamino)-4-(3-m-tolylamino)pyrimidine-5-carboxamide



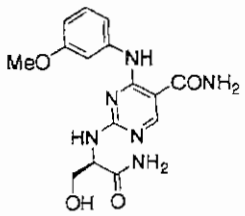
[0957] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Ser-NH_2 HCl to replace H-D-Val-NH_2 HCl and m-toluidine to replace 3,5-dimethylaniline. MS found for $C_{15}H_{18}N_6O_3$ as $(M+H)^+$ 330.34.

Example 397. (R)-2-(1-amino-3-hydroxy-1-oxo-2-ylamino)-4-(3-bromophenylamino)pyrimidine-5-carboxamide



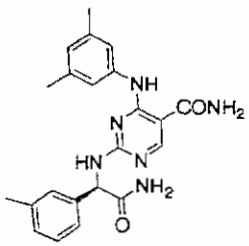
[0958] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Ser-NH_2 HCl to replace H-D-Val-NH_2 HCl and 3-bromoaniline to replace 3,5-dimethylaniline. MS found for $C_{14}H_{15}BrN_6O_3$ as $(M+H)^+$ 395.22.

Example 398. (R)-2-(1-amino-3-hydroxy-1-oxo-2-ylamino)-4-(3-methoxyphenylamino)pyrimidine-5-carboxamide



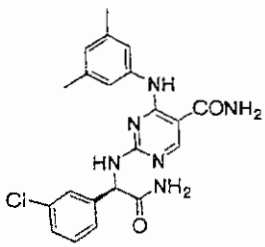
[0959] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with H-D-Ser-NH_2 HCl to replace H-D-Val-NH_2 HCl and 3-methoxyaniline to replace 3,5-dimethylaniline. MS found for $C_{15}H_{18}N_6O_4$ as $(M+H)^+$ 346.34.

Example 399. (R)-2-(2-amino-2-oxo-1-m-tolylethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



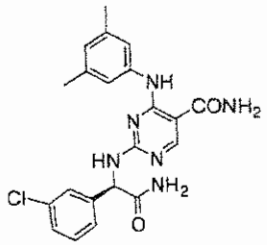
[0960] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-2-m-tolylacetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{22}H_{24}N_6O_2$ as $(M+H)^+$ 404.47.

Example 400. (R)-2-(2-amino-1-(3-chlorophenyl)-2-oxoethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



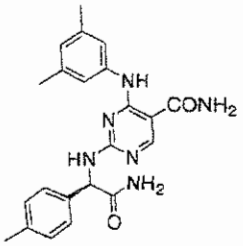
[0961] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-2-(3-chlorophenyl)acetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{21}H_{21}ClN_6O_2$ as $(M+H)^+$ 424.89.

Example 401. (R)-2-(2-amino-1-(3-fluorophenyl)-2-oxoethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



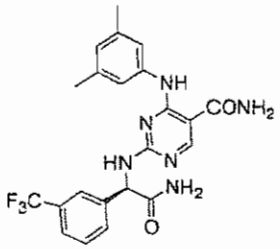
[0962] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-2-(3-fluorophenyl)acetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{21}H_{21}FN_6O_2$ as $(M+H)^+$ 408.43.

Example 402. (R)-2-(2-amino-2-oxo-1-p-tolylethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



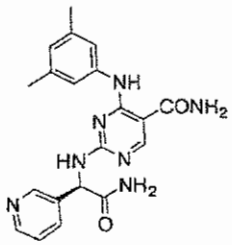
[0963] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-p-tolylacetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{22}H_{24}N_6O_2$ as $(M+H)^+$ 404.47.

Example 403. (R)-2-(2-amino-2-oxo-3(trifluoromethylphenyl)ethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



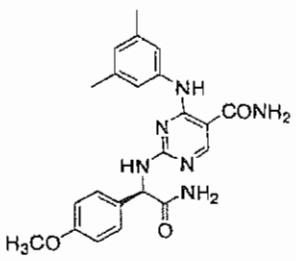
[0964] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-2-(3-fluoromethylphenyl)acetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{22}H_{21}F_3N_6O_2$ as $(M+H)^+$ 404.47.

Example 404. (R)-2-(2-amino-2-oxo-1(pyridine-3-yl)ethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



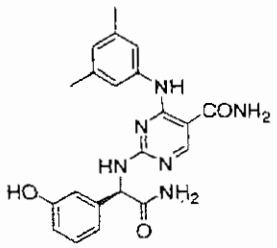
[0965] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-2-(pyridine-3-yl)acetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{20}H_{21}N_7O_2$ as $(M+H)^+$ 391.43.

Example 405. (R)-2-(2-amino-1(4-methoxyphenyl)-2-oxoethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



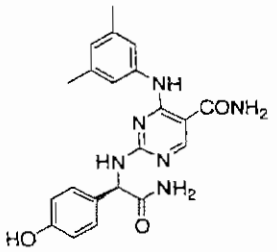
[0966] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-2-(4-methoxyphenyl)acetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{22}H_{24}N_6O_3$ as $(M+H)^+$ 420.47.

Example 406. (R)-2-(2-amino-1(3-hydroxyphenyl)-2-oxoethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



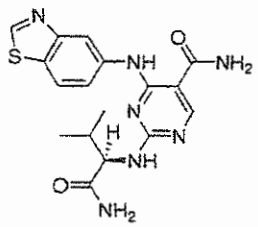
[0967] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-2-(3-hydroxyphenyl)acetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{21}H_{22}N_6O_3$ as $(M+H)^+$ 406.44.

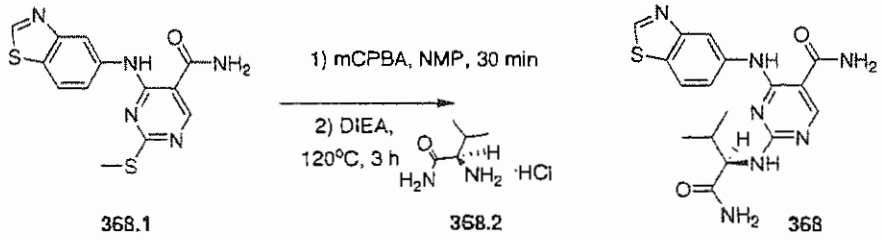
Example 407. (R)-2-(2-amino-1(34-hydroxyphenyl)-2-oxoethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



[0968] The above compound was prepared using the same synthetic scheme demonstrated in Example 373 with (S)-2-amino-2-(4-hydroxyphenyl)acetamide to replace H-D-Val-NH_2 HCl. MS found for $C_{21}H_{22}N_6O_3$ as $(M+H)^+$ 406.44.

Example 408: (R)-2-(1-amino-3-methyl-1-oxobutan-2-ylamino)-4-(benzo[d]thiazol-5-ylamino)pyrimidine-5-carboxamide

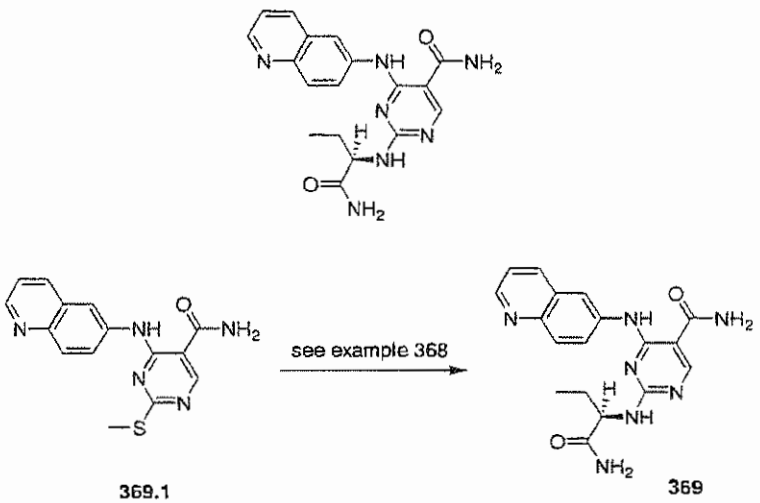




368.1 368.2 368

[0969] To a stirring solution of **368.1** (110. mg, 0.347 mmol) was added mCPBA (65%, 130 mg, 0.49 mmol). The reaction was stirred for 30 min at RT upon which time DIEA (~0.3 mL) and commercially available **368.2** (180 mg, 1.18 mmol) were added. The reaction was heated for 3 h at 120°C in a sealed tube. The reaction was cooled, turned slightly acidic with TFA in water, and subjected to reverse phase preparative HPLC to yield the title compound (28 mg). MS found for $C_{17}H_{19}N_7O_2S$ as $(M+H)^+$ 386.3. UV λ=248, 294 nm

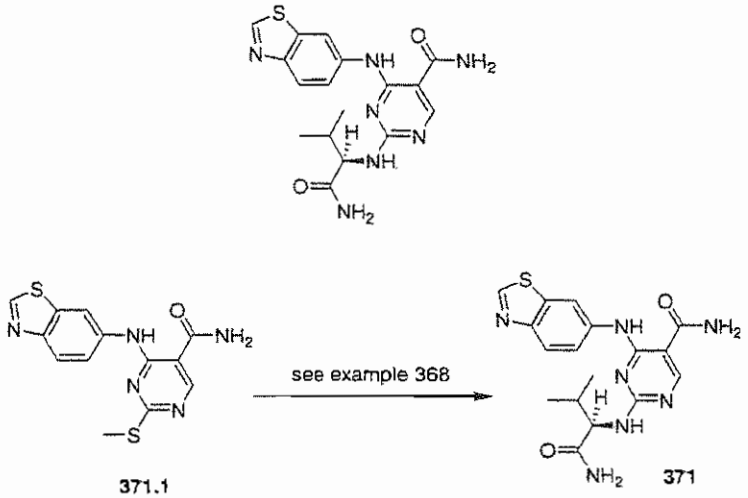
Example 409: (R)-2-(1-amino-1-oxobutan-2-ylamino)-4-(quinolin-6-ylamino)pyrimidine-5-carboxamide



369.1 369

[0970] Intermediate **369.1** was reacted with **346.1** according to Example 408. Reverse phase preparative HPLC afforded the title compound. MS found for $C_{18}H_{19}N_7O_2$ as $(M+H)^+$ 366.2. UV λ=240, 283 nm. δ 1.15 (t, 3H), 1.90-2.10 (m, 2H), 3.10-3.35 (m, 2H), 4.32-4.40 (m, 1H), 7.80-7.90 (m, 1H), 8.07-8.18 (m, 2H), 8.59 (s, 1H), 8.70-8.75 (m, 1H), 8.95-9.05 (m, 2H).

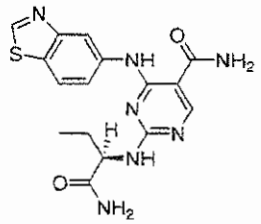
Example 410: (R)-2-(1-amino-3-methyl-1-oxobutan-2-ylamino)-4-(benzo[d]thiazol-6-ylamino)pyrimidine-5-carboxamide



371.1 371

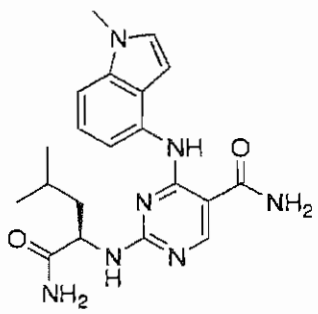
[0971] Intermediate **371.1** was reacted with **368.2** according to the chemistry described in Example 408. Reverse phase preparative HPLC afforded the title compound. MS found for $C_{17}H_{19}N_7O_2S$ as $(M+H)^+$ 386.4. UV λ=243, 302 nm.

Example 411: (R)-2-(1-amino-1-oxobutan-2-ylamino)-4-(benzo[d]thiazol-5-ylamino)pyrimidine-5-carboxamide



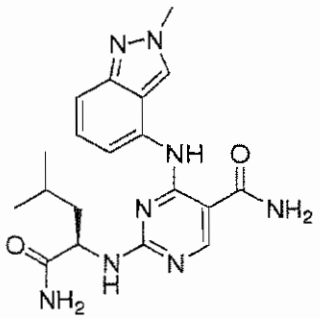
[0972] Intermediate **368.1** was reacted with **346.1** according to the chemistry described in Example 408. Reverse phase preparative HPLC afforded the title compound. MS found for $C_{16}H_{17}N_7O_2S$ as $(M+H)^+$ 372.3. UV λ=246, 293 nm

Example 412. (*R*)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(1-methyl-1H-indol-4-ylamino)pyrimidine-5-carboxamide



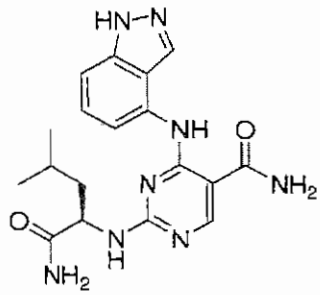
[0973] The title compound was prepared using the same synthetic scheme demonstrated in Example 417. MS found for $C_{20}H_{25}N_7O_2$ as $(M+H)^+$ 396.3. UV: λ = 216.9, 244.0.

Example 413. (*R*)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(2-methyl-2*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



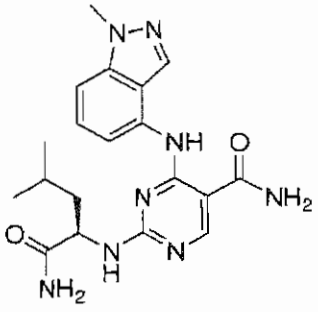
The title compound was prepared using the same synthetic scheme demonstrated in Example 315. MS found for $C_{19}H_{24}N_8O_2$ as $(M+H)^+$ 397.4. UV: λ = 213.3, 244.0, 333.1.

Example 414. (*R*)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



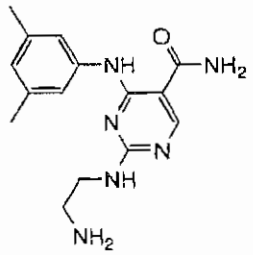
[0974] The title compound was prepared using the same synthetic scheme demonstrated in Example 315. MS found for $C_{18}H_{22}N_8O_2$ as $(M+H)^+$ 383.4. UV: λ = 241.6, 318.8.

Example 415. (*R*)-2-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-(1-methyl-1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide

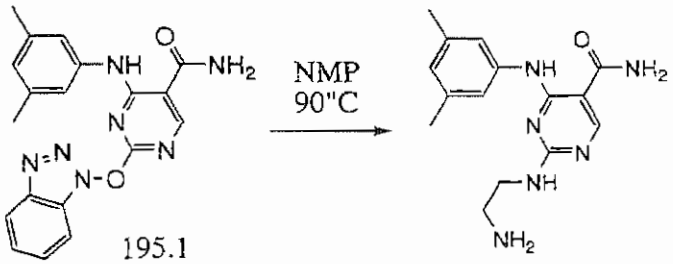


[0975] The title compound was prepared using the same synthetic scheme demonstrated in Example 315. MS found for $C_{19}H_{24}N_8O_2$ as $(M+H)^+$ 397.4. UV: λ = 207.5, 244.0, 325.9.

Example 416. 2-(2-aminoethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide

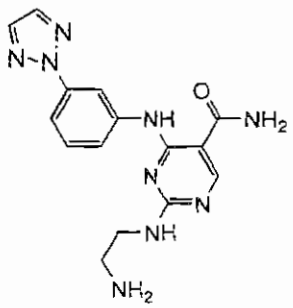


Scheme:

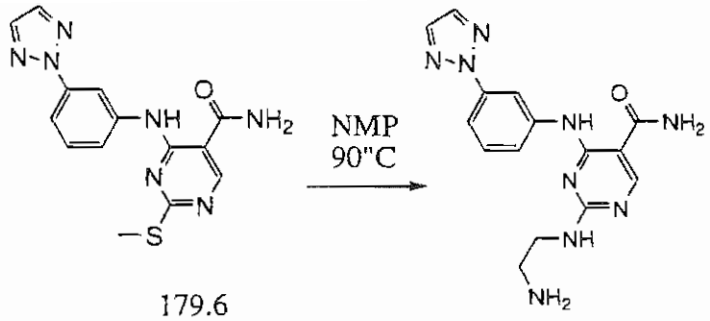


[0976] Compound 195.1 (64 mg, 0.17 mmol) was dissolved in 3 mL NMP. To it was added commercially available ethylenediamine (41 mg, 0.68 mmol). The mixture was stirred at 90°C for 2 h. From this mixture the title compound was isolated using reverse phase prep HPLC. MS found for $C_{15}H_{20}N_6O$ as $(M+H)^+$ 301.2. UV λ=240, 292 nm.

Example 417. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(2-aminoethylamino)pyrimidine-5-carboxamide



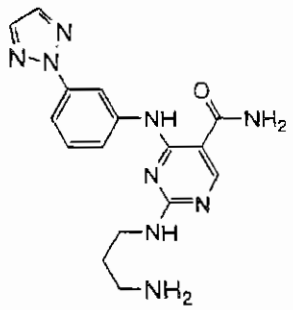
Scheme:



179.6

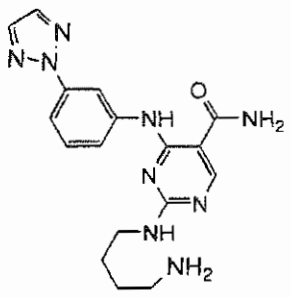
[0977] Compound 179.6 (50 mg, 0.15 mmol) was dissolved in 3 mL NMP. To it was added MCPBA (49 mg, 0.18 mmol) and the mixture was stirred for 30 min. To it was added ethylenediamine (36 mg, 0.60 mmol). The mixture was stirred at 90°C for 2 h. From this mixture the title compound was isolated using reverse phase prep HPLC. MS found for $C_{15}H_{17}N_9O$ as $(M+H)^+$ 340.3. UV λ=249 nm.

Example 418. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(3-aminopropylamino)pyrimidine-5-carboxamide



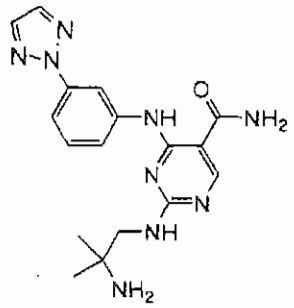
[0978] The title compound was prepared using the same chemistry shown for Example 417. MS found for $C_{16}H_{19}N_9O$ as $(M+H)^+$ 354.4. UV λ=251 nm.

Example 419. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(4-aminobutylamino)pyrimidine-5-carboxamide



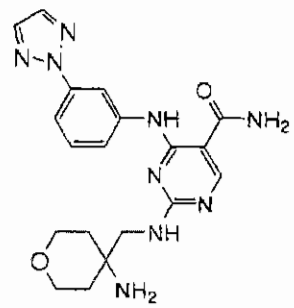
[0979] The title compound was prepared using the same chemistry shown for Example 417. MS found for $C_{17}H_{21}N_9O$ as $(M+H)^+$ 368.4. UV λ=252 nm.

Example 420. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(2-amino-2-methylpropylamino)pyrimidine-5-carboxamide



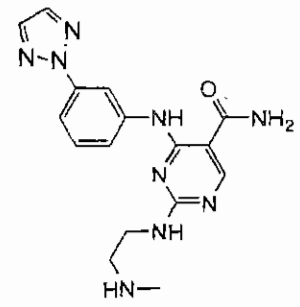
[0980] The title compound was prepared using the same chemistry shown for Example 417. MS found for $C_{17}H_{21}N_9O$ as $(M+H)^+$ 368.4. UV λ=249 nm.

Example 421. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((4-aminotetrahydro-2H-pyran-4-yl)methylamino)pyrimidine-5-carboxamide



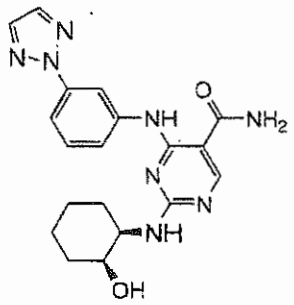
[0981] The title compound was prepared using the same chemistry shown for Example 417. MS found for $C_{19}H_{23}N_9O_2$ as $(M+H)^+$ 410.4. UV λ=249 nm.

Example 422. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(2-(methylamino)ethylamino)pyrimidine-5-carboxamide



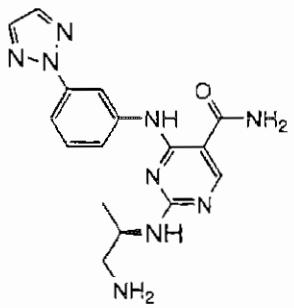
[0982] The title compound was prepared using the same chemistry shown for Example 417 with commercially available tert-butyl 2-aminoethyl(methyl)carbamate, followed by TFA treatment to cleave the BOC group. MS found for $C_{16}H_{19}N_9O$ as $(M+H)^+$ 354.4. UV λ=250 nm.

Example 423. 4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-((1R,2S)-2-hydroxycyclohexylamino)pyrimidine-5-carboxamide (racemic)

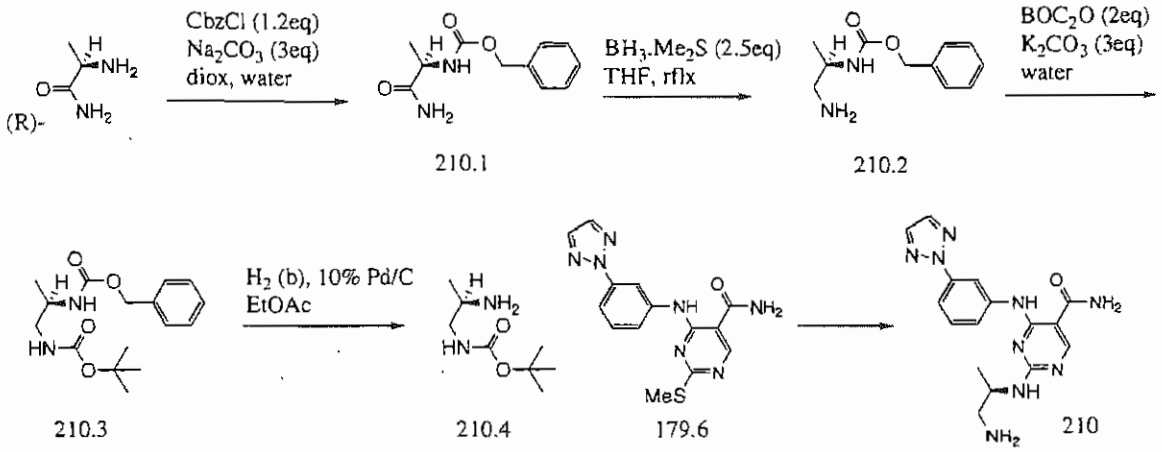


[0983] The title racemic compound was prepared using the same chemistry shown for Example 417 with commercially available cis-2-amino-1-cyclohexanol and DIEA. MS found for $C_{19}H_{22}N_8O_2$ as $(M+H)^+$ 395.4. UV λ=254 nm.

Example 424. (R)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(1-aminopropan-2-ylamino)pyrimidine-5-carboxamide



Scheme:



[0984] Step 1: Commercially available H-D-Ala-NH_2.HCl (2.0 g, 16 mmol) was dissolved in 60 mL water and 20 mL dioxane. To it were added BzCl (2.7 mL, 19.3 mmol) and sodium carbonate (5.1 g, 48 mmol). The mixture was stirred for overnight at RT. It was diluted with ethyl acetate, washed with brine x3, dried, concentrated. The residue was then taken into 450 mL hexane and 50 mL DCM, stirred vigorously at 30°C for 30 min, filtered. Compound 210.1 (>90% yield) stayed in the solid phase, and most impurities and by-products were in the filtrate.

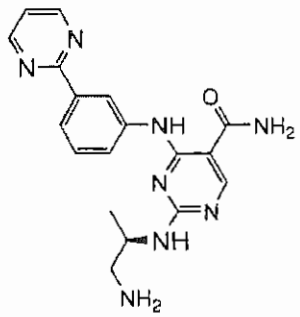
[0985] Step 2: Compound 210.1 (16 mmol) from Step 1 was dissolved in 100mL THF. To it was added $BH_3.Me_2S$ (3.8 mL, 40 mmol) at RT. The mixture was heated to 85°C and gently refluxed for 5 h. It was cooled to RT. To it was added 100 mL water. The mixture was stirred for 1 h at RT. Then K_2CO_3 (6.62 g, 48 mmol) and BOC_2O (7.00 g, 32 mmol) were added. The mixture was stirred at RT for 1 h. It was diluted with ethyl acetate, washed with brine x3, dried, concentrated, subjected to silica flash column with 35% ethyl acetate in hexane to isolate compound 210.3 (1.22 g, 25% for 3 steps overall) as white solid.

[0986] Step 3: Compound 210.3 (3.96 mmol) from Step 2 was dissolved in 200 mL ethyl acetate. To it was added 500 mg 10% Pd/C and the mixture was stirred under H_2 balloon overnight. It was filtered through celite, and the celite was thoroughly rinsed with methanol. The filtrate was concentrated in vacuo to afford compound 210.4 as thick oil. It was dissolved in NMP to make a 0.20M stocking solution.

[0987] Step 4: Compound 179.6 (100 mg, 0.30 mmol) was dissolved in 6 mL NMP. To it was added MCPBA (96 mg, 0.36 mmol). The mixture was stirred for 40 min at RT. TO it were added DIEA (0.21 mL, 1.2 mmol) and compound 210.4 (0.20 M, 3 mL, 0.60 mmol). The mixture was stirred at 90°C for 2 h. It was cooled to RT, diluted with ethyl acetate,

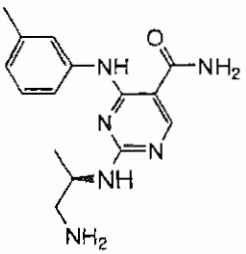
washed with sat. Na_2CO_3 x2 and brine, dried, concentrated in vacuo. The residue was treated with neat TFA at RT for 1 h and then concentrated. The residue was then subjected to reverse phase prep HPLC to isolate the title compound. MS found for $C_{16}H_{19}N_9O$ as $(M+H)^+$ 354.3. UV λ=250 nm.

Example 425. (R)-2-(1-aminopropan-2-ylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



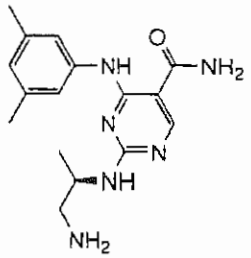
[0988] The title compound was made using the same chemistry scheme shown for Example 424 with compound 249.4 (given in Example 172). MS found for $C_{18}H_{20}N_8O$ as $(M+H)^+$ 365.3. UV λ=247 nm.

Example 426. (R)-2-(1-aminopropan-2-ylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



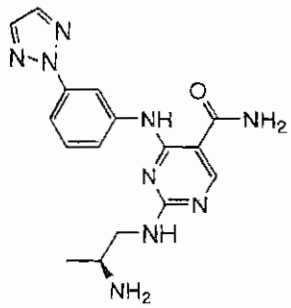
[0989] The title compound was made using the same chemistry scheme shown for Example 424 with compound 187.10 (given in Example 187). MS found for C15H20N6O as $(M+H)^+$ 301.3. UV λ=243, 289 nm.

Example 427. (R)-2-(1-aminopropan-2-ylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



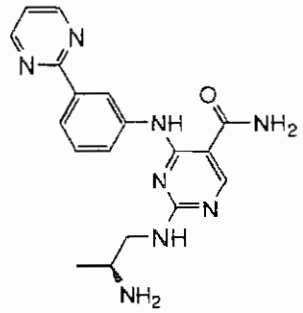
[0990] The title compound was made using the same chemistry scheme shown for Example 424 with compound 185.1 (given in Example 195). MS found for $C_{16}H_{22}N_6O$ as $(M+H)^+$ 315.3. UV λ=243, 289 nm.

Example 428. (S)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(2-aminopropylamino)pyrimidine-5-carboxamide



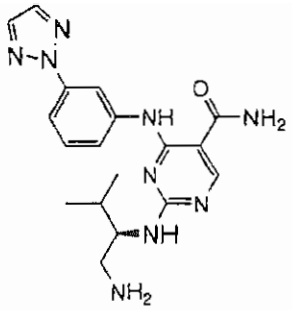
The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{16}H_{19}N_9O$ as $(M+H)^+$ 354.3. UV λ=250 nm.

[0991] Example 215. (S)-2-(2-aminopropylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



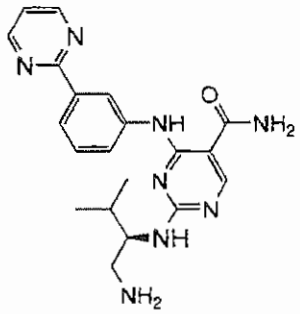
The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{18}H_{20}N_8O$ as $(M+H)^+$ 365.3. UV λ=247 nm.

Example 216. (R)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(1-amino-3-methylbutan-2-ylamino)pyrimidine-5-carboxamide



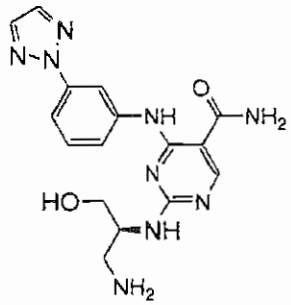
[0992] The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{18}H_{23}N_9O$ as $(M+H)^+$ 382.4. UV λ=251 nm.

Example 217. (R)-2-(1-amino-3-methylbutan-2-ylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



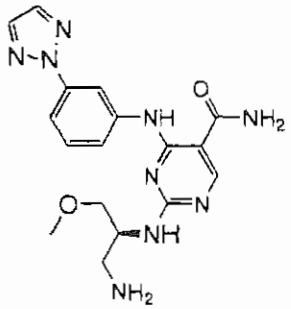
[0993] The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{20}H_{24}N_8O$ as $(M+H)^+$ 393.4. UV λ=249 nm.

Example 218. (S)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(1-amino-3-hydroxypropan-2-ylamino)pyrimidine-5-carboxamide

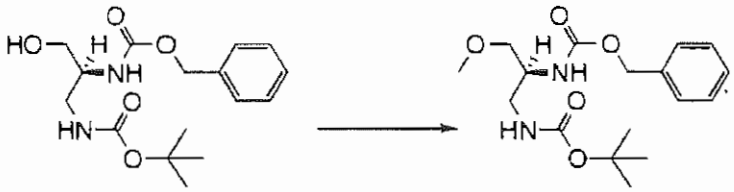


[0994] The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{16}H_{19}N_9O_2$ as $(M+H)^+$ 370.3. UV λ=248 nm.

Example 219. (S)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(1-amino-3-methoxypropan-2-ylamino)pyrimidine-5-carboxamide



Scheme:

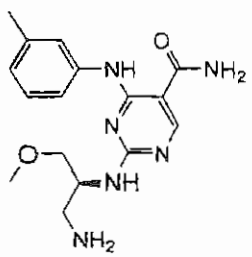


219.1 219.2

[0995] Compound 219.1 was prepared using the same chemistry for compound 210.3 shown in Example 414. Compound 219.1 (2.0 g, 6 mmol) was dissolved in 100 mL DCM. To it were added proton sponge (3.2 g, 15 mmol) at RT. Three min later, $Me_3O^+BF_4^-$ (2.2 g, 15 mmol) was added. The mixture was stirred at RT for 3 days. It was diluted with 500 mL ethyl acetate, washed with brine x2, dried, concentrated, subjected to silica flash column (40% ethyl acetate in hexane) to give compound 219.2 (1.77 g, 87%) as white solid.

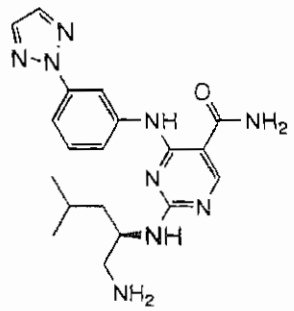
[0996] The title compound was completed using the similar chemistry scheme shown for Example 424 with compound 218.2. MS found for $C_{17}H_{21}N_9O_2$ as $(M+H)^+$ 384.3. UV λ=249 nm.

Example 220. (S)-2-(1-amino-3-methoxypropan-2-ylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



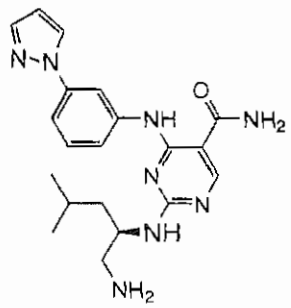
[0997] The title compound was made using the similar chemistry scheme shown for Example 219. MS found for $C_{16}H_{22}N_6O_2$ as $(M+H)^+$ 331.3. UV λ=240, 289 nm.

Example 221. (R)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)-2-(1-amino-4-methylpentan-2-ylamino)pyrimidine-5-carboxamide



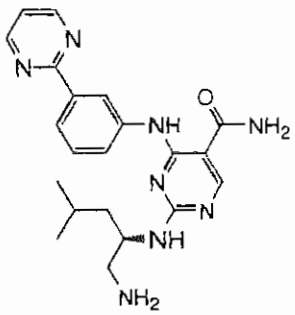
[0998] The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{19}H_{25}N_9O$ as $(M+H)^+$ 396.4. UV λ=250 nm.

Example 428. (R)-4-(3-(1H-pyrazol-1-yl)phenylamino)-2-(1-amino-4-methylpentan-2-ylamino)pyrimidine-5-carboxamide



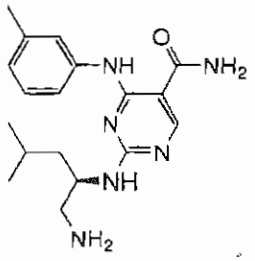
[0999] The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{20}H_{26}N_8O$ as $(M+H)^+$ 395.4. UV λ=247 nm.

Example 429. (R)-2-(1-amino-4-methylpentan-2-ylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



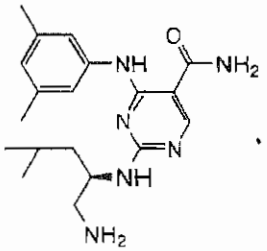
[1000] The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{21}H_{26}N_8O$ as $(M+H)^+$ 405.4. UV λ=247 nm.

Example 431. (R)-2-(1-amino-4-methylpentan-2-ylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



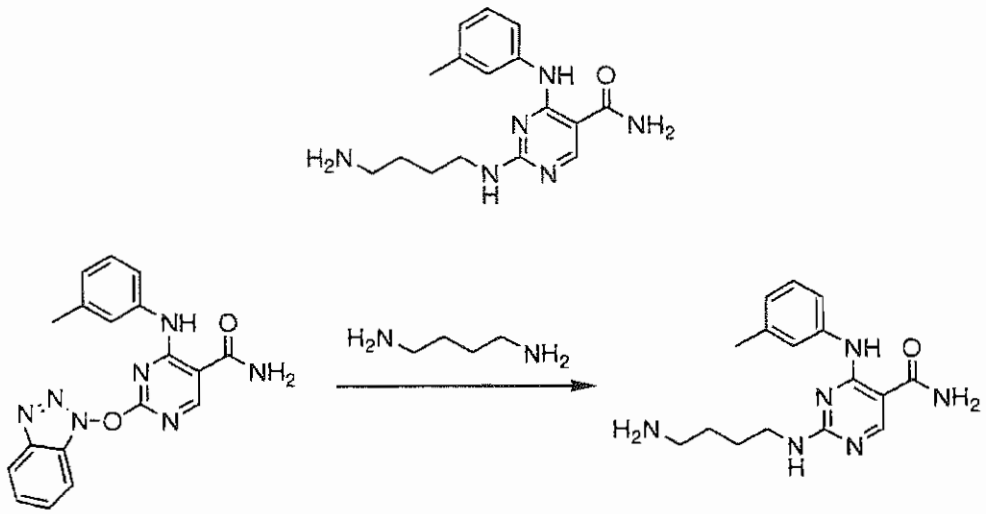
[1001] The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{18}H_{26}N_6O$ as $(M+H)^+$ 343.4. UV λ=244, 288 nm.

Example 432. (R)-2-(1-amino-4-methylpentan-2-ylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



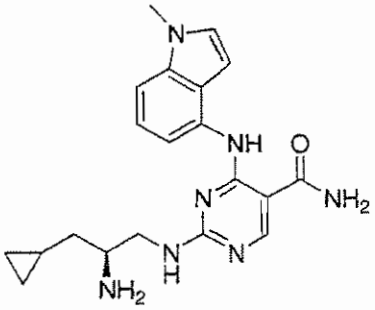
[1002] The title compound was made using the similar chemistry scheme shown for Example 424. MS found for $C_{19}H_{28}N_6O$ as $(M+H)^+$ 357.4. UV λ=241, 290 nm.

Example 433 2-(4-aminobutylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



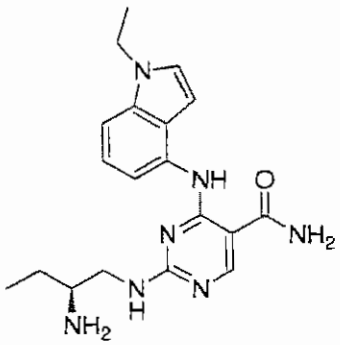
[1003] To a solution of 1,4-diaminobutane (0.48 g, 5.5 mmol) in DMF (5 mL), a solution of compound 2-(1H-benzo[d][1,2,3]triazol-1-yloxy)-4-(m-tolylamino)pyrimidine-5-carboxamide (0.53 g, 1.47 mmol) in DMF (5 mL) was added dropwise. It was then stirred at room temperature for 20 h. It was concentrated in vacuo. The residue was purified by HPLC to give the titled compound as trifluoroacetic acid salt (0.55 g). MS 315.2 (M+H); UV 249.7.

Example 434. (*S*)-2-(2-amino-3-cyclopropylpropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



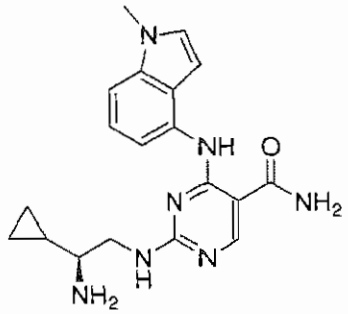
[1004] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{20}H_{25}N_7O$ as $(M+H)^+$ 380.4. UV: λ = 219.8, 241.1, 330.3.

Example 435. (*S*)-2-(2-aminobutylamino)-4-(1-ethyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



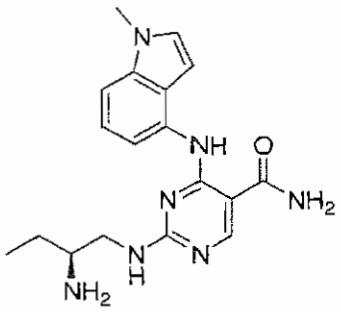
[1005] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{25}N_7O$ as $(M+H)^+$ 368.4. UV: λ = 219.2, 240.4, 331.9.

Example 436. (*S*)-2-(2-amino-2-cyclopropylethylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



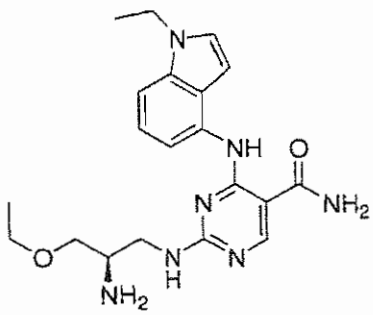
[**1006**] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{23}N_7O$ as $(M+H)^+$ 366.4. UV: λ = 220.2, 241.4, 330.6. NMR (CD_3OD): δ 8.27 (s, 1H), 8.08 (s, 1H), 7.85 (d, J=2.4 Hz, 1H), 7.34 (s, 1H), 7.06-7.00 (m, 3H), 6.80 (m, 1H), 6.12 (m, 1H), 4.18 (m, 1H), 2.67 (m, 2H), 1.19 (m, 3H), 0.97 (m, 1H), 0.42-0.31 (m, 6H) ppm.

Example 437. (*S*)-2-(2-aminobutylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



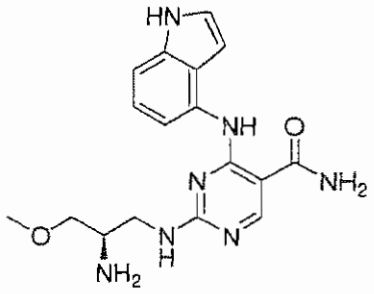
[**1007**] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{23}N_7O$ as $(M+H)^+$ 354.4. UV: λ = 219.2, 240.4, 333.1.

Example 438. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(1-ethyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



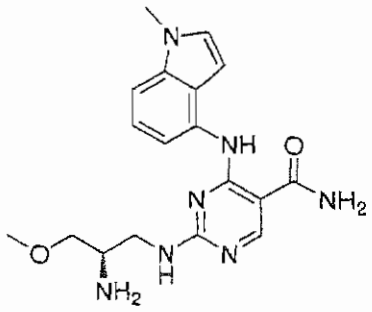
[1008] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{20}H_{27}N_7O$ as $(M+H)^+$ 398.4. UV: λ = 219.3, 239.4, 326.7.

Example 439. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



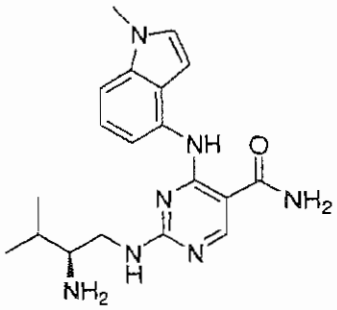
[1009] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{17}H_{21}N_7O_2$ as $(M+H)^+$ 356.4. UV: λ = 216.7, 238.7, 327.2.

Example 440. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



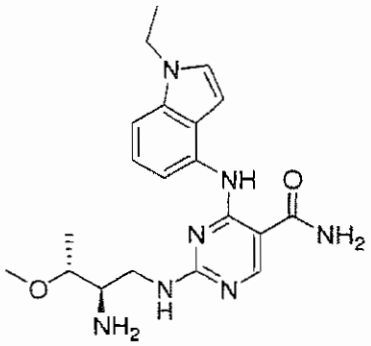
[1010] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{23}N_7O_2$ as $(M+H)^+$ 370.4. UV: λ = 219.2, 239.3, 331.9.

Example 441. (*R*)-2-(2-amino-3-methylbutylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



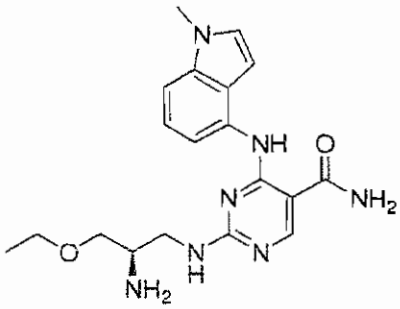
[1011] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{25}N_7O$ as $(M+H)^+$ 368.4. UV: λ = 220.4, 325.9.

Example 442. 2-((2R, 3R)-2--amino-3-methoxylbutylamino)-4-(1-ethyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



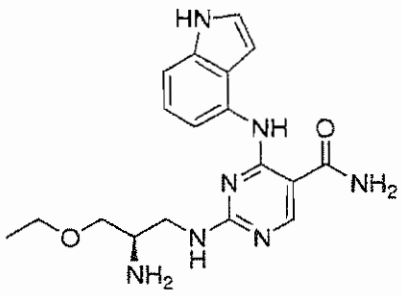
[1012] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{20}H_{27}N_7O_2$ as $(M+H)^+$ 398.4. UV: λ = 220.4, 239.9, 331.6.

Example 443. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



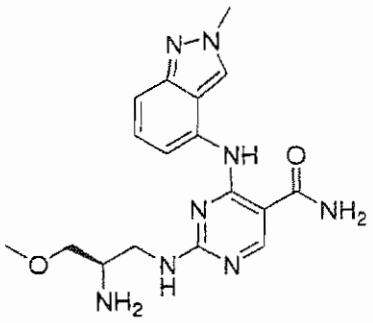
[1013] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{25}N_7O_2$ as $(M+H)^+$ 384.3. UV: λ = 219.2, 239.3, 331.9.

Example 444. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



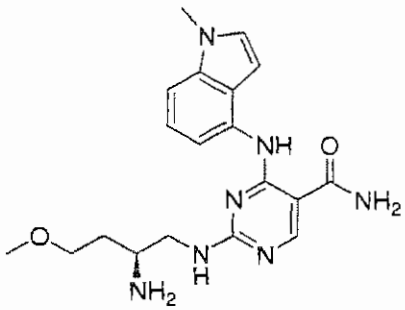
[1014] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{23}N_7O_2$ as $(M+H)^+$ 370.3. UV: λ = 215.7, 238.1, 327.1.

Example 445. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(2-methyl-2*H*-indol-4-ylamino)pyrimidine-5-carboxamide



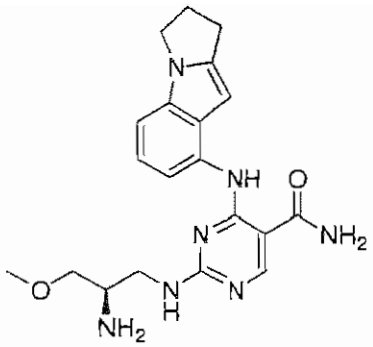
[1015] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{22}N_8O_2$ as $(M+H)^+$ 371.3. UV: λ = 214.9, 241.7, 324.1.

Example 446. (*R*)-2-(2-amino-4-methoxypropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



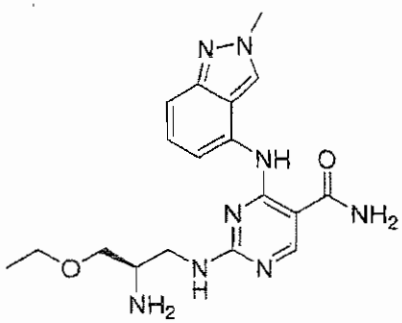
[1016] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{25}N_7O_2$ as $(M+H)^+$ 384.3. UV: λ = 219.2, 240.4, 331.9.

Example 447. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



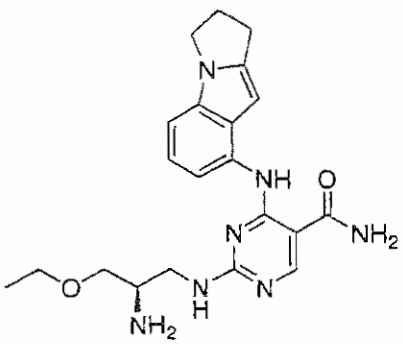
[1017] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{25}N_7O_2$ as $(M+H)^+$ 396.4. UV: λ = 203.9, 244.0, 303.3.

Example 448. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(2-methyl-2*H*-indol-4-ylamino)pyrimidine-5-carboxamide



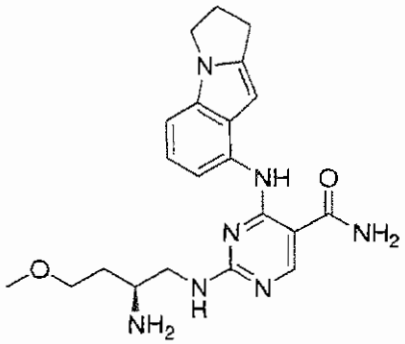
[1018] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{24}N_8O_2$ as $(M+H)^+$ 385.4. UV: λ = 208.6, 240.4, 283.1, 324.7.

Example 449. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



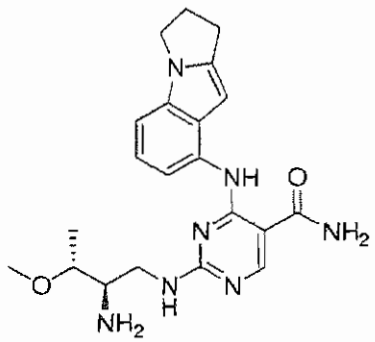
[1019] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{27}N_7O_2$ as $(M+H)^+$ 410.4. UV: λ = 221.6, 336.7.

Example 450. (*S*)-2-(2-amino-4-methoxypropylamino)-4-(2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



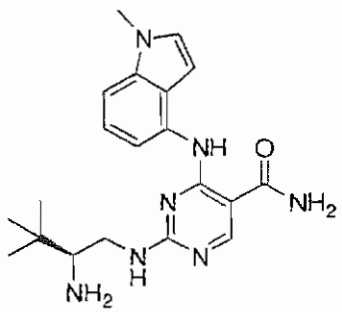
[1020] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{27}N_7O_2$ as $(M+H)^+$ 410.4. UV: λ = 222.8, 336.7.

Example 451. 2-((2*R*, 3*R*)-2-amino-3-methoxylbutylamino)-4-(2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



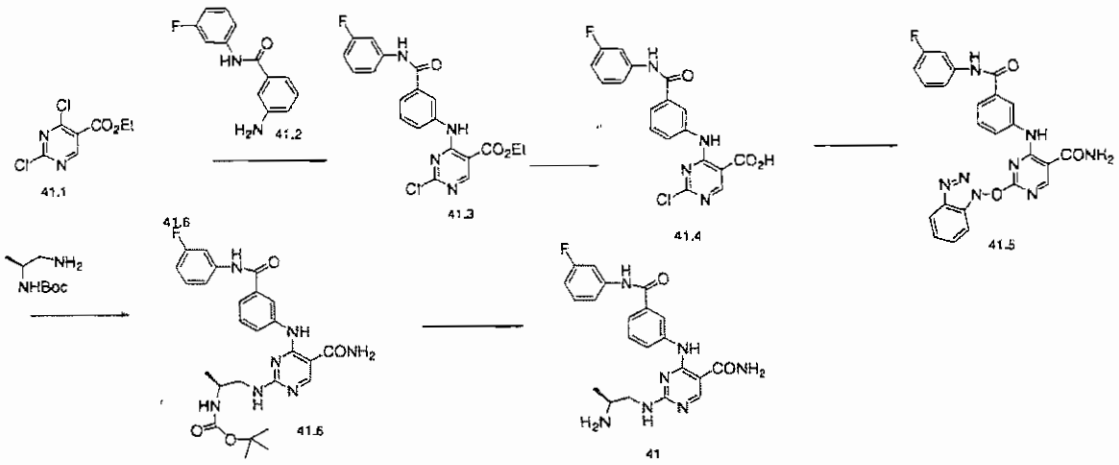
[1021] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{27}N_7O_2$ as $(M+H)^+$ 410.4. UV: λ = 221.6, 335.5.

Example 452. (*S*)-2-(2-amino-3,3-dimethylbutylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



[1022] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{20}H_{27}N_7O$ as $(M+H)^+$ 382.4. UV: λ = 219.2, 239.3, 327.1.

Example 453 (S)-2-(2-aminopropylamino)-4-(3-(3-fluorophenylcarbamoyl)phenylamino)pyrimidine-5-carboxamide (41)



[1023] Step1: Dichloropyrimidine ester 41.1(3.44g, 15.5 mmol) was dissolved in acetonitrile (20 mL) and stirred in ice bath. To it was added a solution of aniline **41.2** (3.0g, 14.1 mmol) and ethyldiisopropylamine (DIEA, 3.85 mL, 35.5 mmol) in 10 mL acetonitrile dropwise using an additional funnel. The mixture was stirred for 1 hour, solvent evaporated followed by dilution with water to precipitate compound **41.3** as a yellow solid (4.2g, 75%). MS: $(M+H)^+$ 416.09

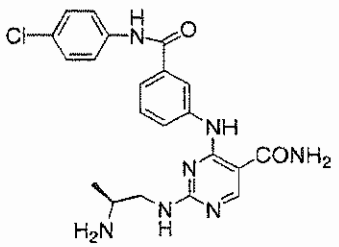
[1024] Step 2: Ethyl ester **41.3** (2 g, 5 mmol) was dissolved in 10 mL THF. To it were added lithium hydroxide hydrate (275 mg, 6.5 mmol) and 10 mL water. The mixture was stirred for 1 hour and to it was carefully added 1N HCl solution till pH reaching 3. The mixture was concentrated in vacuo to remove THF. White solid crashed out and was isolated using a Büchner funnel. It was washed with water and dried in vacuum oven to give compound **41.4** (1.65g, 89%) as a white solid. MS: $(M+H)^+$ 388.06

[1025] Step 3: Carboxylic acid **41.4** (1 g, 2.7 mmol) was dissolved in 15 mL DMF. To it were added EDC hydrochloride (934 mg, 4.86 mmol) and HOBt hydrate (660mg, 4.86 mmol). The mixture was stirred at RT for 90 minutes. To it was then added ammonia (commercial 0.5N solution in dioxane, 14 mL, 6.75 mmol) at 0°C. The mixture was stirred for overnight at room temperature. To the reaction mixture added water to afford compound **41.5** as a white solid (1.26 g, 86%). MS: $(M+H)^+$ 485.14.

[1026] Step 4: Benzotriazolyl ether **41.5** (500 mg, 1 mmol) was dissolved in 15 mL ACN. To it was added (S)-tert-butyl-1-aminopropane-2-yl-carbamate (373 mg, 2.1 mmol). The mixture was stirred for overnight at 50°C. After cooling added water and stirred for 1 hr to afford compound **41.6** as a white solid (0.541 g, 92%) . MS found for $C_{26}H_{30}FN_7O_4$ as $(M+H)^+$ 524.24.

[1027] Step 5: Compound **41.6** (100 mg, 0.2 mmol) was stirred in a 1:1 (5 mL) mixture of TFA and dichloromethane at RT for 15 minutes. It was concentrated in vacuo followed by addition of diisopropyl ether to afford compound **No. 41** as a white solid (50 mg, 59%). MS found for $C_{21}H_{22}FN_7O_2$ as $(M+H)^+$ 424.19.

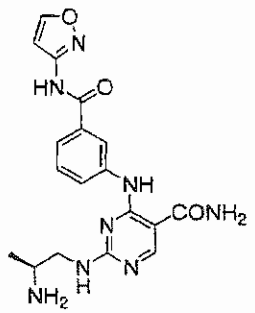
Example 454 (S)-2-(2-aminopropylamino)-4-(3-(4-chlorophenylcarbamoyl)phenylamino)pyrimidine-5-carboxamide (57)



57

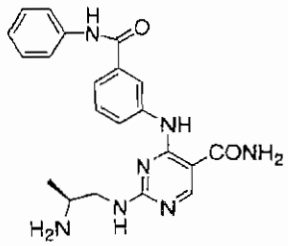
[1028] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-(4-chlorophenyl)benzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{21}H_{22}ClN_7O_2$ as $(M+H)^+$ 440.

Example 455. (S)-2-(2-aminopropylamino)-4-(3-(isoxazol-3-ylcarbamoyl) phenylamino)pyrimidine-5-carboxamide



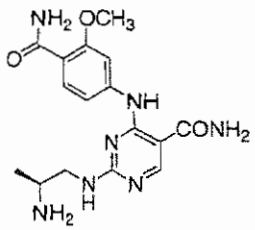
[1029] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-(isoxazol-3-yl)benzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{18}H_{20}N_8O_3$ as $(M+H)^+$ 396

Example 456. (S)-2-(2-aminopropylamino)-4-(3-(phenylcarbamoyl) phenylamino)pyrimidine-5-carboxamide



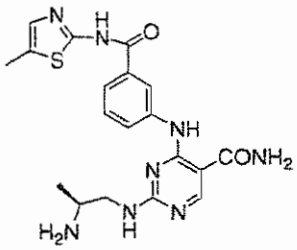
[1030] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-phenylbenzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{21}H_{23}N_7O_3$ as $(M+H)^+$ 406

Example 457. (S)-2-(2-aminopropylamino)-4-(4-carbamoyl-3-methoxyphenylamino)pyrimidine-5-carboxamide (121)



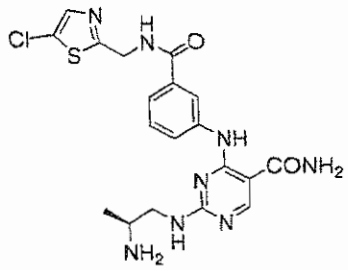
[1031] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 4-amino-2-methoxybenzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{16}H_{21}N_7O_3$ as $(M+H)^+$ 360

Example 458. (S)-2-(2-aminopropylamino)-4-(3-(5-methylthiazol-2-ylcarbamoyl)phenylamin)opyrimidine-5-carboxamide (123)



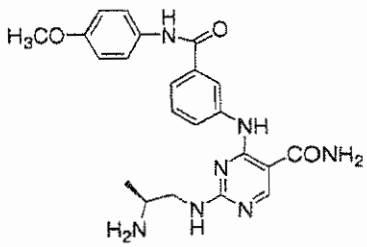
[1032] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-(5-methylthiazol-2-yl)benzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{19}H_{22}N_8O_2S$ as $(M+H)^+$ 427

Example 459. (S)-2-(2-aminopropylamino)-4-(3-((5-chlorothiazol-2-ylmethylcarbamoyl)phenylamino)pyrimidine-5-carboxamide (125)



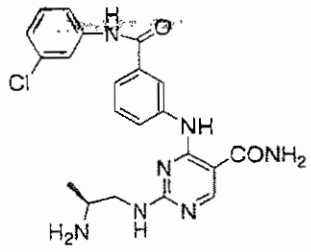
[1033] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-((5-chlorothiazol-2-yl)methyl)benzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{19}H_{21}ClN_8O_2S$ as $(M+H)^+$ 447

Example 460. (S)-2-(2-aminopropylamino)-4-(3-(methoxyphenylcarbamoyl)phenylamino)pyrimidine-5-carboxamide



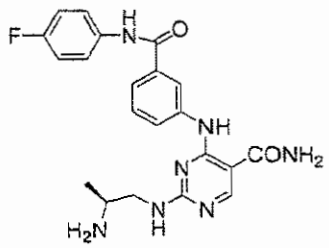
[1034] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-(4-methoxyphenyl)benzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{22}H_{25}N_7O_3$ as $(M+H)^+$ 436

Example 461. (S)-2-(2-aminopropylamino)-4-(3-(3-chlorophenylcarbamoyl)phenylamino)pyrimidine-5-carboxamide



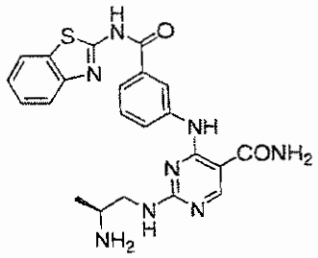
[1035] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-(3-chlorophenyl)benzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{21}H_{22}ClN_7O_2$ as $(M+H)^+$ 440

Example 462. S)-2-(2-aminopropylamino)-4-(3-(4-fluorophenylcarbamoyl)phenylamino)pyrimidine-5-carboxamide



[1036] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-(4-fluoroophenyl)benzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{21}H_{22}FN_7O_2$ as $(M+H)^+$ 424

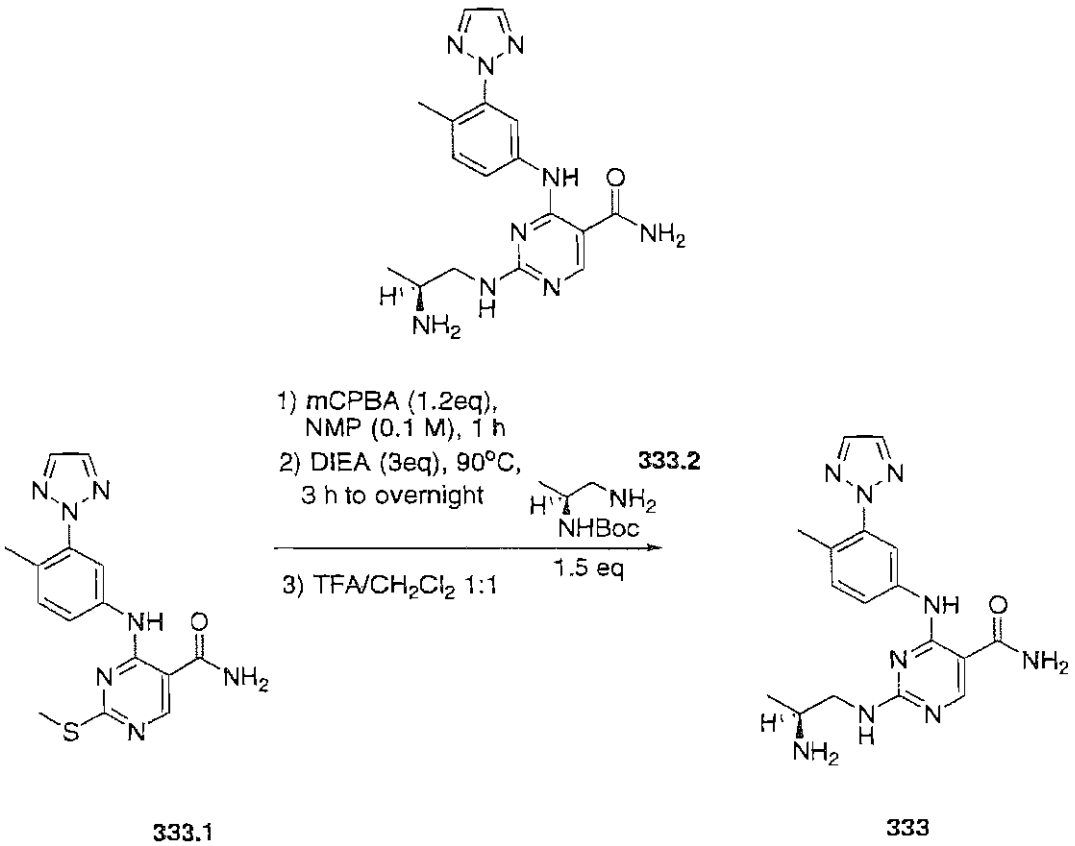
Example 463. S)-2-(2-aminopropylamino)-4-(3-(benzo[d]thiazol-2-ylcarbamoyl)phenylamino)pyrimidine-5-carboxamide



[1037] The title compound was prepared using the same synthetic scheme demonstrated in Example 453 with 3-amino-N-(benzo[d]thiazol-2-yl)benzamide to replace to 3-amino-N-(3-fluorophenyl)benzamide. MS found for $C_{22}H_{22}N_8O_2S$ as $(M+H)^+$ 463

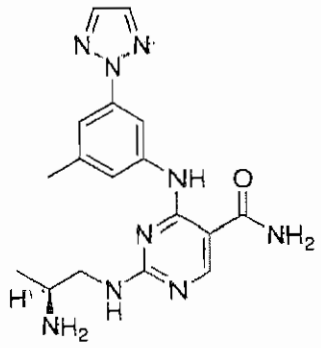
[1038] The compounds No. 140, 141, 144, 156, 163, 164, 166, 172, 173, 176, 177, 180, 191 194, 200, 201, 213, 215, 218, 221, 222, 228, 233, 237, 238, and 239 were prepared using the same synthetic scheme demonstrated in Example 453.

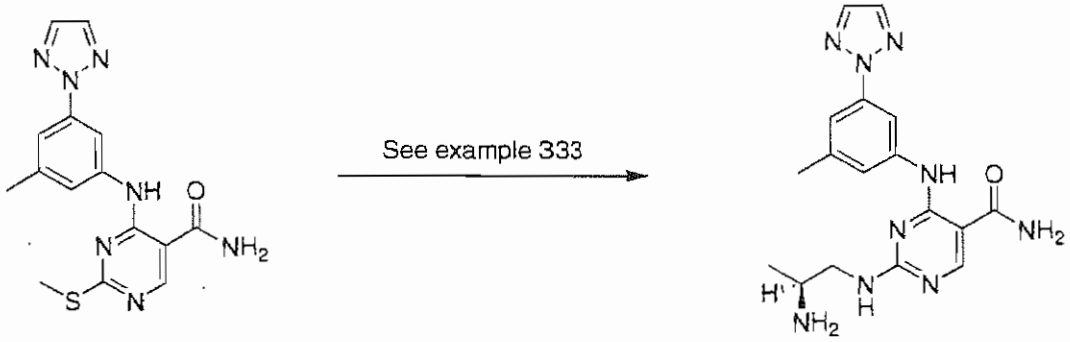
Example 464: (S)-2-(2-aminopropylamino)-4-(4-methyl-3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



[1039] This compound was made in an analogous fashion to **81** in Example 87. However, instead of the 4-(thiazol-4-yl) derivative **81.1**, the 4-methyl-3-(2H-1,2,3-triazol-2-yl) derivative was utilized. Also, instead of tert-butyl (1S,2R)-2-aminocyclohexylcarbamate **81.2**, N-((S)-2-amino-1-methylethyl)carbamic acid tert-butyl ester **333.2**[CAS 146552-71-8] was used. MS found for $C_{17}H_{21}N_9O$ as $(M+H)^+$ 368.4. UV λ= 242 nm.

Example 465: (S)-2-(2-aminopropylamino)-4-(5-methyl-3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



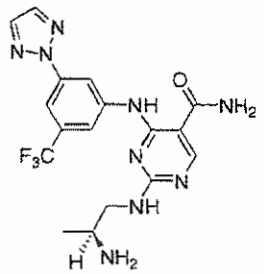


334.1

334

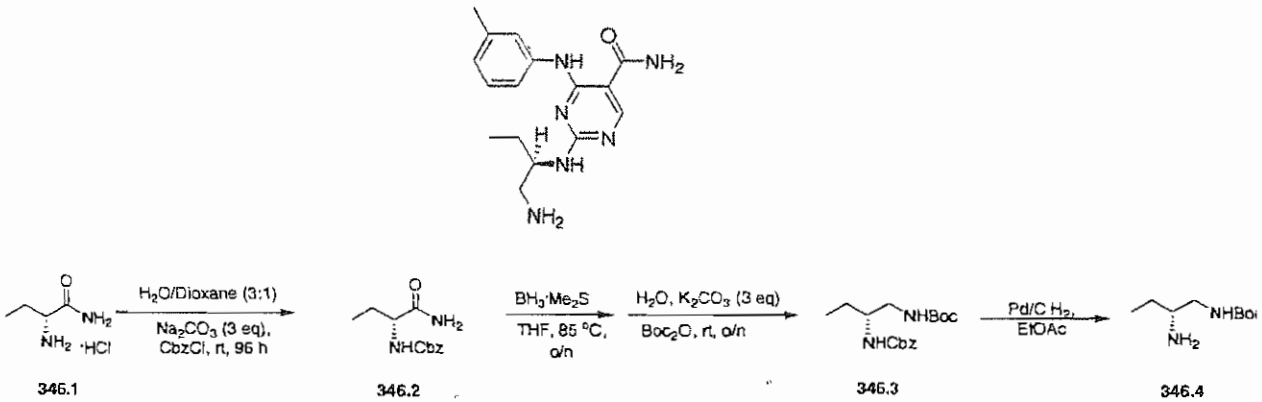
[1040] This compound was made in an analogous fashion to **333** in example 464. However, instead of the 4-methyl-3-(2H-1,2,3-triazol-2-yl) derivative **333.1**, the 5-methyl-3-(2H-1,2,3-triazol-2-yl) derivative **334.1** was utilized. MS found for $C_{17}H_{21}N_9O$ as $(M+H)^+$ 368.3. UV λ= 246 nm

Example 466: (S)-2-(2-aminopropylamino)-4-(3-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)phenylamino)pyrimidine-5-carboxamide



[1041] The title compound was prepared according the scheme 464 using **335.3** as the starting aniline. MS found for $C_{17}H_{18}F_3N_9O$ as $(M+H)^+$ 422.3. UV λ= 260 nm

Example 467: (R)-2-(1-aminobutan-2-ylamino)-4-(3-methylphenyl)pyrimidine-5-carboxamide



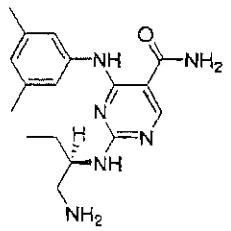
[1042] Commercially available (*R*)-(-)-2-butanamide hydrochloride (**346.1**; 2.41 g, 17.4 mmol) [CAS 103765-03-3] was dissolved in water/dioxane (60 mL/20 mL) containing Na_2CO_3 (5.53 g, 52.2 mmol). To this stirring solution was added benzyl chloroformate (2.81 mL, 20.9 mmol) [CAS 501-53-1]. The reaction was stirred for 96 h at RT. The reaction mixture was diluted with EtOAc (400 mL) and water (100 mL). The layers were separated and the organics were further washed with water (2x150 mL) and brine (2x150 mL). The EtOAc layer was dried ($MgSO_4$) and concentrated. The resulting white solid was triturated with 360 mL hexanes/50 mL CH_2Cl_2 for 1 h. The solid was filtered, washed with hexanes, and dried to give **346.2** (3.46 g).

[1043] To a stirring solution of **346.2** (3.46 g, 14.7 mmol) in anhydrous THF (100 mL) was added $BH_3 \cdot Me_2S$ (3.45 mL, 36.6 mmol) dropwise. The resulting solution was heated under an argon atmosphere at 85°C for 18 h. The reaction mixture was cooled and ice-cold water was slowly added (100 mL). The resulting solution was stirred for 1 h. Next, K_2CO_3 was added (6.08 g, 44.1 mmol) followed by Boc anhydride (6.40 g, 29.4 mmol). The reaction was stirred for 18 h and then diluted with EtOAc. The organic layer was washed with 5% K_2CO_3, 5% $NaHCO_3$, water, and brine. It was then dried over $MgSO_4$ and concentrated to yield **346.3**.

[1044] Crude **346.3** was dissolved in ~ 50 mL EtOAc and a catalytic amount of 10% Pd/C was added. To this suspension was amounted a hydrogen balloon for overnight stirring. The mixture was filtered through celite and concentrated in vacuo to afford **346.4**.

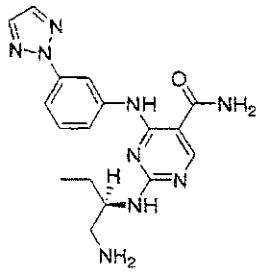
[1045] Intermediate **346.4** was reacted with **344.1** according to the chemistry described in example 13. After Boc-deprotection, reverse phase preparative HPLC afforded the title compound. MS found for $C_{16}H_{22}N_6O$ as $(M+H)^+$ 315.4. UV λ=238, 284 nm.

Example 468: (R)-2-(1-aminobutan-2-ylamino)-4-(3,5-dimethylphenyl)pyrimidine-5-carboxamide



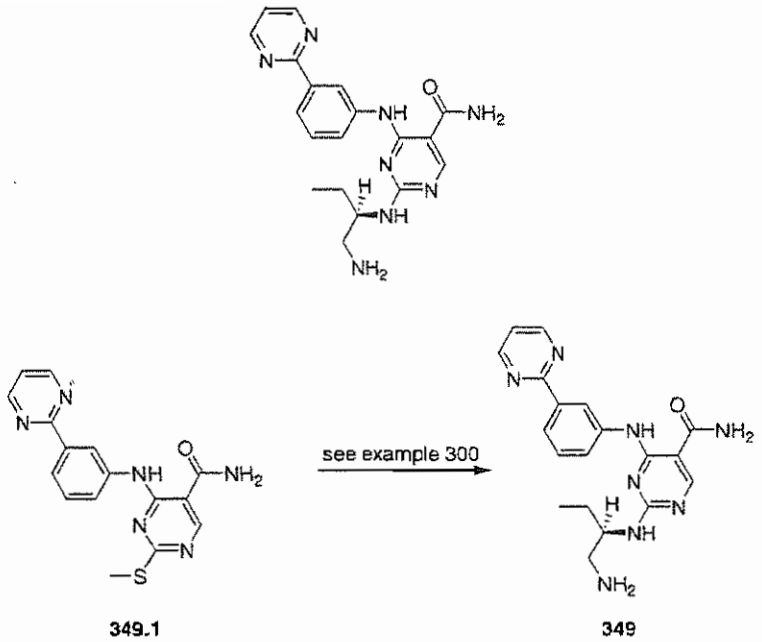
[**1046**] Intermediate **346.4** was reacted with **345.1** according to the chemistry described in example 13. After Boc-deprotection, reverse phase preparative HPLC afforded the title compound. MS found for $C_{17}H_{24}N_6O$ as $(M+H)^+$ 329.5. UV λ=240, 290 nm. δ 1.05 (t, 3H), 1.70-1.80 (m, 2H), 2.38 (s, 6H), 3.15-3.35 (m, 2H), 4.16-4.23 (m, 1H), 6.90 (s, 1H), 7.19-7.25 (m, 2H), 8.50 (s, 1H)

Example 469: (R)-2-(1-aminobutan-2-ylamino)-4-(3-(2H-1,2,3-triazol-2-yl) phenylamino)pyrimidine-5-carboxamide



[**1047**] Intermediate **346.4** was reacted with **343.5** according to the chemistry described in Example 424. After Boc-deprotection, reverse phase preparative HPLC afforded the title compound. MS found for $C_{17}H_{21}N_9O$ as $(M+H)^+$ 368.4. UV λ=248 nm. δ 1.05 (t, 3H), 1.70-1.80 (m, 2H), 3.10-3.35 (m, 2H), 4.55-4.61 (m, 1H), 7.35 (d, 1H), 7.55 (t, 1H), 7.92 (d, 1H), 8.00 (s, 2H), 8.58 (s, 1H), 9.00 (s, 1H)

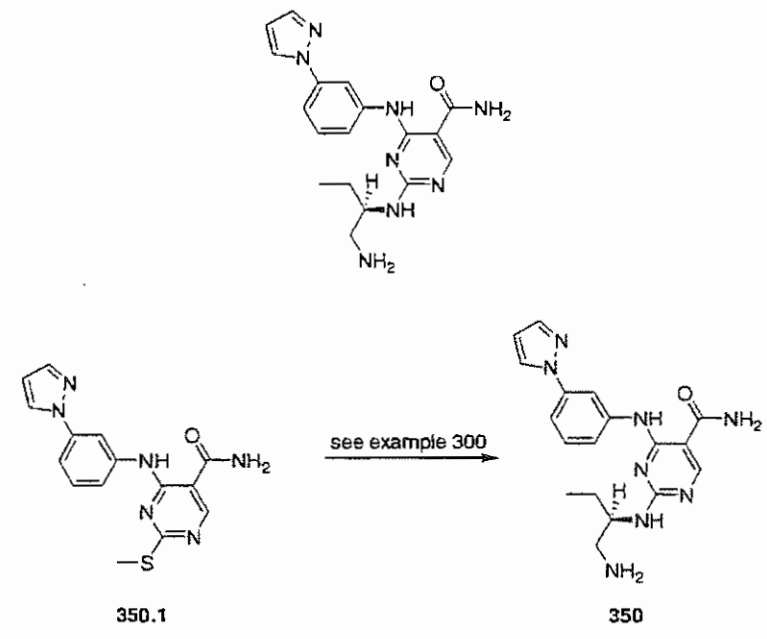
Example 470: (R)-2-(1-aminobutan-2-ylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



349.1 349

[1048] Intermediate **346.4** was reacted with **349.1** according to the chemistry described in Example 424. After Boc-deprotection, reverse phase preparative HPLC afforded the title compound. MS found for $C_{19}H_{22}N_8O$ as $(M+H)^+$ 379.5. UV λ=248 nm. δ 1.05 (t, 3H), 1.70-1.80 (m, 2H), 3.10-3.35 (m, 2H), 4.48-4.55 (m, 1H), 7.41 (t, 1H), 7.55-7.60 (m, 2H), 8.25-8.35 (m, 1H), 8.55 (s, 1H), 8.89 (d, 2H), 9.00 (s, 1H)

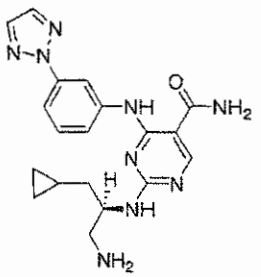
Example 471: 2-((R)-1-aminobutan-2-ylamino)-4-(3-(1H-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide

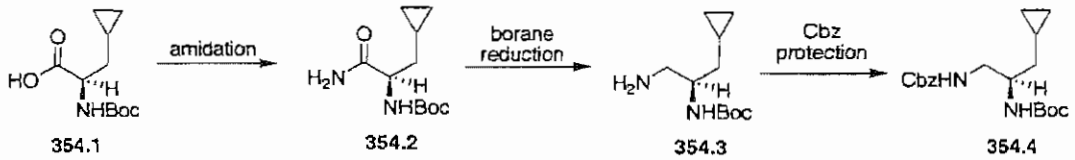


350.1 350

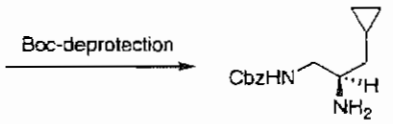
[1049] Intermediate **346.4** was reacted with **350.1** according to the chemistry described in Example 424. After Boc-deprotection, reverse phase preparative HPLC afforded the title compound.MS found for $C_{18}H_{22}N_8O$ as $(M+H)^+$ 367.4. UV λ=246 nm. δ 1.05 (t, 3H), 1.70-1.80 (m, 2H), 3.10-3.35 (m, 2H), 4.48-4.55 (m, 1H), 6.58 (br s, 1H), 7.30 (d, 1H), 7.50-7.62 (m, 2H), 7.80 (br s, 1H), 8.32 (br s, 1H), 8.55 (s, 1H), 8.68 (br s, 1H)

Example 472: (R)-2-(1-amino-3-cyclopropylpropan-2-ylamino)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide





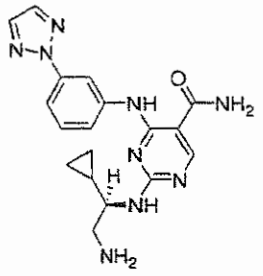
354.1 354.2 354.3 354.4



354.5

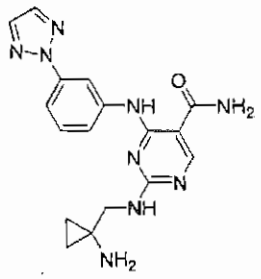
[1050] Intermediate **354.5** was reacted with **343.5** according to the chemistry described in Example 424. After Cbz-deprotection, reverse phase preparative HPLC afforded the title compound. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV λ=250 nm.

Example 473: (R)-2-(1-amino-3-cyclopropylethylamino)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



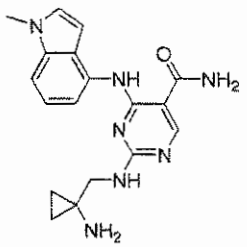
[1051] The title compound was made in an analogous fashion to Example 424. MS found for $C_{18}H_{21}N_9O$ as $(M+H)^+$ 380.4. UV λ=250 nm. δ 0.50-0.85 (m, 4H), 1.15-1.25 (m, 1H), 3.10-3.35 (m, 2H), 3.90-4.00 (m, 1H), 7.30-7.36 (m, 1H), 7.60 (t, 1H), 7.93-8.00 (m, 1H), 8.05 (s, 2H), 8.56 (s, 1H), 8.90 (br s, 1H).

Example 474: 2-((1-aminocyclopropylmethyl)amino)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



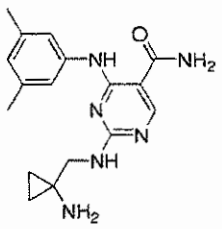
[1052] The title compound was made in an analogous fashion to Example 424. MS found for $C_{17}H_{19}N_9O$ as $(M+H)^+$ 366.4. UV λ=248 nm.

Example 475: 2-((1-aminocyclopropylmethyl)amino)-4-(1-methyl-1H-indol-4-ylamino)pyrimidine-5-carboxamide



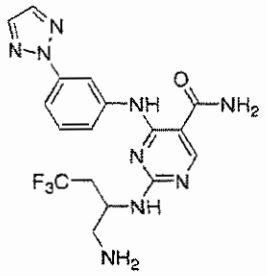
[1053] The title compound was made in an analogous fashion to Example 424. MS found for $C_{18}H_{21}N_7O$ as $(M+H)^+$ 352.4. UV λ=217, 239, 331 nm.

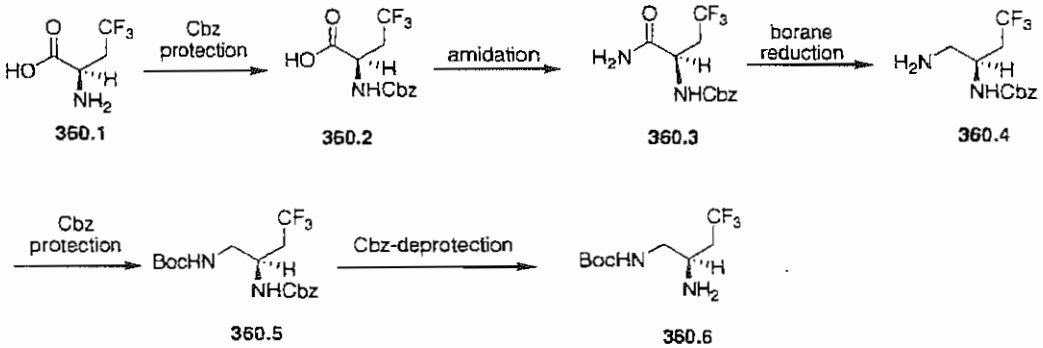
Example 476: 2-((1-aminocyclopropylmethyl)amino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



[1054] The title compound was made in an analogous fashion to Example 424. MS found for $C_{17}H_{22}N_6O$ as $(M+H)^+$ 327.4. UV λ=241, 290 nm.

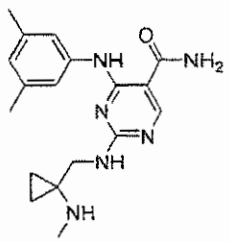
Example 478: 2-(1-amino-4,4,4-trifluorobutan-2-ylamino)-4-(3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide





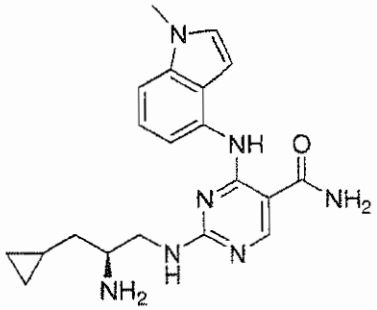
[1055] Intermediate **360.6** was reacted with **343.5** according to the chemistry described in Example 424. After Boc-deprotection, reverse phase preparative HPLC afforded the title compound. MS found for $C_{17}H_{18}F_3N_9O$ as $(M+H)^+$ 422.4. UV λ=245 nm. 2.70-2.80 (m, 2H), 4.25-4.35 (m, 1H), 7.35-7.41 (m, 1H), 7.49-7.55 (m, 1H), 7.88-7.94 (m, 1H), 7.98 (s, 2H), 8.59 (s, 1H), 8.86 (br s, 1H).

Example 479: 2-((1-methylaminocyclopropylmethyl)amino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



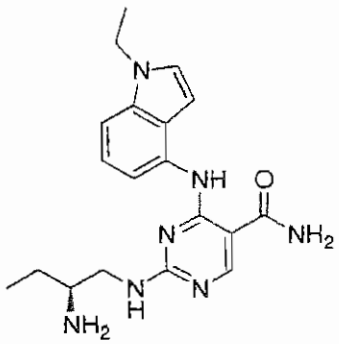
[1056] Intermediate **345.1** was reacted with 1-(aminomethyl)-N-methylcyclopropanamine according to Example 408. Reverse phase preparative HPLC afforded the title compound. MS found for $C_{18}H_{24}N_6O$ as $(M+H)^+$ 341.5. UV λ=240 nm.

Example 480. (*S*)-2-(2-amino-3-cyclopropylpropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



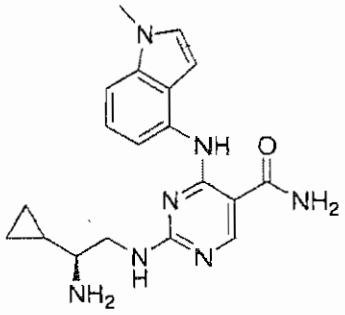
[1057] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{20}H_{25}N_7O$ as $(M+H)^+$ 380.4. UV: λ = 219.8, 241.1, 330.3.

Example 481. (*S*)-2-(2-aminobutylamino)-4-(1-ethyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



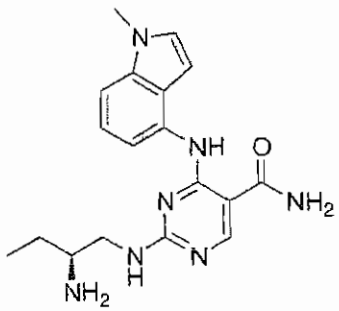
[1058] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{25}N_7O$ as $(M+H)^+$ 368.4. UV: λ = 219.2, 240.4, 331.9.

Example 482. (*S*)-2-(2-amino-2-cyclopropylethylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



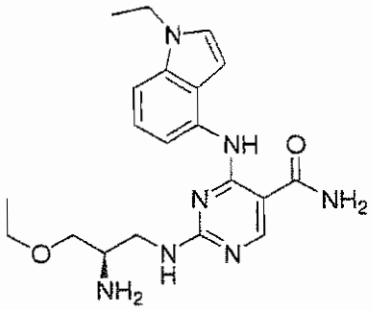
[1059] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{23}N_7O$ as $(M+H)^+$ 366.4. UV: λ = 220.2, 241.4, 330.6.

Example 483. (*S*)-2-(2-aminobutylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



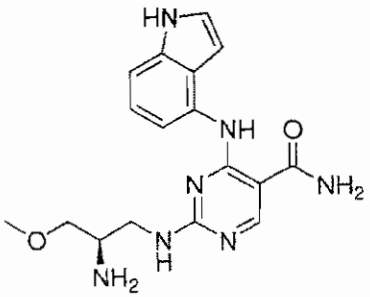
[1060] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{23}N_7O$ as $(M+H)^+$ 354.4. UV: λ = 219.2, 240.4, 333.1.

Example 484. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(1-ethyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



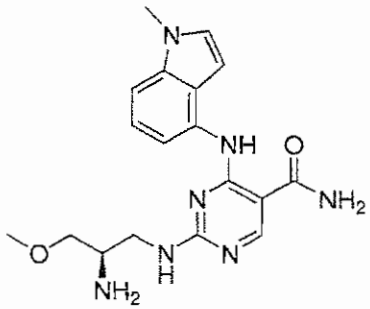
[1061] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{27}N_7O$ as $(M+H)^+$ 398.4. UV: λ = 219.3, 239.4, 326.7.

Example 485. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



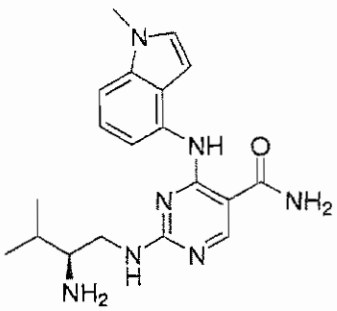
[1062] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{21}N_7O_2$ as $(M+H)^+$ 356.4. UV: λ = 216.7, 238.7, 327.2.

Example 486. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



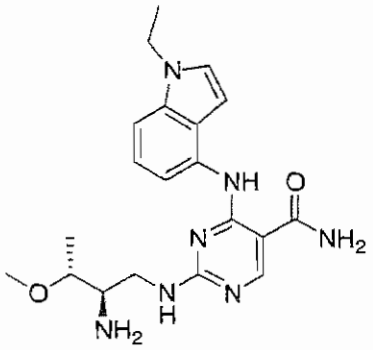
[1063] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{23}N_7O_2$ as $(M+H)^+$ 370.4. UV: λ = 219.2, 239.3, 331.9.

Example 487. (*R*)-2-(2-amino-3-methylbutylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



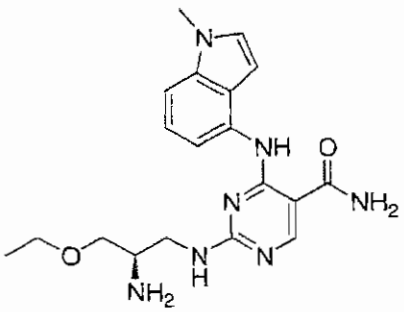
[1064] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{25}N_7O$ as $(M+H)^+$ 368.4. UV: λ = 220.4, 325.9.

Example 488. 2-((2R, 3R)-2--amino-3-methoxylbutylamino)-4-(1-ethyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



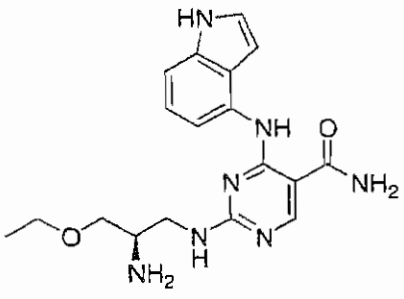
[**1065**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{27}N_7O_2$ as $(M+H)^+$ 398.4. UV: λ = 220.4, 239.9, 331.6.

Example 489. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



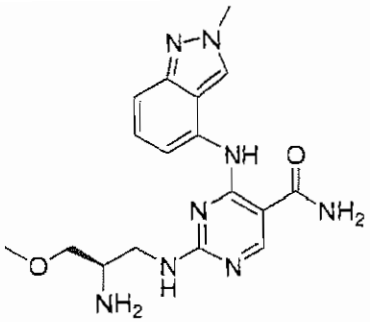
[**1066**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{25}N_7O_2$ as $(M+H)^+$ 384.3. UV: λ = 219.2, 239.3, 331.9.

Example 490. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



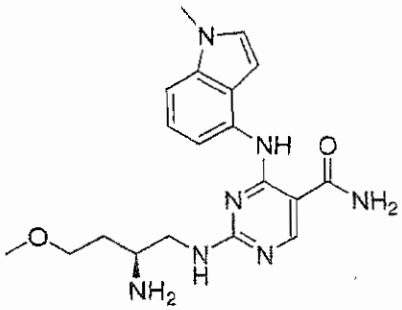
[**1067**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{23}N_7O_2$ as $(M+H)^+$ 370.3. UV: λ = 215.7, 238.1, 327.1.

Example 491. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(2-methyl-2*H*-indol-4-ylamino)pyrimidine-5-carboxamide



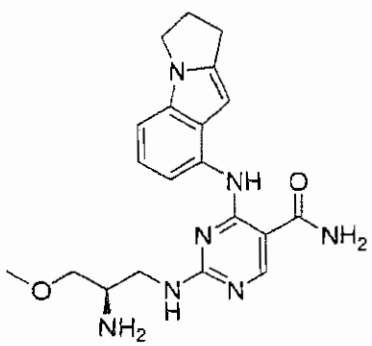
[1068] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{22}N_8O_2$ as $(M+H)^+$ 371.3. UV: λ = 214.9, 241.7, 324.1.

Example 492. (*R*)-2-(2-amino-4-methoxypropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



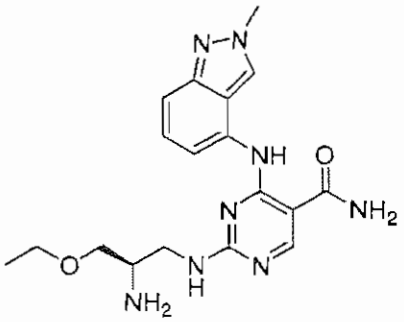
[1069] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{25}N_7O_2$ as $(M+H)^+$ 384.3. UV: λ = 219.2, 240.4, 331.9.

Example 493. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



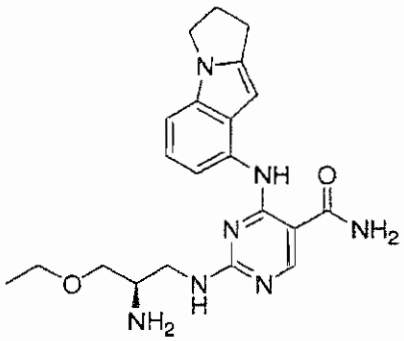
[1070] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{25}N_7O_2$ as $(M+H)^+$ 396.4. UV: λ = 203.9, 244.0, 303.3.

Example 494. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(2-methyl-2*H*-indol-4-ylamino)pyrimidine-5-carboxamide



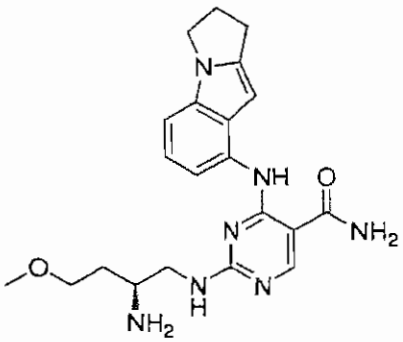
[1071] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{24}N_8O_2$ as $(M+H)^+$ 385.4. UV: λ = 208.6, 240.4, 283.1, 324.7.

Example 495. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



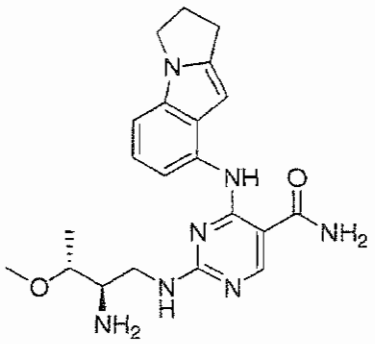
[1072] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{27}N_7O_2$ as $(M+H)^+$ 410.4. UV: λ = 221.6, 336.7.

Example 496. (*S*)-2-(2-amino-4-methoxypropylamino)-4-(2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



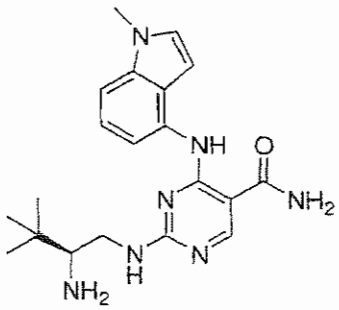
[1073] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{27}N_7O_2$ as $(M+H)^+$ 410.4. UV: λ = 222.8, 336.7.

Example 497. 2-((2*R*, 3*R*)-2-amino-3-methoxylbutylamino)-4-(2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-8-ylamino)pyrimidine-5-carboxamide



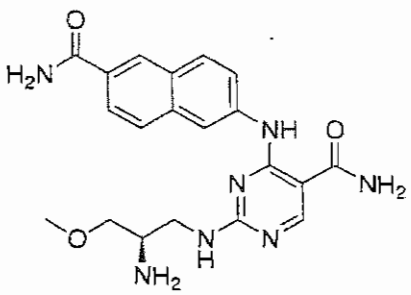
[1074] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{27}N_7O_2$ as $(M+H)^+$ 410.4. UV: λ = 221.6, 335.5.

Example 498. (*S*)-2-(2-amino-3,3-dimethylbutylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



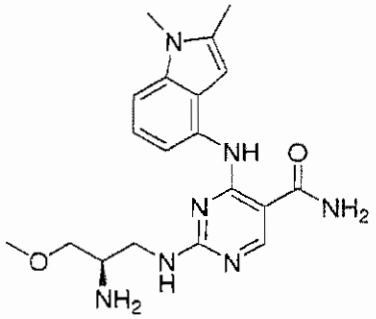
[1075] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{20}H_{27}N_7O$ as $(M+H)^+$ 382.4. UV: λ = 219.2, 239.3, 327.1.

Example 499. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(6-carbomoylnaphthalen-2-ylamino)pyrimidine-5-carboxamide



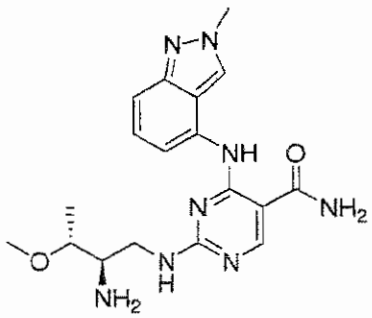
[1076] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{23}N_7O_3$ as $(M+H)^+$ 410.2. UV: λ = 224.9, 316.2.

Example 500. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(1,2-dimethyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



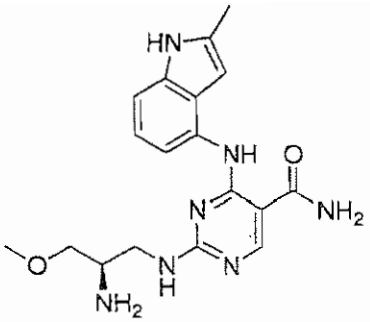
[1077] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{25}N_7O_2$ as $(M+H)^+$ 384.4. UV: λ = 223.9.

Example 501. 2-((2*R*,3*R*)-2-amino-3-methoxybutylamino)-4-(2-methyl-2*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



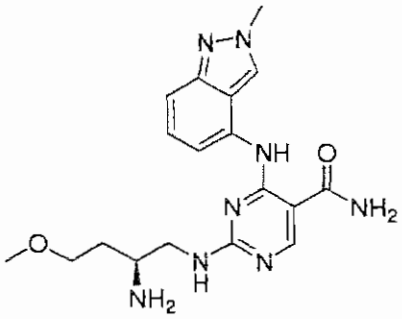
[1078] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{24}N_8O_2$ as $(M+H)^+$ 385.3. UV: λ = 203.9, 241.6.

Example 502. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(2-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



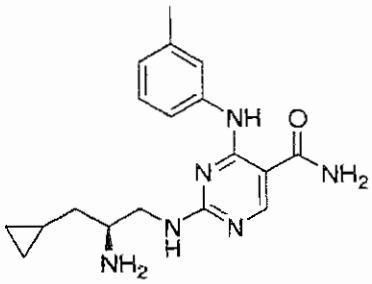
[1079] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{23}N_7O_2$ as $(M+H)^+$ 370.4. UV: λ = 220.4, 333.1.

Example 503. (*S*)-2-(2-amino-4-methoxybutylamino)-4-(2-methyl-2*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



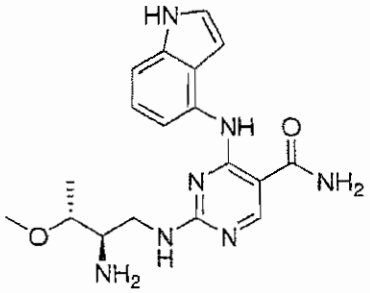
[1080] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{24}N_8O_2$ as $(M+H)^+$ 385.4. UV: λ = 209.8, 240.4, 283.1, 325.9.

Example 504. (*S*)-2-(2-amino-3-cyclopropylpropylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



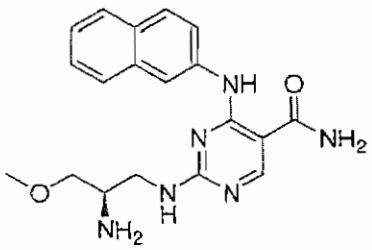
[1081] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{24}N_6O$ as $(M+H)^+$ 341.4. UV: λ = 241.7, 285.9.

Example 505. 2-((2*R*,3*R*)-2-amino-3-methoxybutylamino)-4-(1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



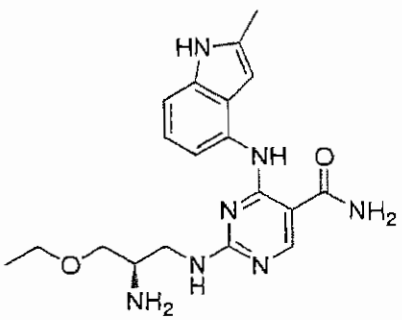
[**1082**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{23}N_7O_2$ as $(M+H)^+$ 370.4. UV: λ = 216.7, 238.1, 324.8.

Example 506. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(naphthalen-2-ylamino)pyrimidine-5-carboxamide



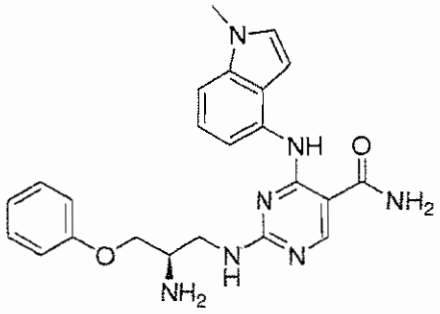
[**1083**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{22}N_6O_2$ as $(M+H)^+$ 367.2. UV: λ = 213.3, 239.3, 305.6.

Example 507. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(2-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



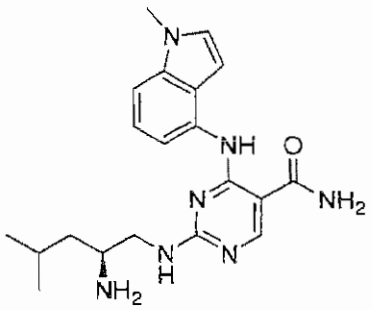
[**1084**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{25}N_7O_2$ as $(M+H)^+$ 384.4. UV: λ = 220.4, 240.4.

Example 508. (*R*)-2-(2-amino-3-phenoxypropylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



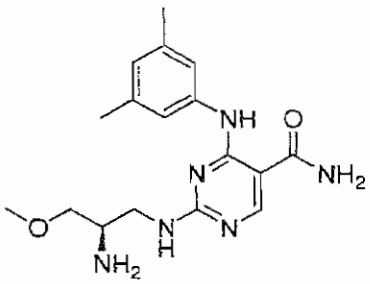
[1085] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{23}H_{25}N_7O_2$ as $(M+H)^+$ 432.4. UV: λ = 218.6, 242.3.

Example 509. (*S*)-2-(2-amino-4-methylpentylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



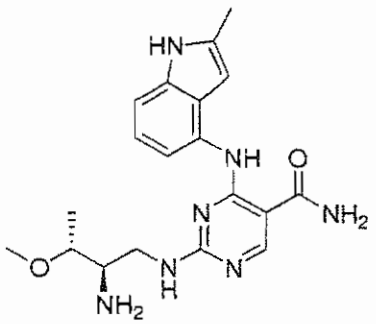
[1086] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{27}N_7O$ as $(M+H)^+$ 382.4. UV: λ = 219.8, 241.7.

Example 510. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



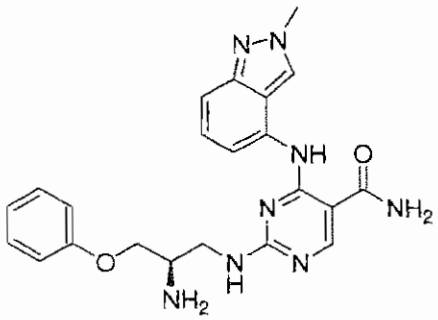
[1087] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.4. UV: λ = 240.3, 290.0.

Example 511. 2-((2*R*,3*R*)-2-amino-3-methoxybutylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



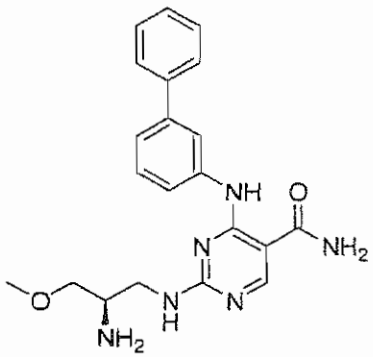
[1088] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{25}N_7O_2$ as $(M+H)^+$ 384.4. UV: λ = 218.0

Example 512. (*R*)-2-(2-amino-3-phenoxypropylamino)-4-(2-methyl-2*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



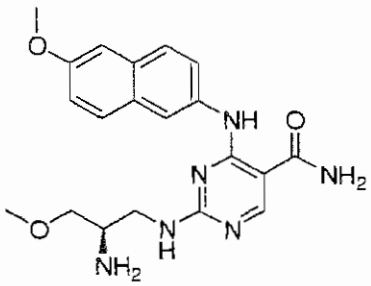
[1089] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{22}H_{25}N_8O_2$ as $(M+H)^+$ 433.4. UV: λ = 211.3, 242.3, 330.9.

Example 513. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(biphenyl-3-ylamino)pyrimidine-5-carboxamide



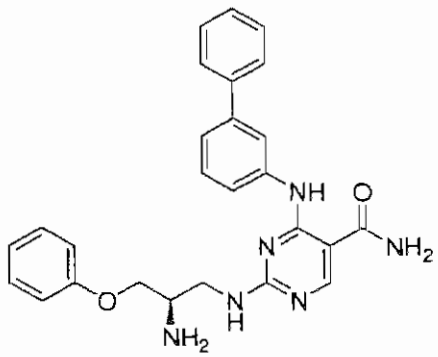
[1090] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{24}N_6O_2$ as $(M+H)^+$ 393.4. UV: λ = 202.8, 246.3.

Example 514. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(6-methoxynaphthalen-2-ylamino)pyrimidine-5-carboxamide



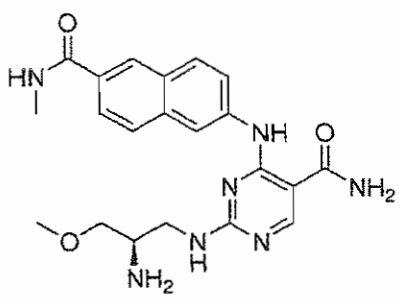
[1091] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{24}N_6O_3$ as $(M+H)^+$ 397.0. UV: λ = 221.6, 315.2.

Example 515. (*R*)-2-(2-amino-3-phenoxypropylamino)-4-(biphenyl-3-ylamino)pyrimidine-5-carboxamide



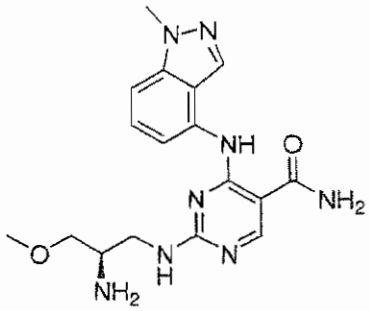
[1092] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{26}H_{26}N_6O_2$ as $(M+H)^+$ 455.4. UV: λ = 203.4, 246.6.

Example 516. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(6-(methylcarbamoylnaphthalen-2-ylamino)pyrimidine-5-carboxamide



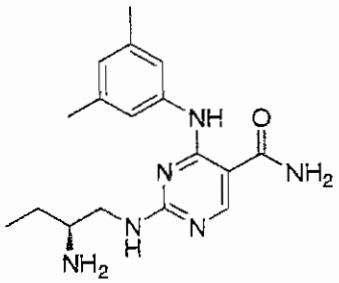
[1093] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{25}N_7O_3$ as $(M+H)^+$ 424.4. UV: λ = 222.8, 316.4.

Example 517. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(1-methyl-1H-indazol-4-ylamino)pyrimidine-5-carboxamide



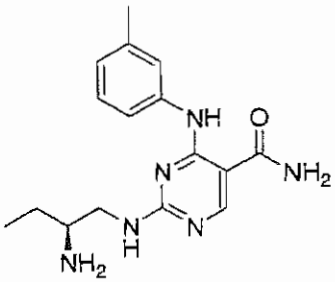
[1094] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{22}N_8O_2$ as $(M+H)^+$ 371.5. UV: λ = 208.8, 241.7, 316.7.

Example 518. (*S*)-2-(2-aminobutylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



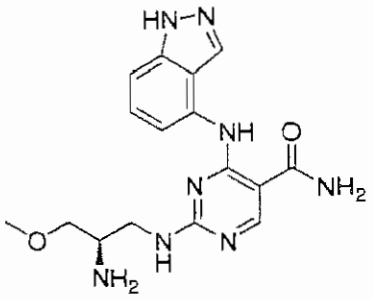
[1095] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{17}H_{24}N_6O$ as $(M+H)^+$ 329.5. UV: λ = 240.5, 288.4.

Example 519. (*S*)-2-(2-aminobutylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



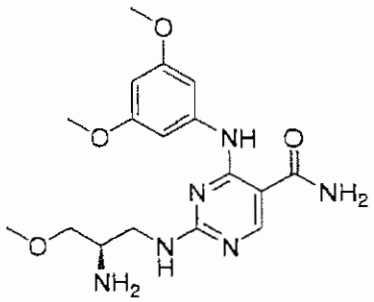
[1096] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{16}H_{22}N_6O$ as $(M+H)^+$ 315.4. UV: λ = 241.1, 286.5.

Example 520. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



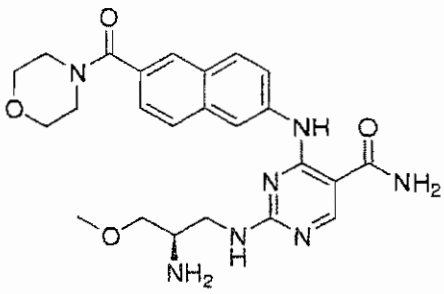
[**1097**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{16}H_{20}N_8O_2$ as $(M+H)^+$ 357.3. UV: λ = 206.3, 240.4, 311.6.

Example 521. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3,5-dimethoxyphenylamino)pyrimidine-5-carboxamide



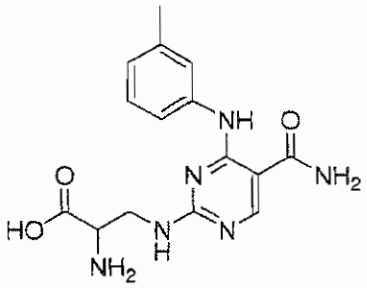
[**1098**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_4$ as $(M+H)^+$ 377.3. UV: λ = 203.8, 235.5, 290.0.

Example 522. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(6-(morpholine-4-carbonyl)naphthalen-2-ylamino)pyrimidine-5-carboxamide



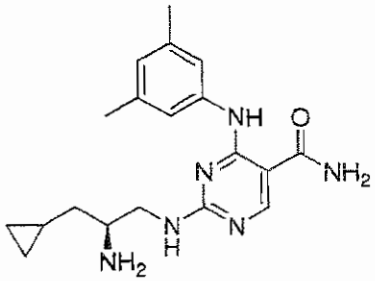
[**1099**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{24}H_{29}N_7O_4$ as $(M+H)^+$ 480.4. UV: λ = 218.0, 311.6.

Example 523. 2-amino-3-(5-carbamoyl)-4-(*m*-tolylamino)pyrimidin-2-ylamino)propanoic acid



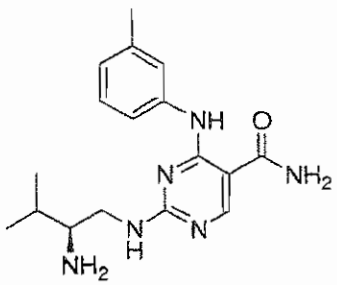
[1100] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{15}H_{18}N_6O_3$ as $(M+H)^+$ 331.1. UV: λ = 239.3, 289.0.

Example 524. (*S*)-2-(2-amino-3-cyclopropylpropylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



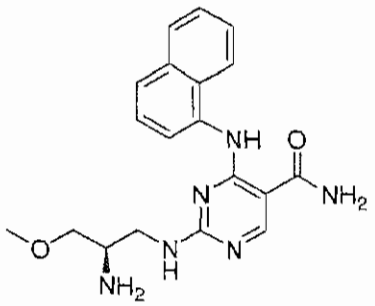
[1101] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{26}N_6O$ as $(M+H)^+$ 355.5. UV: λ = 241.1, 287.7.

Example 525. (*S*)-2-(2-amino-3-methylbutylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



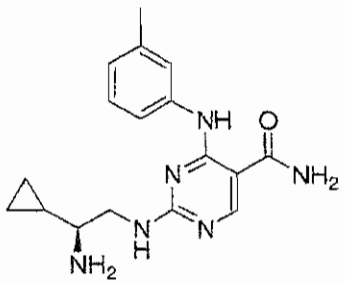
[1102] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{17}H_{24}N_6O$ as $(M+H)^+$ 329.4. UV: λ = 241.7, 285.9.

Example 526. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(naphthalen-1-ylamino)pyrimidine-5-carboxamide



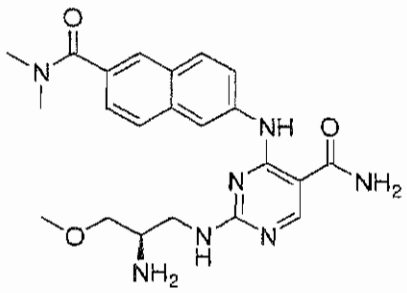
[1103] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{22}N_6O_2$ as $(M+H)^+$ 367.4. UV: λ = 219.2, 282.8.

Example 527. (*S*)-2-(2-amino-2-cyclopropylethylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



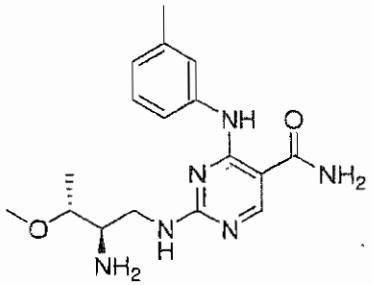
[1104] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{17}H_{22}N_6O$ as $(M+H)^+$ 327.4. UV: λ = 241.7, 286.5.

Example 528. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(6-(dimethylcarbamoyl)naphthalen-2-ylamino)pyrimidine-5-carboxamide



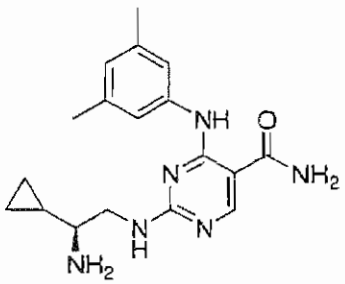
[1105] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{22}H_{27}N_7O_3$ as $(M+H)^+$ 438.2. UV: λ = 216.9, 309.2.

Example 529. 2-((2*R*,3*R*)-2-amino-3-methoxybutylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



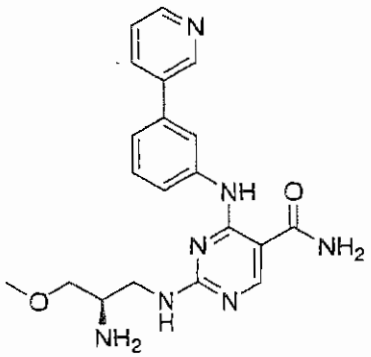
[1106] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.4. UV: λ = 240.4, 284.2.

Example 530. (*S*)-2-(2-amino-2-cyclopropylethylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



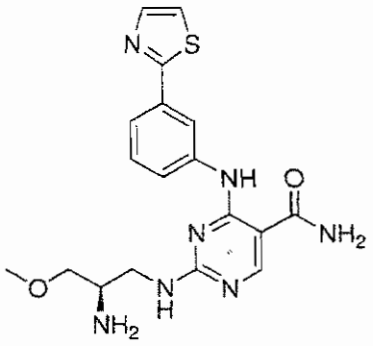
[1107] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{24}N_6O$ as $(M+H)^+$ 341.4. UV: λ = 241.4, 287.7.

Example 531. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-(pyridine-3-yl)phenylamino)pyrimidine-5-carboxamide



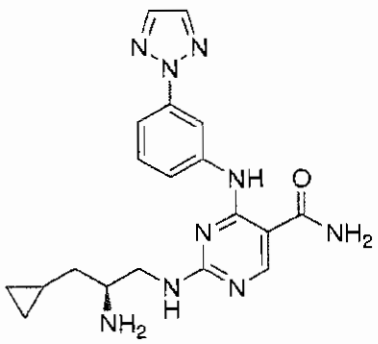
[1108] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{23}N_7O_2$ as $(M+H)^+$ 394.4. UV: λ = 242.8.

Example 532. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-(thiazol-2-yl)phenylamino)pyrimidine-5-carboxamide



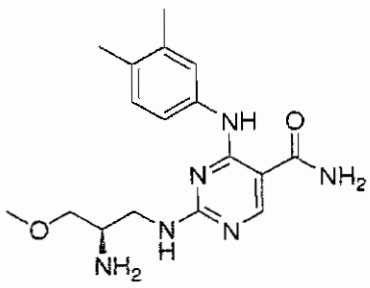
[1109] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{21}N_7O_2S$ as $(M+H)^+$ 400.2. UV: λ = 240.4, 290.2.

Example 533. (*S*)-2-(2-amino-3-cyclopropylpropylamino)-4-(3-(2*H*-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



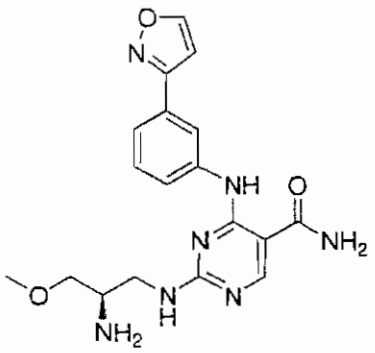
The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{23}N_9O$ as $(M+H)^+$ 394.4. UV: λ = 204.6, 251.5.

Example 534. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3,4-dimethylphenylamino)pyrimidine-5-carboxamide



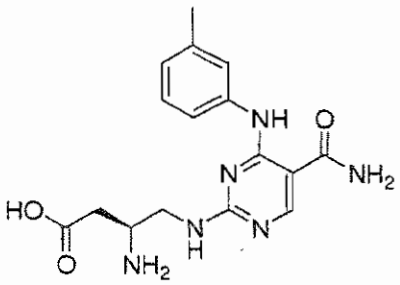
[1110] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.5. UV: λ = 239.3, 291.4.

Example 535. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-(isoxazol-3-yl)phenylamino)pyrimidine-5-carboxamide



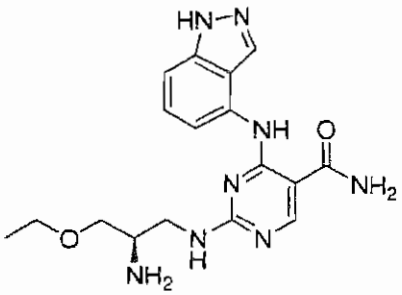
The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{21}N_7O_3$ as $(M+H)^+$ 384.3. UV: λ = 242.3, 285.4.

Example 536. (*S*)-3-amino-4-(5-carbamoyl)-4-(*m*-tolylamino)pyrimidin-2-ylamino)butanoic acid



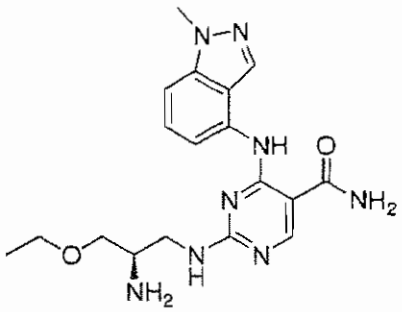
[1111] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{16}H_{20}N_6O_3$ as $(M+H)^+$ 345.1. UV: λ = 239.3, 285.4.

Example 537. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



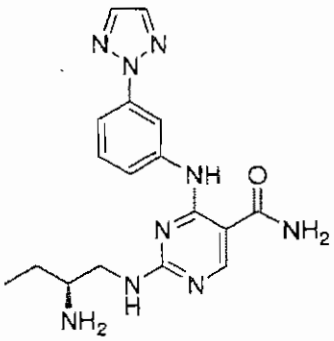
[1112] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{22}N_8O_2$ as $(M+H)^+$ 371.3. UV: λ = 202.8, 238.1, 308.0.

Example 538. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(1-methyl-1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



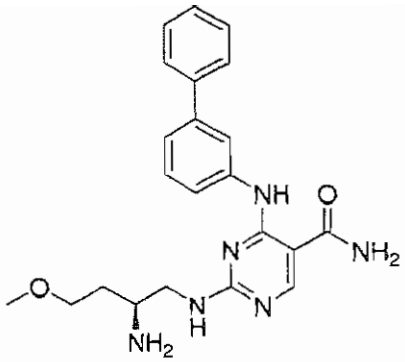
[1113] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{24}N_8O_2$ as $(M+H)^+$ 385.3. UV: λ = 208.6, 240.4, 319.9.

Example 539. (*R*)-2-(2-aminobutylamino)-4-(3-(2*H*-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



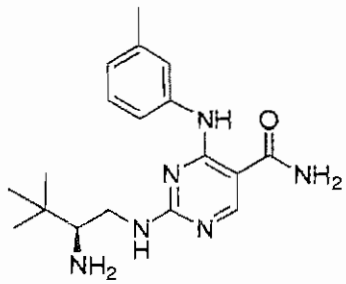
[1114] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{17}H_{21}N_9O$ as $(M+H)^+$ 368.4. UV: λ = 203.9, 249.9.

Example 540. (*S*)-2-(2-amino-4-methoxybutylamino)-4-(biphenyl-3-ylamino)pyrimidine-5-carboxamide



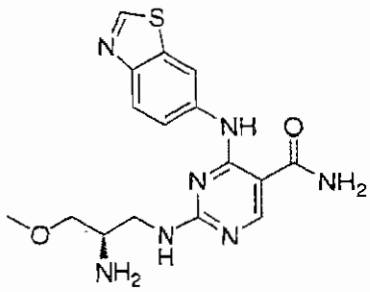
[1115] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{22}H_{26}N_6O_2$ as $(M+H)^+$ 407.4. UV: λ = 202.1, 246.0.

Example 541. (*S*)-2-(2-amino-3,3-dimethylbutylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



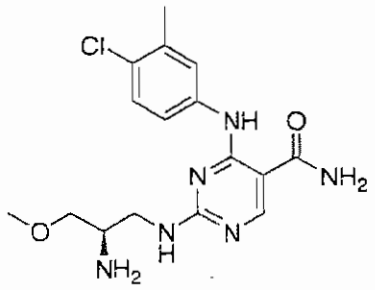
[1116] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{26}N_6O$ as $(M+H)^+$ 343.4. UV: λ = 240.5.

Example 542. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(benzo[*d*]thiazol-6-ylamino)pyrimidine-5-carboxamide



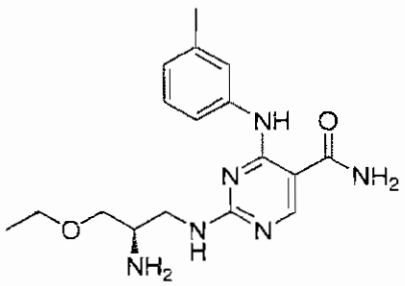
[1117] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{21}N_7O_2S$ as $(M+H)^+$ 374.4. UV: λ = 238.7, 295.1.

Example 543. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(4-chloro-3-methylphenylamino)pyrimidine-5-carboxamide



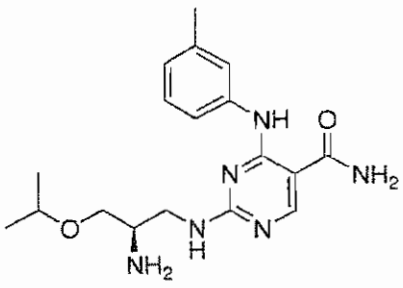
[1118] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{16}H_{21}lN_6O_2$ as $(M+H)^+$ 365.2, 367.1 (Cl pattern). UV: λ = 215.7, 240.4, 289.0.

Example 544. (*R*)-2-(2-amino-3-ethoxypropylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



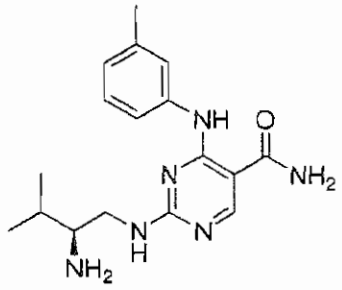
[1119] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.6. UV: λ = 238.1, 284.2.

Example 545. (*R*)-2-(2-amino-3-isopropoxypropylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



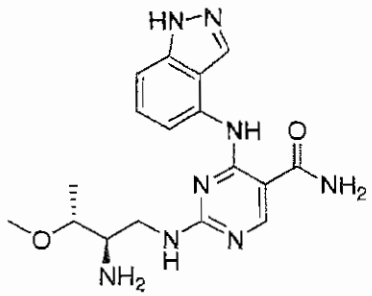
[1120] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{26}N_6O_2$ as $(M+H)^+$ 359.8. UV: λ = 241.6, 286.6.

Example 546. (*S*)-2-(2-amino-3-methylbutylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



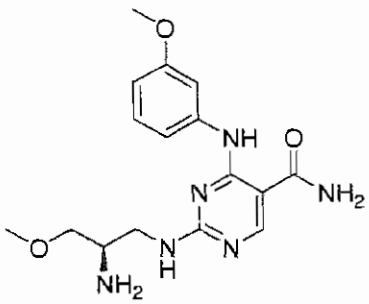
[1121] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{17}H_{24}N_6O$ as $(M+H)^+$ 343.5. UV: λ = 239.9, 284.7.

Example 547. 2-((2*R*,3*R*)-2-amino-3-methoxybutylamino)-4-(1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



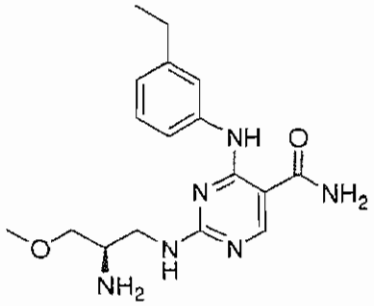
[1122] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{22}N_8O_2$ as $(M+H)^+$ 371.4. UV: λ = 238.1, 299.7.

Example 548. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-methoxyphenyl)pyrimidine-5-carboxamide



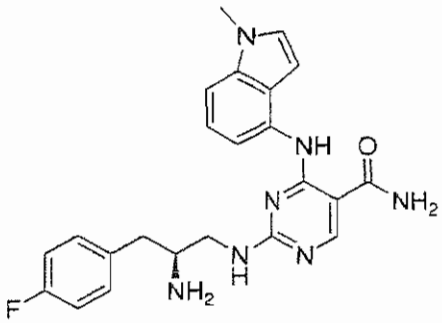
[1123] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{16}H_{22}N_6O_3$ as $(M+H)^+$ 347.2. UV: λ = 239.7.

Example 549. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-ethylphenyl)pyrimidine-5-carboxamide



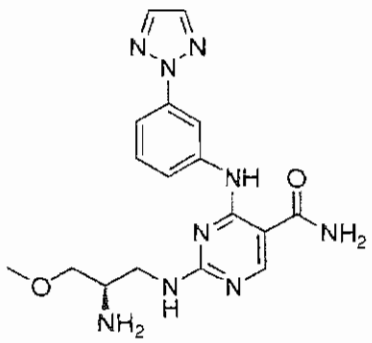
[1124] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.2. UV: λ = 239.3, 286.6.

Example 550. (*S*)-2-(2-amino-4-(fluorophenyl)propylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



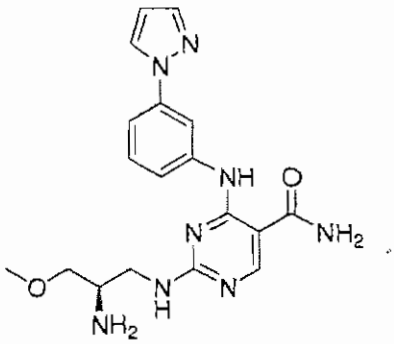
[1125] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{23}H_{24}FN_7O$ as $(M+H)^+$ 434.5. UV: λ = 215.5, 241.7, 330.9.

Example 551. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-(2*H*-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



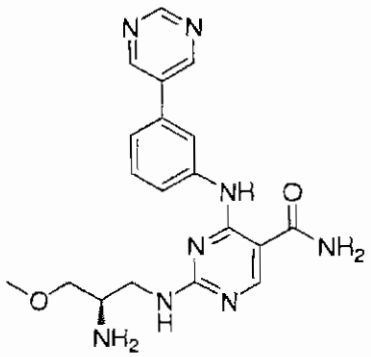
[1126] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{21}N_9O_2$ as $(M+H)^+$ 384.3. UV: λ = 249.9.

Example 552. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-(1*H*-pyrazol-1-yl)phenylamino)pyrimidine-5-carboxamide



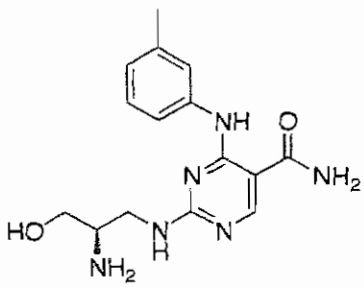
[1127] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{22}N_8O_2$ as $(M+H)^+$ 383.3. UV: λ = 247.2.

Example 553. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-(pyrimidin-5-yl)phenylamino)pyrimidine-5-carboxamide



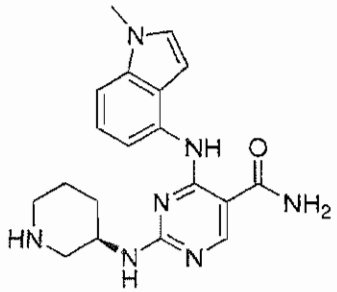
[1128] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{22}N_8O_2$ as $(M+H)^+$ 395.3. UV: λ = 243.6.

Example 554. (*R*)-2-(2-amino-3-hydroxypropylamino)-4-(*m*-tolyl)pyrimidine-5-carboxamide



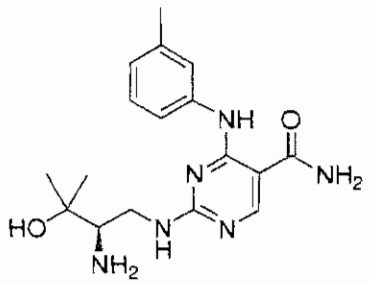
[1129] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{15}H_{20}N_6O_2$ as $(M+H)^+$ 317.2. UV: λ = 238.1, 286.6.

Example 555. (*R*)- 4-(1-methyl-1*H*-indol-4-ylamino)-2-(piperidin-3-ylamino)pyrimidine-5-carboxamide



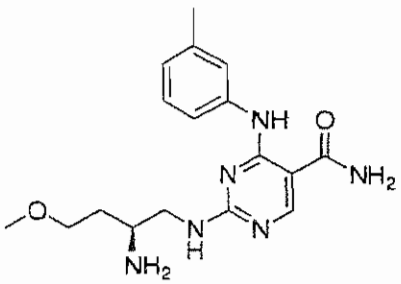
[1130] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{23}N_7O$ as $(M+H)^+$ 366.4. UV: λ = 218.0, 241.6, 335.5.

Example 556. (*R*)-2-(2-amino-3-hydroxy-3-methylbutylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



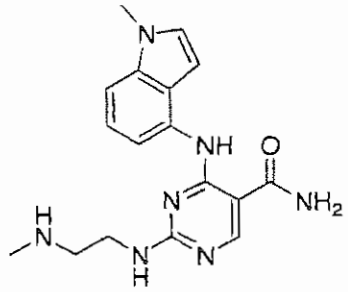
[1131] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.2. UV: λ = 239.3.

Example 557. (*S*)-2-(2-amino-4-methoxybutylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



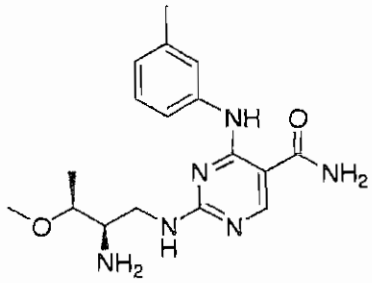
[1132] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.4. UV: λ = 240.5, 286.5.

Example 558. 4-(1-methyl-1*H*-indol-4-ylamino)-2-(2-(methylamino)ethylamino)pyrimidine-5-carboxamide



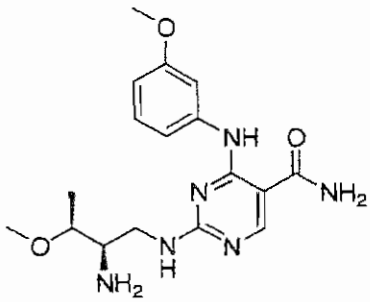
[1133] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{17}H_{21}N_7O$ as $(M+H)^+$ 340.4. UV: λ = 220.4, 239.3.

Example 559. 2-((2*R*,3*S*)-2-amino-3-methoxybutylamino)-4-(*m*-tolyl)pyrimidine-5-carboxamide



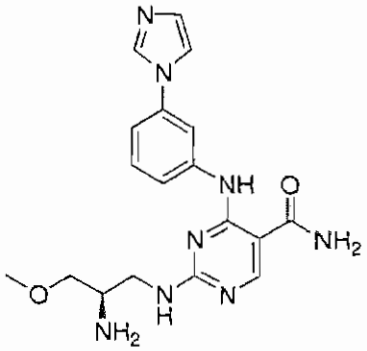
[1134] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 345.2. UV: λ = 239.3, 285.4.

Example 560. 2-((2*R*,3*S*)-2-amino-3-methoxybutylamino)-4-(3-methoxyphenyl)pyrimidine-5-carboxamide



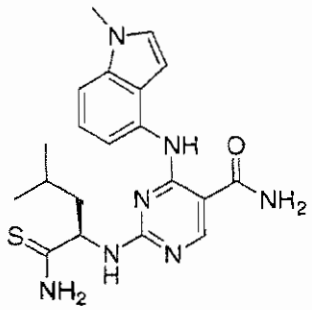
[1135] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_3$ as $(M+H)^+$ 361.2. UV: λ = 239.3.

Example 561. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-(1*H*-imidazol-1-yl)phenylamino)pyrimidine-5-carboxamide



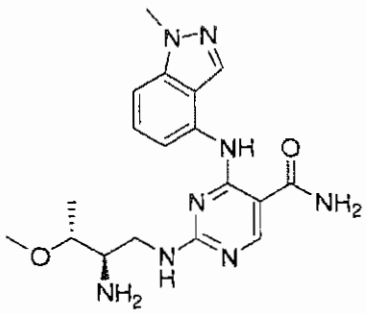
[**1136**] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{22}N_8O_2$ as $(M+H)^+$ 383.5. UV: λ = 238.1, 281.9.

Example 562. (*R*)-2-(1-amino-4-methyl-1-thioxopentan-2-ylamino)-4-(1-methyl-1*H*-indol-4-ylamino)pyrimidine-5-carboxamide



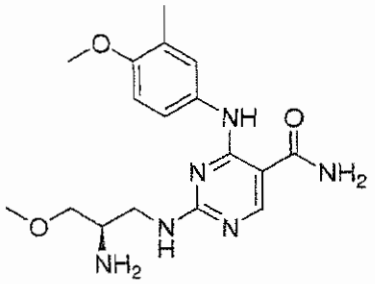
[**1137**] The title compound was prepared using the same synthetic scheme demonstrated in Example 318. MS found for $C_{20}H_{25}N_7OS$ as $(M+H)^+$ 412.4. UV: λ = 250.3.

Example 563. 2-((2*R*,3*R*)-2-amino-3-methoxybutylamino)-4-(1-methyl-1*H*-indazol-4-ylamino)pyrimidine-5-carboxamide



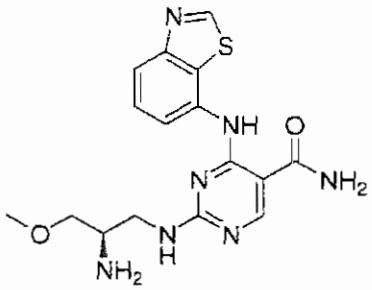
[1138] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{24}N_8O_2$ as $(M+H)^+$ 385.3. UV: λ = 208.6, 240.4, 311.6.

Example 564. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(4-methoxy-3-methylphenylamino)pyrimidine-5-carboxamide



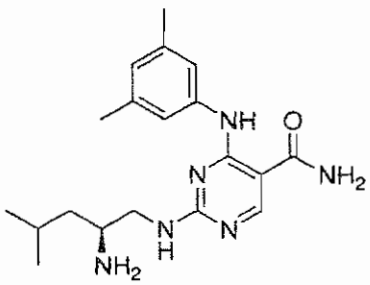
[1139] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_3$ as $(M+H)^+$ 361.2. UV: λ = 238.1, 292.6.

Example565. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(benzo[*d*]thiazol-7-ylamino)pyrimidine-5-carboxamide



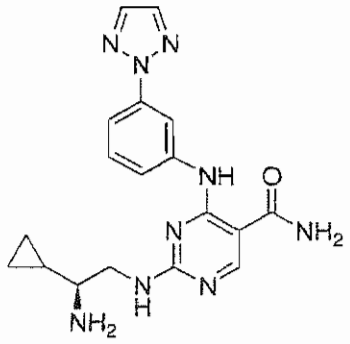
[1140] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{16}H_{19}N_7O_2S$ as $(M+H)^+$ 374.3. UV: λ = 232.6, 287.8.

Example 566. (*S*)-2-(2-amino-4-methylpentylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



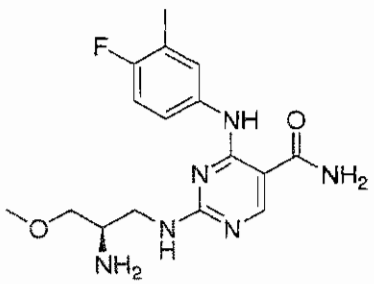
[1141] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{28}N_6O$ as $(M+H)^+$ 357.4. UV: λ = 239.3, 287.8.

Example 567. (*S*)-2-(2-amino-2-cyclopropylethylamino)-4-(3-(2*H*-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



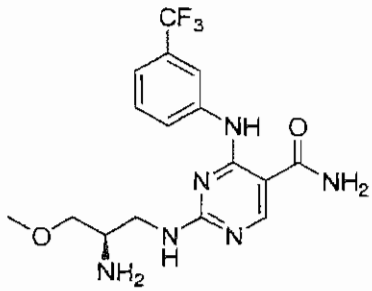
[1142] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{21}N_9O$ as $(M+H)^+$ 380.4. UV: λ = 204.6, 250.9.

Example 568. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(4-fluoro-3-methylphenylamino)pyrimidine-5-carboxamide



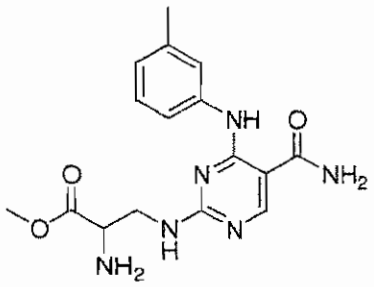
[1143] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{16}H_{21}FN_6O_2$ as $(M+H)^+$ 349.0. UV: λ = 211.0, 239.3.

Example 569. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-trifluoromethylphenylamino)pyrimidine-5-carboxamide



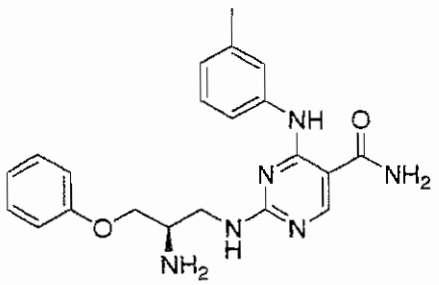
[1144] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{16}H_{19}F_3N_6O_2$ as $(M+H)^+$ 385.2. UV: λ = 242.8.

Example 570. Methyl 2-amino-3-(5-carbamoyl)-4-(*m*-tolylamino)pyrimidin-2-ylamino)propanoate



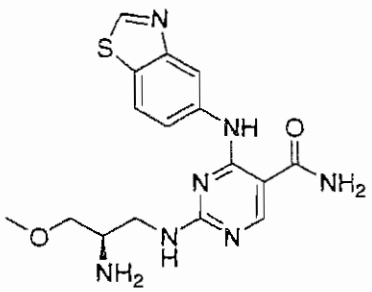
[1145] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{16}H_{20}N_6O_3$ as $(M+H)^+$ 345.1. UV: λ = 238.1, 290.2.

Example 580. (*R*)-2-(2-amino-3-phenoxypropylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



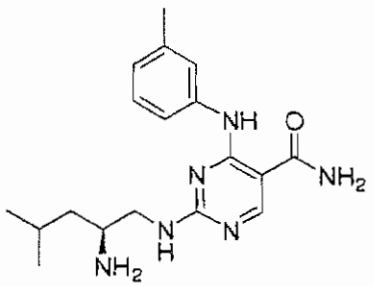
[1146] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{21}H_{24}N_6O_2$ as $(M+H)^+$. ..UV: λ = 213.3, 239.3.

Example 581. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(benzo[*d*]thiazol-5-ylamino)pyrimidine-5-carboxamide



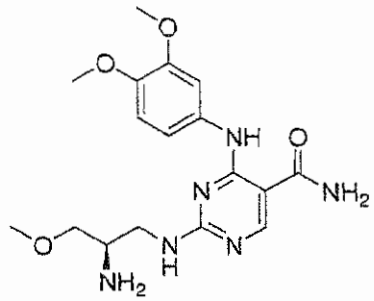
[1147] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{16}H_{19}N_7O_2S$ as $(M+H)^+$ 374.3. UV: λ = 243.6, 292.1.

Example 582. (*S*)-2-(2-amino-4-methylpentylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide



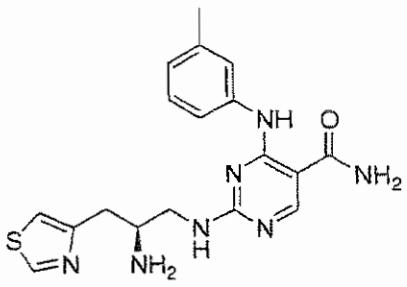
[1148] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{26}N_6O$ as $(M+H)^+$ 343.4. UV: λ = 239.3, 285.4.

Example 583. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3,4-dimethoxyphenylamino)pyrimidine-5-carboxamide



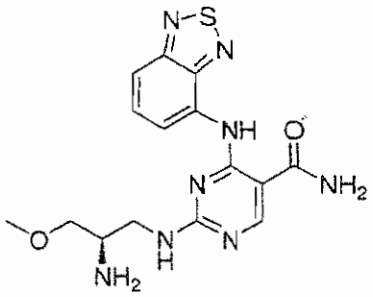
[1149] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_4$ as $(M+H)^+$ 377.1. UV: λ = 235.7, 285.4.

Example 584. (*S*)-2-(2-amino-3-(thiazol-4-yl)propylamino)-4-(*m*-tolylamino)pyrimidine-5-carboxamide



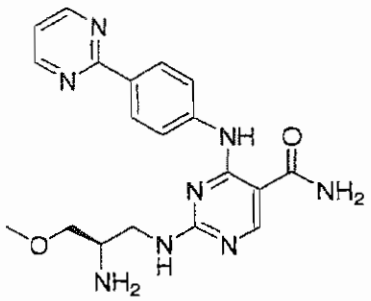
[1150] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{18}H_{21}N_7OS$ as $(M+H)^+$ 384.1. UV: λ = 240.4, 287.8.

Example 585. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(benzo[*c*][1,2,5]thiadiazol-4-ylamino)pyrimidine-5-carboxamide



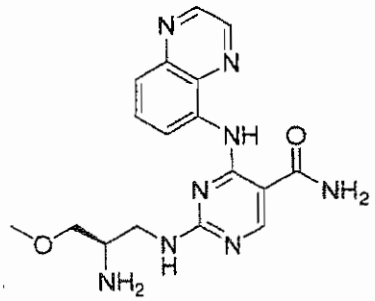
[1151] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{15}H_{18}N_8O_2S$ as $(M+H)^+$ 375.2. UV: λ = 235.7, 315.2.

Example 586. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(4-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide



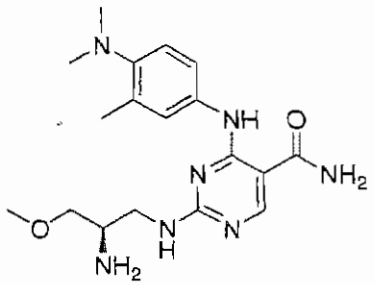
[1152] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{19}H_{22}N_8O_2$ as $(M+H)^+$ 395.4. UV: λ = 230.1, 311.2.

Example 587. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(quinoxalin-5-ylamino)pyrimidine-5-carboxamide



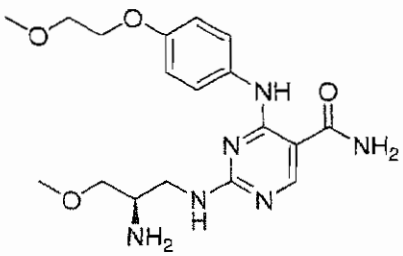
[1153] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{20}N_8O_2$ as $(M+H)^+$ 369.2. UV: λ = 245.4.

Example 588. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(4-(dimethylamino)-3-methylphenylylamino)pyrimidine-5-carboxamide



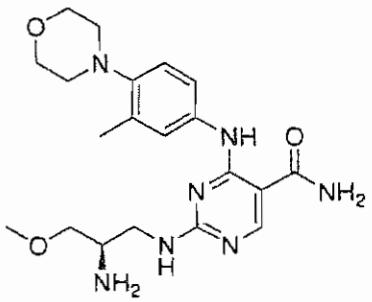
[1154] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{27}N_7O_2$ as $(M+H)^+$ 374.3.

Example 589. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(4-(2-methoxyethoxy)phenylamino)pyrimidine-5-carboxamide



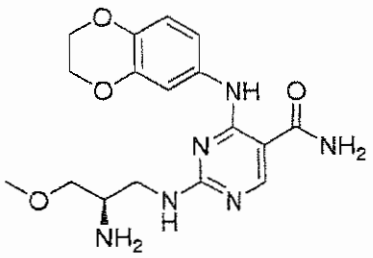
[1155] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{18}H_{26}N_6O_4$ as $(M+H)^+$ 391.4. UV: λ = 202.8, 239.9, 282.2.

Example 590. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(3-methyl-4-morpholinophenylylamino)pyrimidine-5-carboxamide



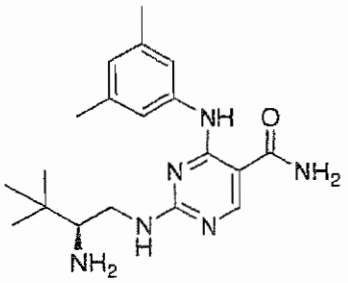
[1156] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{20}H_{29}N_7O_3$ as $(M+H)^+$ 416.2. UV: λ = 238.1, 293.8.

Example 591. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-ylamino)pyrimidine-5-carboxamide



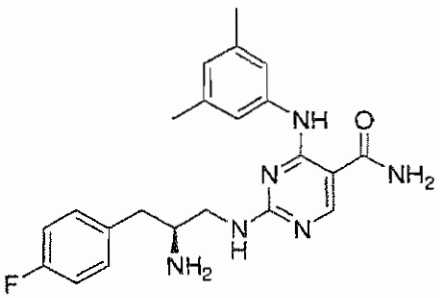
[1157] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{22}N_6O_4$ as $(M+H)^+$ 375.3. UV: λ = 239.3, 292.7.

Example 592. (*S*)-2-(2-amino-3,3-dimethylbutylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



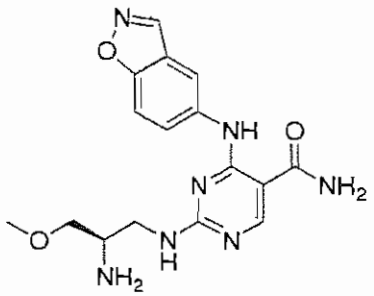
[1158] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{28}N_6O$ as $(M+H)^+$ 357.4. UV: λ = 240.4.

Example 593. (*S*)-2-(2-amino-4-(fluorophenyl)propylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



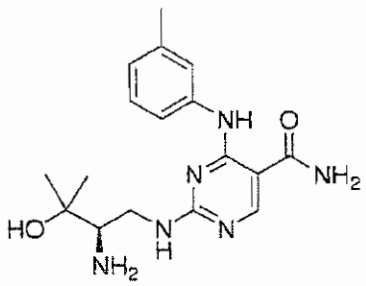
[1159] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{22}H_{25}FN_6O$ as $(M+H)^+$ 409.4. UV: λ = 241.7, 288.4.

Example 594. (*R*)-2-(2-amino-3-methoxypropylamino)-4-(benzo[d]isoxazol-5-ylamino)pyrimidine-5-carboxamide



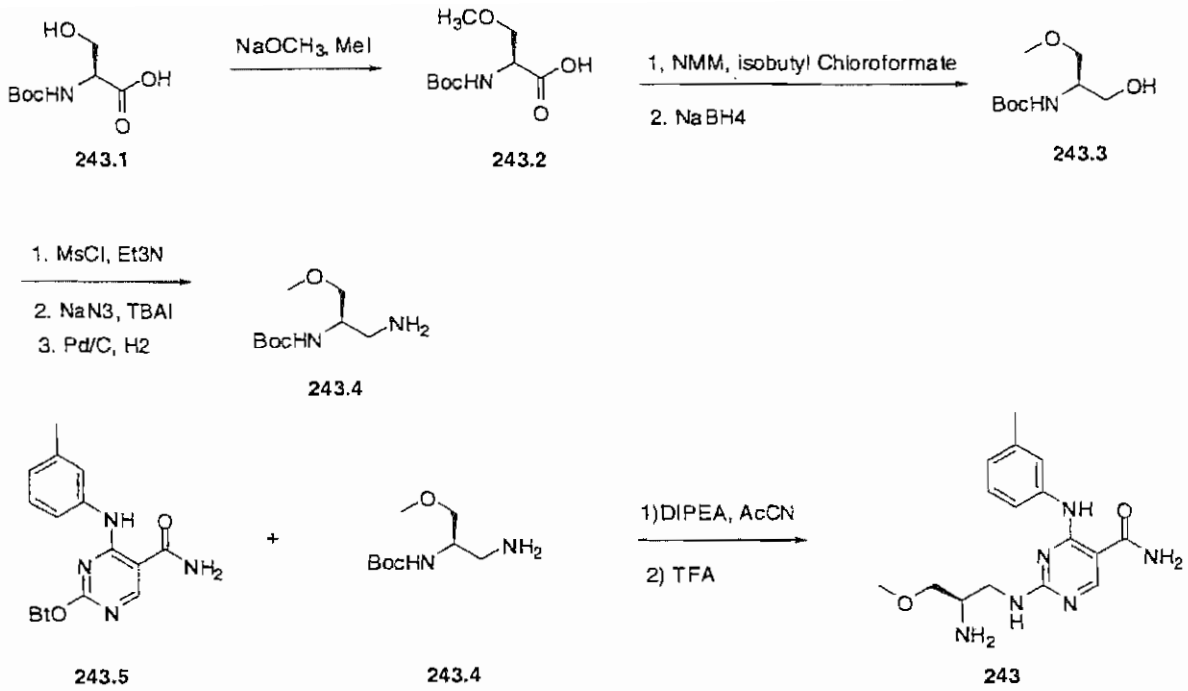
[1160] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{16}H_{19}N_7O_3$ as $(M+H)^+$ 358.3. UV: λ = 203.9, 235.7, 292.6.

Example 595. (*R*)-2-(2-amino-3-hydroxy-3-methylbutylamino)-4-(3,5-dimethylphenylamino)pyrimidine-5-carboxamide



[1161] The title compound was prepared using the same synthetic scheme demonstrated in Example 596. MS found for $C_{17}H_{24}N_6O_2$ as $(M+H)^+$ 359.2. UV: λ = 239.3.

Example 596



[1162] **Synthesis of 243.2**: To a suspension of NaH (6g, 0.25 mol) in THF (220 mL) at 0 °C was added MeOH (18 mL) dropwise, the mixture was then stirred at ambient temperature for 1 h, and the resulting solution was used next.

[1163] To a solution of N-Boc L-serine **243.1** (6 g, 0.029 mol) in THF (300 mL) was added 120 mL of above solution and MeI (3 mL). After stirring at ambient temperature for 1 h, the remaining above solution was added, followed by more MeI (6 mL), and the mixture was stirred for additional 18 h. The mixture was then concentrated under vacuum to remove THF, the residue was dissolved in water; the aqueous solution was washed with ether, and acidified with citric acid to pH 2. The acidified aqueous solution was extracted with EtOAc (3X), EtOAc layer was combined, washed with diluted $Na_2S_2O_3$, brine, dried and concentrated to give a mixture of **243.2** and recovered **243.1**. The residue was taken up in H_2O (100 mL), and was extracted with DCM (3X). DCM layer was combined, washed with brine, dried over Na_2SO_4, and was concentrated in vacuo to give **243.2** as pale yellow oil (3.2 g).

[1164] **Synthesis of 243.3**: To a solution of **243.2** (3.2 g, 14.60 mmol) in THF (20 mL) at -15 °C was added N-methyl Morpholine (1.60 mL, 14.60 mmol) and isobutyl chloroformate (1.91 mL, 14.60 mmol). After stirring for 5 min at -15 °C, the mixture was added a solution of Sodium Borohydride (1.66 g, 43.8 mmol) in water (7 mL) slowly (gas evolution). The mixture was kept stirring at -15 °C for 10 min, and was diluted with EtOAc, the organics

were washed with water, Sat. $NaHCO_3$, brine, dried and concentrated to give crude residue, which was purified by column (Hex/EtOAc = 2:1 to 2:3) to give **243.3** (2.1 g, 70%).

[1165] **Synthesis of 243.4:** To a solution of **243.3** (2.1 g, 10.24 mmol) in DCM (30 mL) at 0 °C was added Triethylamine (2.15 mL, 15.36 mmol) and Methanesulfonyl Chloride (1.19 mL, 15.36 mmol). After stirring at 0 °C for 30 min, it was diluted with DCM, the organics were washed with water, Sat. $NaHCO_3$, brine, dried and concentrated to give crude mesylate.

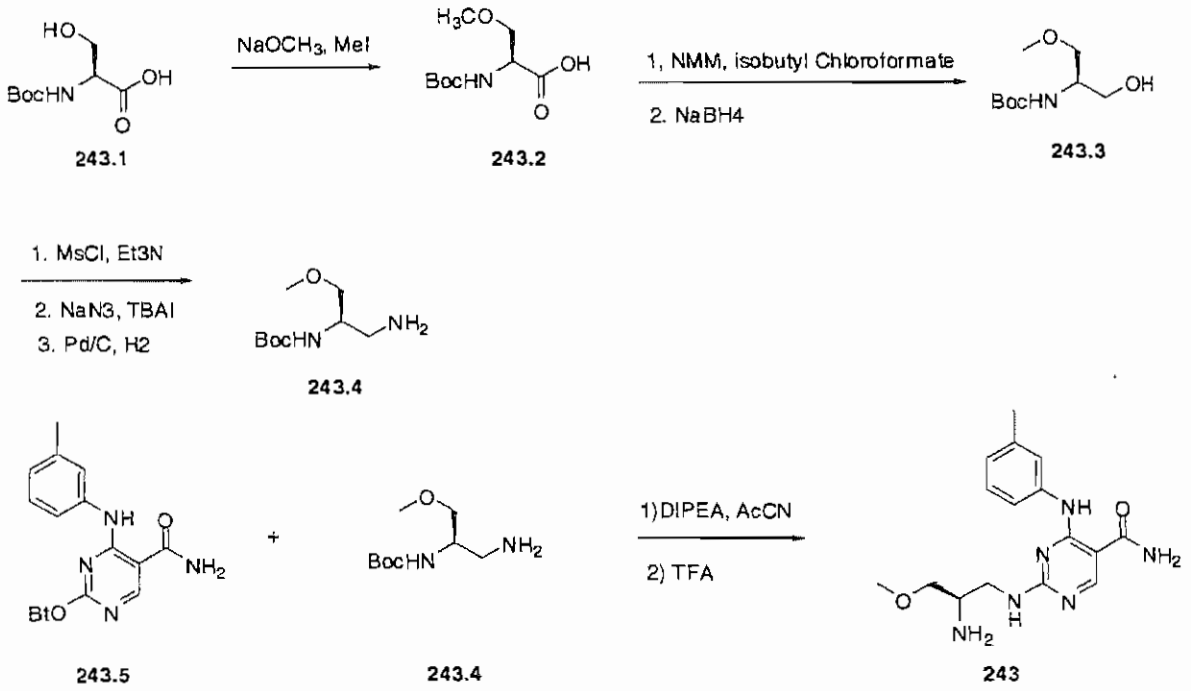
[1166] To a solution of the above crude mesylate in DMF (20 mL) was added NaN_3 (1.95 g, 30.72 mmol) and TBAI (37 mg, 0.124 mmol). After heating at 75 °C for 2 h, it was diluted with EtOAc, the organics were washed with water, brine, dried and concentrated to give crude azide (1.7 g).

[1167] To a solution of the above crude azide (1.7 g) in EtOAc (16 mL) was added Pd/C (400 mg), and was charged with H_2 (1 atm). After stirring at ambient temperature for 15 h, Pd/C was filtered off, and the filtrate was concentrated to give **243.4** (1.5 g).

[1168] **Synthesis of 243:** To a solid sample of **243.5** (0.76 g, 2.1 mmol) in sealed tube was added a solution of **243.4** (0.75 g, 3.68 mmol) in AcCN (8.5 mL). After heating at 65 °C for 5 h, the mixture was cooled and added water (40 mL). The precipitates were collected by filtration to give coupling product (0.85 g).

[1169] To a suspension of the above coupling product (0.85 g) in DCM (6 mL) was added TFA (2 mL). After stirring at ambient temperature for 15 min, the mixture was concentrated, and the residue was purified by preparative HPLC to give F (0.99 g) as TFA salt.

Example 597



[1170] **Synthesis of 243.2**: To a suspension of NaH (6g, 0.25 mol) in THF (220 mL) at 0 °C was added MeOH (18 mL) dropwise, the mixture was then stirred at ambient temperature for 1 h, and the resulting solution was used next.

[1171] To a solution of N-Boc L-serine **243.1** (6 g, 0.029 mol) in THF (300 mL) was added 120 mL of above solution and MeI (3 mL). After stirring at ambient temperature for 1 h, the remaining above solution was added, followed by more MeI (6 mL), and the mixture was stirred for additional 18 h. The mixture was then concentrated under vacuum to remove THF, the residue was dissolved in water; the aqueous solution was washed with ether, and acidified with citric acid to pH 2. The acidified aqueous solution was extracted with EtOAc (3X), EtOAc layer was combined, washed with diluted $Na_2S_2O_3$, brine, dried and concentrated to give a mixture of **243.2** and recovered **243.1**. The residue was taken up in H_2O (100 mL), and was extracted with DCM (3X). DCM layer was combined, washed with brine, dried over Na_2SO_4, and was concentrated in vacuo to give **243.2** as pale yellow oil (3.2 g).

[1172] **Synthesis of 243.3**: To a solution of **243.2** (3.2 g, 14.60 mmol) in THF (20 mL) at -15 °C was added N-methyl Morpholine (1.60 mL, 14.60 mmol) and isobutyl chloroformate (1.91 mL, 14.60 mmol). After stirring for 5 min at -15 °C, the mixture was added a solution of Sodium Borohydride (1.66 g, 43.8 mmol) in water (7 mL) slowly (gas evolution). The mixture was kept stirring at -15 °C for 10 min, and was diluted with EtOAc, the organics

were washed with water, Sat. $NaHCO_3$, brine, dried and concentrated to give crude residue, which was purified by column (Hex/EtOAc = 2:1 to 2:3) to give **243.3** (2.1 g, 70%).

[1173] **Synthesis of 243.4:** To a solution of **243.3** (2.1 g, 10.24 mmol) in DCM (30 mL) at 0 °C was added Triethylamine (2.15 mL, 15.36 mmol) and Methanesulfonyl Chloride (1.19 mL, 15.36 mmol). After stirring at 0 °C for 30 min, it was diluted with DCM, the organics were washed with water, Sat. $NaHCO_3$, brine, dried and concentrated to give crude mesylate.

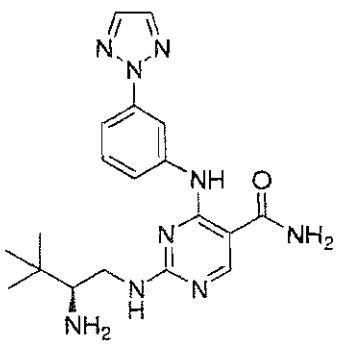
[1174] To a solution of the above crude mesylate in DMF (20 mL) was added NaN_3 (1.95 g, 30.72 mmol) and TBAI (37 mg, 0.124 mmol). After heating at 75 °C for 2 h, it was diluted with EtOAc, the organics were washed with water, brine, dried and concentrated to give crude azide (1.7 g).

[1175] To a solution of the above crude azide (1.7 g) in EtOAc (16 mL) was added Pd/C (400 mg), and was charged with H_2 (1 atm). After stirring at ambient temperature for 15 h, Pd/C was filtered off, and the filtrate was concentrated to give **243.4** (1.5 g).

[1176] **Synthesis of 243:** To a solid sample of **243.5** (0.76 g, 2.1 mmol) in sealed tube was added a solution of **243.4** (0.75 g, 3.68 mmol) in AcCN (8.5 mL). After heating at 65 °C for 5 h, the mixture was cooled and added water (40 mL). The precipitates were collected by filtration to give coupling product (0.85 g).

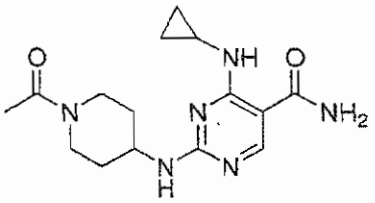
[1177] To a suspension of the above coupling product (0.85 g) in DCM (6 mL) was added TFA (2 mL). After stirring at ambient temperature for 15 min, the mixture was concentrated, and the residue was purified by preparative HPLC to give F (0.99 g) as TFA salt.

Example 598. (*S*)-2-(2-amino-2-cyclopropylethylamino)-4-(2-amino-3,3-dimethylbutylamino)pyrimidine-5-carboxamide



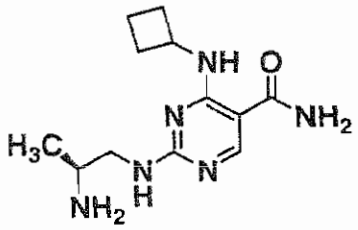
[1178] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{19}H_{25}N_9O$ as $(M+H)^+$ 396.4. UV: λ = 248.7.

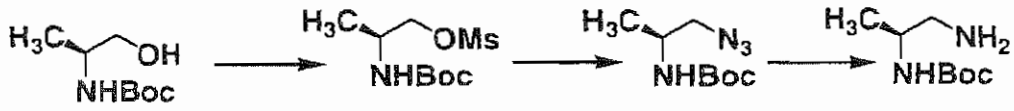
Example 599. 2-(1-acetylpiperidin-4-ylamino)-4-(cyclopropylamino)pyrimidine-5-carboxamide



[1179] The title compound was prepared using the same synthetic scheme demonstrated in Example 218. MS found for $C_{15}H_{22}N_6O_2$ as $(M+H)^+$ 319.4. UV: λ = 238.7.

Example 600. (S)-2-(2-aminopropylamino)-4-(cyclobutylamino)pyrimidine-5-carboxamide





3.1 3.2 3.3 3.4

[1180] Step 1: To a stirring solution of alcohol 3.1 (4.16g, 24 mmol) in dichloromethane (30 mL) was added diisopropylethylamine (5.8 mL, 33 mmol) followed by methanesulfonyl chloride (2.23 mL, 29 mmol) which was added dropwise. After 30 min the reaction was diluted with 1 M HCl and the two phases separated. The organic layer was then washed with sodium carbonate (saturated, aq) and dried over magnesium sulfate. Concentration afforded the desired product 3.2 as a light brown solid (5.07g, 83%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.93 (d, 1H), 4.03 (d, 2H), 3.72 (m, 1H), 3.15 (s, 3H), 1.37 (s, 9H), 1.06 (d, 3H).

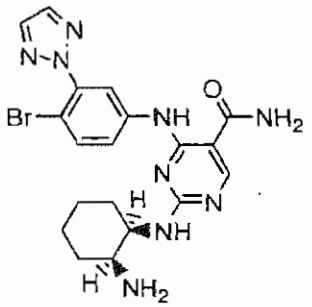
[1181] Step 2: Mesylate 3.2 (2.0g, 7.9 mmol) was dissolved in 20 mL of DMF, treated with sodium azide (2.6g, 39.5 mmol) and heated to 80°C overnight. The following day the reaction was cooled to rt, partitioned with water and ethyl acetate and the two layers separated. The aq phase was extracted with ethyl acetate and the combined organic phases

dried over magnesium sulfate. Concentration afforded the desired azide 3.3 which was immediately used for the next step. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.91 (d, 1H), 3.62 (m, 1H), 3.20 (d, 2H), 1.38 (s, 9H), 1.01 (d, 3H).

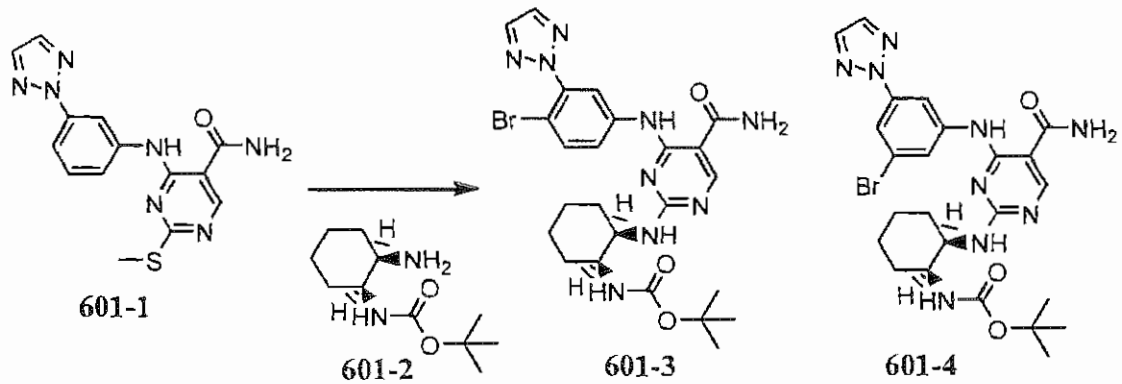
[1182] Step 3: The crude azide from the previous step 3.3 was diluted with methanol (20 mL), treated with ca. 200 mg of Pd/C (10% by weight, wet) and placed under an atmosphere of hydrogen. After three hours the mixture was filtered through celite and concentrated affording a quantitative amount of the desired amine which crystallized upon standing to a white waxy solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.52 (d, 1H), 3.38 (m, 1H), 2.42 (m, 2H), 1.36 (s, 9H), 0.96 (d, 3H).

[1183] Step 4: Benzotriazolyl ether 1.7, intermediate 3.4, diisopropylethylamine, and 5 mL of 1,4-dioxane were combined and heated to 120°C overnight. The reaction mixture was then cooled, diluted with water and purified by preparative HPLC to give the desired compound. MS found for $C_{12}H_{20}N_6O$ as $(M+H)^+$ 265.2.

Example 601: 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-bromo-3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



Scheme

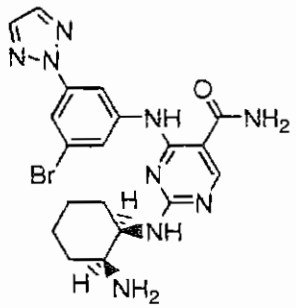


[1184] Compound 601-1 (150 mg, 0.46 mmol) was dissolved in 15 mL DMF. To it was added N-bromosuccinimide (NBS, 122 mg, 0.69 mmol). The mixture was stirred at RT for 12

min. All compound 601-1 had thus been converted to the corresponding sulfoxide. To it was again added N-bromosuccinimide (122 mg, 0.69 mmol). The mixture was stirred at RT for 1 h. To it were added DIEA (0.4 mL, 2.3 mmol) and compound 601-2 (200mg, 0.92 mmol). The mixture was stirred at 90°C for 3 h to give products 601-3 and 601-4 in ratio of 4:1. The mixture was diluted with ethyl acetate, washed with brine x3, dried, concentrated and subjected to flash column to isolate compound 601-3 and compound 601-4.

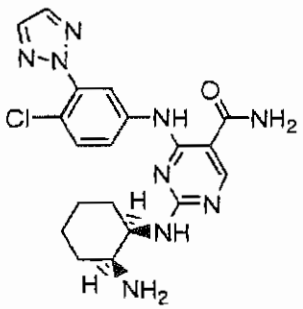
[1185] Compound 601-3 was treated with 1:1 TFA and DCM at RT. The mixture was stirred for overnight at RT. It was concentrated and subjected to reverse phase HPLC to isolate the title compound. MS found for $C_{19}H_{22}BrN_9O$ as $(M+H)^+$ 472.3, 474.3. λ=246, 294 nm.

Example 602: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-bromo-5-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide

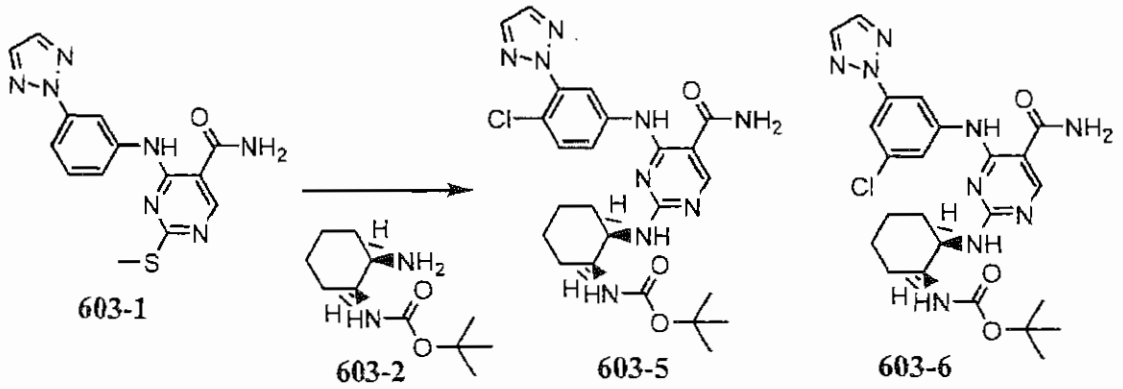


[1186] Compound 602-1 (as prepared in Example 601) was treated with 1:1 TFA and DCM at RT. The mixture was stirred for overnight at RT. It was concentrated and subjected to reverse phase HPLC to isolate the title compound. MS found for $C_{19}H_{22}BrN_9O$ as $(M+H)^+$ 472.3, 474.3. λ=253, 272 nm.

Example 603: 2-((1R,2S)-2-aminocyclohexylamino)-4-(4-chloro-3-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



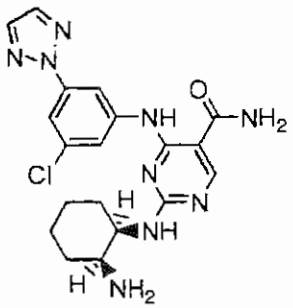
Scheme:



[1187] Compound 603-1 (150 mg, 0.46 mmol) was dissolved in 15 mL DMF. To it was added N-chlorosuccinimide (NCS, 300 mg, 2.2 mmol). The mixture was stirred at RT for 80 min. To it were added DIEA (0.4 mL, 2.3 mmol) and compound 603-2 (200mg, 0.92 mmol). The mixture was stirred at 90°C for 2 h to give products 603-5 and 603-6 in ratio of 2.6:1. The mixture was diluted with ethyl acetate, washed with brine x3, dried, concentrated and subjected to flash column to isolate compound 603-5 and compound 603-6.

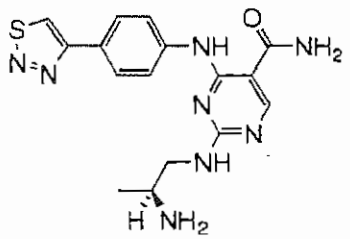
[1188] Compound 603-5 was treated with TFA at RT. The mixture was stirred for 30 m at RT. It was concentrated and subjected to reverse phase HPLC to isolate the title compound. MS found for $C_{19}H_{22}ClN_9O$ as $(M+H)^+$ 428.3. λ=246, 291 nm.

Example 604: 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-chloro-5-(2H-1,2,3-triazol-2-yl)phenylamino)pyrimidine-5-carboxamide



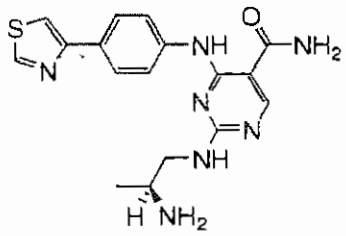
[1189] Compound 604-6 (as prepared in Example 603) was treated with TFA at RT. The mixture was stirred for 30 m at RT. It was concentrated and subjected to reverse phase HPLC to isolate the title compound. MS found for $C_{19}H_{22}ClN_9O$ as $(M+H)^+$ 428.3. λ=252 nm.

Example 605: (S)-4-(4-(1,2,3-thiadiazol-4-yl)phenylamino)-2-(2-aminopropylamino)pyrimidine-5-carboxamide



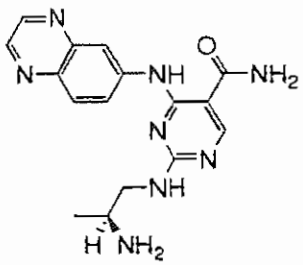
[1190] The title compound was prepared using the same chemistry shown for Example 424. UV λ=230, 306 nm. MS found for $C_{16}H_{18}N_8OS$ as $(M+H)^+$ 371.3. NMR (CD_3OD): δ 9.23 (s, 1H), 8.54 (s, 1H), 8.15 (m, 2H), 7.81 (m, 2H), 3.70 (m, 2H), 3.46 (m, 1H), 1.32 (d, J=6.8 Hz, 3H) ppm.

Example 606: (S)-2-(2-aminopropylamino)-4-(4-(thiazol-4-yl)phenylamino)pyrimidine-5-carboxamide



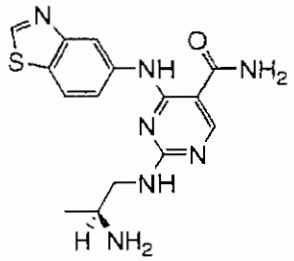
[1191] The title compound was prepared using the same chemistry shown for Example 424. UV λ=238, 311 nm. MS found for $C_{17}H_{19}N_7OS$ as $(M+H)^+$ 370.3. NMR (CD_3OD): δ 9.05 (d, J=2.0 Hz, 1H), 8.51 (s, 1H), 8.00 (d, J=8.0 Hz, 2H), 7.89 (s, 1H), 7.70 (d, J=7.2 Hz, 2H), 3.70 (m, 2H), 3.47 (m, 1H), 1.30 (d, J=6.0 Hz, 3H) ppm.

Example 607 (S)-2-(2-aminopropylamino)-4-(quinoxalin-6-ylamino)pyrimidine-5-carboxamide



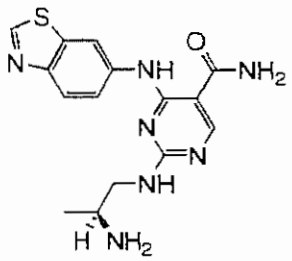
[1192] The title compound was prepared using the same chemistry shown for Example 424. UV λ=242, 273 nm. MS found for $C_{16}H_{18}N_8O$ as $(M+H)^+$ 339.3. NMR (CD_3OD): δ 8.85 (s, 1H), 8.82 (s, 1H), 8.86 (s, 1H), 8.59 (s, 1H), 8.10 (d, J=8.8 Hz, 1H), 7.84 (d, J=-8.4 Hz, 1H), 3.75 (m, 2H), 3.62 (m, 1H), 1.38 (d, J=6.0 Hz, 3H) ppm.

Example 608 (S)-2-(2-aminopropylamino)-4-(benzo[d]thiazol-5-ylamino)pyrimidine-5-carboxamide



[1193] The title compound was prepared using the same chemistry shown for Example 424. UV λ=246, 291 nm. MS found for $C_{15}H_{17}N_7OS$ as $(M+H)^+$ 344.3. NMR (CD_3OD): δ 9.34 (s, 1H), 8.72 (s, 1H), 8.56 (s, 1H), 8.11 (d, J=8.8 Hz, 1H), 7.52(d, J=8.8 Hz, 1H), 3.78-3.54 (m, 3H), 1.29 (d, J=6.4 Hz, 3H) ppm.

Example 609 (S)-2-(2-aminopropylamino)-4-(benzo[d]thiazol-6-ylamino)pyrimidine-5-carboxamide



[1194] The title compound was prepared using the same chemistry shown for Example 424. UV λ=241, 297 nm. MS found for $C_{15}H_{17}N_7OS$ as $(M+H)^+$ 344.3. NMR (CD_3OD): δ 9.24 (s, 1H), 8.56 (s, 1H), 8.41 (s, 1H), 8.10 (d, J=8.8 Hz, 1H), 7.72(d, J=8.8 Hz, 1H), 3.71-3.44 (m, 3H), 1.23 (d, J=6.4 Hz, 3H) ppm.

Example 610

[1195] This example illustrates methods for evaluating the compounds of the invention, along with results obtained for such assays. The *in vitro* and *in vivo* human syk activities of the inventive compounds can be determined by various procedures known in the art, such as a

test for their ability to inhibit the activity of human plasma syk. The potent affinities for human syk inhibition exhibited by the inventive compounds can be measured by an IC_{50} value (in nM). The IC_{50} value is the concentration (in nM) of the compound required to provide 50% inhibition of human syk proteolytic activity. The smaller the IC_{50} value, the more active (potent) is a compound for inhibiting syk activity.

[1196] An *in vitro* assay for detecting and measuring inhibition activity against syk is as follows:

Inhibition of syk tyrosine phosphorylation activity

[1197] Potency of candidate molecules for inhibiting syk tyrosine phosphorylation activity is assessed by measuring the ability of a test compound to inhibit syk-mediated tyrosine phosphorylation of a syk-specific substrate.

[1198] SYK tyrosine phosphorylation activity is measured using the LANCE™ Technology developed by Perkin Elmer Life and Analytical Sciences (Boston, MA). LANCE™ refers to homogeneous time resolved fluorometry applications using techniques such as time-resolved fluorescence resonance energy transfer assay (TR-FRET) (see generally for procedures in Perkin Elmer Application Note- How to Optimize a Tyrosine Kinase Assay Using Time Resolved Fluorescence-Based LANCE Detection, wwww.perkinelmer.com/lifesciences). The assay principle involves detection of a phosphorylated substrate using energy transfer from a phosphospecific europium-labeled antibody to streptavidin-allophycocyanin as an acceptor.

[1199] To test the ability of candidate molecules to inhibit SYK tyrosine phosphorylation activity, molecules are reconstituted in 30 % DMSO and serially diluted 1:3 with the final dilution containing DMSO in the absence of the candidate molecule. The final DMSO concentration in the assay is 3%. Kinase assays are performed as a two part reaction. The first reaction is a kinase reaction and which comprises of a candidate molecule, full length active recombinant SYK enzyme (Millipore, CA) and biotin-labeled SYK-specific substrate biotin-DEEDYESP-OH. The second reaction involves termination of the kinase reaction and the simultaneous addition of the detection reagents- europium-labeled anti-phosphotyrosine reagent (Eu-W1024-PY100, Perkin Elmer, Boston, MA) and Streptavidin-Allophycocyanin detection reagent (SA-APC, Prozyme, CA). The kinase reaction is performed in a black U-bottom 96-well microtitre plate. The final reaction volume is 50 µL and contains a final

concentration of 1 nM active SYK enzyme, 550 nM SYK-substrate, and 100 μM ATP diluted in a buffer containing 50 mM Tris pH 7.5, 5 mM $MgCl_2$, and 1mM DTT. The reaction is allowed to proceed for 1 hour at room temperature. The quench buffer contains 100 mM Tris pH 7.5, 300 mM $NaCl_2$, 20 mM EDTA, 0.02% Brij35, and 0.5% BSA. The detection reagents are added to the reaction mixture at the following dilutions- 1:500 for Eu-W1024-PY100 and 1:250 for SA-APC. The kinase reaction is terminated by the addition of 50 μL quench buffer containing the detection reagents. The detection is allowed to proceed for 1 hr at room temperature. Detection of the phosphorlated substrate in the absence and presence of inhibitors is measured in the TR-FRET instrument, Analyst HT (Molecular Probes, Sunnyvale, CA) and the condition for measurements are set up using CriterionHost Release 2.0 (Molecular Probes, Sunnyvale, CA). The settings used are a follows: excitation 360 nm, emission 665 – 7.5 nm, beam splitter 350 nm 50/50, flash 100 pulses, delay 60 us, integration 400 us, z-height 2 mm. Inhibition of SYK-tyrosine kinase activity is calculated as the maximum response observed in the presence of inhibitor, compared to that in the absence of inhibitor. IC_{50}s were derived by non-linear regression analysis.

[1200] Intracellular phospho-flow cytometry was used to test compound inhibition of Syk activity in intact non-Hodgkin's lymphoma cell lines Ramos and SUDHL-6. $10x10^6$ cells in log phase growth were aliqoted; Syk kinase is activated by incubating cells for 10 minutes with 3μg/ml antibody specific to the B cell receptor. Directly following, cells are fixed in 1% paraformaldehyde for 5 minutes at room temperature, washed in phosphate buffered saline, and then permeablized by incubation for 2 hours in ice cold methanol. Cells are again washed in phosphate buffered saline, then incubated for 30 minutes with antibody specific for phosphorylated Erk (Y204) and BLNK (Y84), which are indicators of Syk kinase activity, and phosphorylated Syk (Y352), a measure of Src family kinase activity. All antibodies used are purchased from BD Pharmingen (San Jose, CA). After incubation with antibodies, cells are again washed and subjected to flow cytometry. Representative data detailing inhibition of B cell receptor singaling by compounds are shown in Table 1 as IC_{50} ranges.

[1201] The anti-proliferative effects of compounds on non-Hodgkin's lymphoma B cell lines SUDHL-4, SUDHL-6, and Toledo was also assessed. SUDHL-4 and SUDHL-6 require B cell receptor signaling for growth and survival, while the Toledo cell line (serving here as a negative control) does not. Cells were aliquoted into each well of a 96-well plate and incubated with increasing concentrations of compound for 72 hours, after which cell survival and proliferation was determined using the MTT assay (Chemicon International, Inc.,

Temecula, CA) following protocols supplied by the manufacturer. Data are detailed in the Tables and Figures herein as IC_{50} values plus or minus standard deviations from 5 or 6 independent experiments.

[1202] Induction of apoptosis in non-Hodgkin's lymphoma B cell lines SUDHL-4, SUDHL-6, and Toledo was assessed by measuring the apoptotis marker Caspase 3. Cells were incubated with 1, 3, or 10μM compound for 24, 48, and 72 hours. At the conclusion of each time point, cells were processed for flow cytometry analysis using the Monoclonal Rabbit Anti-Active Caspase-3 Antibody Kit and related protocols (BD Pharmingen). Data from two independent experiments are presented in Tables 7A and 7B, representing the percent of total cells undergoing apoptosis following incubation with compounds under the indicated conditions.

[1203] Syk activity is not only required for B cell signaling, proliferation, and survival, as shown, but is also critical for cellular activation upon cross-linking of the B cell receptor. B cell activation leads to increased cell surface expression of several proteins involved in cell signaling, antigen presentation, and adhesion. Among these, CD80, CD86, and CD69 are commonly measured to determine B cell activation status. Therefore, primary mouse B cells isolated from spleen were aliquoted and incubated with increasing concentrations of compound (0.05 to 2μM) in the presence of goat anti-mouse IgD (eBiosciences, Inc., San Diego, CA) for 20 hours to cross-link the B cell receptor. Following, cells were washed and incubated for 30 minutes on ice with antibodies specific for the CD80, CD86, and CD69 B cell activation markers. B cells were identified from the pooled population by staining with the B cell marker CD45RO. All antibodies were purchased from BD Pharmingen. Table 8 depicts the IC_{50} range in which these compounds inhibited B cell receptor induced activation of mouse primary B cells

[1204] In the table below, activity in the Syk and/or Jak assays is provided as follows: +++++ = $IC_{50} < 0.0010$ μM; ++++ = 0.0010 μM < $IC_{50} < 0.010$ μM, +++ = 0.010 μM < $IC_{50} < 0.10$ μM, ++ = 0.10 μM < $IC_{50} < 1$ μM, + = $IC_{50} > 1$ μM..

Table 6a:

Example	UV	MW	MH+	Syk IC50
1	240, 297	452.6	453.2	++
2	236, 312	459.6	460.1	++
3	239, 304	392.5	393.2	++
4	231, 311	410.5	411.2	+++

Example	UV	MW	MH+	Syk IC50
5	238, 337	403.5	404.2	+++
6	239, 311	403.5	404.2	+++
7	241, 330	403.5	404.2	+++
8	243, 308	404.5	405.2	+++
9	239, 313	409.5	410.2 410.4	+++
10	233, 308	410.5	411.2	+++
11	240, 311	403.5	404.2	+++
12	245	404.5	405.2 405.3	+++
13	240, 312	403.5	404.2	+++
14	240, 318	409.5	410.2	+++
15	243, 332	409.5	410.2	+++
16	240, 302	392.5	393.2 393.3 393.4	+++
17	248	403.5	404.2	++++
18	243, 294	411.5	412.2 412.3	+++
19	242, 307	404.5	405.3	+++
20	244, 293	425.5	426.3	++
21	239, 327	404.5	405.4	+++
22	235, 319	404.5	405.4	+++
23	239, 334	403.5	404.4	+++
24	242, 300	393.5	394.4	+++
25	241, 300	406.5	407.4	+++
26	241, 296	397.4	398.4	++
27	246, 292	392.5	393.2 393.5	+++
28	246, 287	409.5	410.5	++
29	239, 309	429.5	430.4	+++
30	241, 236	460.5	461.4	++
31	247	392.5	393.4	++++
32		410.5	411.3 411.5	++
33		427.5	428.4	+++
34		410.5	411.3	+++
35		424.5	425.3	++
36	201.6, 240.4, 289.0	410.5	411.09	++
37	202.8, 245.2	409.5	410.2, 411.2	++++
38	240.4, 312.8	427.5	428.5, 429.4	+++
39	206.3, 242.8, 291.4	409.5	410.2, 411.4	++++
40	201.6, 244.0, 277.1	409.5	410.5, 411.6	++++
41	242.8, 292.6	403.5	404.2, 405.3	+++
42	244.0, 289.0	404.5	405.3, 406.5	+++
43	246.3	404.5	405.2, 406.2	+++

Example	UV	MW	MH+	Syk IC50
44	242.8	406.5	407.2, 408.2	+++
45	247.5	433.5	434.3, 435.3	+++
46	240.4, 306.8	433.5	434.3, 435.3	+++
47	240.4, 296.1	425.5	426.3, 427.3	+++
48		418.5	419.5 (M+1)	+++
49		438.6	439.6 (M+1)	++
50		393.5	MS: 394.2 (M + H)	+++
51		393.5	MS: 394.3 (M + H)	+++
52		394.4	MS: 395.28 (M + H)	++
53		393.5	MS: 394.28 (M + H)	+++
56		408.5	MS: 409.28 (M + H)	+++
57		423.5	MS: 424.37 (M + H)	+++
58		408.5	MS: 409.32 (M + H)	+++
59		392.5	MS: 393.0 (M+H)	++++
60		408.5	MS: 410 (M + H)	+++
61		423.5	MS: 424.5 (M + H)	+++
62		406.5	MS: 407.5 (M + H)	+++
63		409.5	MS: 410.5 (M + H)	+++
64		420.5	MS: 421.5 (M + H)	++
65		424.5	MS: 425.4 (M + H)	++++
66		394.4	MS: 395.5 (M + H)	++++
67		408.5	MS: 409.5 (M + H)	+++
68		408.5	MS: 409.5 (M+H)	+++
69		408.5	MS: 409.5 (M+H)	+++
70		391.5	MS: 392.5 (M + H)	++++
71		391.5	MS: 392.4 (M + H)	+++
72		406.5	MS: 407.5 (M + H)	+++
73		395.5	MS: 396.6 (M + H)	+++
74		411.5	MS: 412.5 (M+H)	+++
75		394.4	MS: 395.3 (M + H)	+++
76		394.4	MS: 395.2 (M + H)	++++

Example	UV	MW	MH+	Syk IC50
78		394.4	MS: 395.2 (M + H)	+++
79	243, 302	478.5	479.4	++
80	246, 301	594.5	595.4	+
81	247	477.6	478.4	+
82	241	392.5	393.4	++++
83	241, 319	424.5	425.3	+++
84	246, 293	406.5	407.3	++
85	243, 285	406.5	407.3	++
86	244	393.5	394.3	++++
87	250	393.5	394 394 (M+H) 394.3 394.8 (M +H) ES(+) MS ES(+) MS [M+1]=394	++++
88	242, 300	423.5	424.3	+++
89	242, 301	422.5	423.3	+++
90	242, 300	436.5	437.3	+++
91	249, 301	489.6	490.3	+
92	247	411.4	412.3	+++
93	259	418.5	419.4	+
94	252	418.5	419.4	++
95	244, 288	418.5	419.4	++
96	245, 296	433.5	434.4	+++
98	249	422.5	423.4	+++
101a	250	394.4	395.3	+++
101b	250	408.5	409.3	++++
102	246, 304	407.5	408.3	+++
103	249	442.5	443.3	+++
104a	240, 295	442.5	443.4	+++
104b	240, 295	442.5	443.4	+++
105a	234, 303	443.5	444.4	+++
105b	234, 303	443.5	444.4	+++
106	240, 292	442.5	443.3	+++
107	243, 290	459.6	460.3	++
108	245	486.6	487.5	++
109	263	453.6	454.3	+++
110	249	453.6	454.3	+++
111	240, 311	406.5	407.3	+++
113	239, 314	406.5	407.3	++++
114	239, 310	393.5	394.3	+++
115	250	411.4	412.3	+++
116	244, 295	423.5	424.3	++++
117	249	423.5	424.3	++++
118	243, 281	407.5	408.3	++++

Example	UV	MW	MH+	Syk IC50
119	248	407.5	MW=407.47, M+H=408.8	++++
120	249	404.5	405.3 405.4	+++
121	231, 314	404.5	405.3	+++
122	249	406.5	407.3	++++
123	247	406.5	407.3	+++
124	247	442.5	443.3	+++
125	245, 303	442.5	443.3	+++
127	241, 298	383.5	384.1 384.2	+++
128	246, 295	367.4	368.1	+++
129	246, 295	397.5	398.1	+++
130	239, 309	365.4	366.2	++++
132	241, 283	377.5	378.1 378.2 (M+1)	++++
133	243, 294	366.4	367.2	+++
134	246, 292	383.5	384.2	+++
135	250	366.4	367.1	+++
136	240, 294	384.4	385.1	+++
137	242	378.4	379.2	+++
138	243	384.5	385.1	++
139		391.5	392.2 (M+1)	+++
140		377.5	378.34	+++
142		377.5	378.34 (M+1)	++
143		476.6	477.40 (M+1)	+++
144		406.4	407.28 (M+1)	++
146		381.4	382.35 (M+1)	+++
147		439.5	440.38 (M+1)	++
148		397.4	398.31 (M+1)	+++
149		409.5	410.36 (M+1)	+++
150		402.5	403.32 (M+1)	+++
151		395.5	396.35 (M+1)	++++
152		393.5	394.14 (M+1)	++++
153		411.5	412.5 (M+1)	+++
154		397.4	398.5 (M+1)	++
155		407.5	408.6 (M+1)	+++
156		468.6	469.4	+
157		377.5	378.2 (M+1) 378.5 (M+1) 378.6 (M+1)	++++
158		380.5	381.17 (M+1)	++++
159		380.5	381.17 (M+1)	++++
160		380.5	381.17 (M+1)	+++
161		462.6	463.32 (M+1)	+++
162		397.5	398.2 (M+1)	+++
163		379.5	380.4 (M+1)	+++
165		432.5	433.2 (M+1)	++++

Example	UV	MW	MH+	Syk IC50
166		411.5	412.2 (M+1)	++
167	245	495.6	496.3	+++
168	249	499.6	500.3	+++
169	244	495.6	496 496.3	+++
170	246	499.6	500.3	+++
171	247	487.6	488 488.3	+++
172	246	487.6	488.3	+++
173	238, 309	487.6	488.3	+++
174	241, 314	487.6	488.3	+++
175	246	408.5	409 409.4	+++
176	241, 290	410.5	411.4	++
177	239, 309	408.5	409.3 409.4	+++
178	243, 296	410.5	411.3	++
179	232, 306	466.6	467.3	++
180	238, 290	418.5	419.3	++
181	241, 291	426.5	427.3	+++
183	244, 297	439.5	440.3	++
185	243.8, 290.0	456.5	457.2	++
186		400.4	401.2, racemate	++
187	242.6, 290.0	456.5	457.2, racemate	++
188	242.6, 290.0	400.4	401.2, racemate	+++
189	241.2, 292.1	330.4	331.4	++
190	237.6, 313.1	329.4	330.3	++
191	240.0, 303.2	392.5	393.4	+++
192	244.9, 326.1	346.5	347.3	++++
193	247.3, 325.6	346.5	347.3	+++
194	240.0, 314.3	391.5	392.4	+++
195	244.0, 316.4	446.6	447.3, 448.4	+++
196	240.4, 304.5	447.5	448.1, 449.2	++
197	239.3, 308.7	402.5	403.4	+++
198	243.6, 286.5	393.5	394.4, 395.5	++++
199	245.2, 293.8	393.5	394.4, 395.4	++
200	239.9	393.5	394.5	++
202	243.6, 287.1	407.5	408.4	+++
203	241.4, 288.8	412.5	413.1, 414.2	++
204	240.5, 287.8	398.5	399.2, 400.2	+++
205	238.1, 292.6	370.5	371.2, 372.3	+++
206	236.9, 286.6	386.5	387.1, 388.2	+++
207	240.4, 292.6	418.5	419.3, 420.3	++
209		376.5	377.1, 378.5	+++
210	227.5, 319.9	406.5	407.2, 408.5	++++

Example	UV	MW	MH+	Syk IC50
211a	212.2, 244.0, 306.8	394.5	395.1, 396.3	++++
211b	223.9, 318.8	419.5	420.2, 421.4	++++
212	219.2, 235.7, 318.8	433.5	434.3, 435.3	+++
213	218.0, 314.0	447.5	448.2, 449.4	++++
214	223.9, 293.8	410.9	411.2, 413.1	++
215		455.4	455.1, 457.1	++++
216		381.4	382.3	+++
217	220.4, 315.2	489.6	490.4, 491.4	++++
218	219.2, 241.6, 336.7	379.5	380.4	++++
219		395.5	396.3	++++
219	216.7, 239.9, 330.3	365.4	366.3, 367.4	+++++
220	210.6, 243.0, 329.1	380.5	381.5	++++
221	238.1	381.4	382.4	++
222	234.5, 298.5, 315.2	384.5	385.3	+++
223	203.4, 245.4	378.4	379.3	+++
224	205.1, 242.8, 290.2	383.5	384.3	+++
225	202.8, 239.3	380.5	381.4	++
226	220.4, 239.3, 336.7	379.5	380.4	++++
227	241.6, 293.8	441.5	442.5	++
228	222.8, 242.8	393.5	394.4	+++
229	222.8, 241.6	405.5	406.5	++++
230	203.9, 236.9, 294.9	367.4	368.4	+++
231	220.2, 242.6	393.5	394.4	++++
232	210, 243	462.6	MW=462.5; M+1=463.3	+++
233	248	432.5	MW=432.5, M+1=433.4	+++
234	245	492.6	MW=492.6, M+1=493.4	++
235	241	432.5	MW=432.5, M+1=433.3	+++
236	245, 276	444.5	445 MW=444.5, M+1=445.3	++++
237	244, 288	432.5	MW=432.5, M+1=433.3	+++
238	245	420.5	MW=420.5; M+1= 421.3	++++
239	242	420.5	MW=420.5; M+1=421.3	+++
240	246	462.6	MW=462.5; M+1=463.3	+++
242	245	438.5	MW=438.5; M+1=439.3	+++
243	244, 288	462.6	463.3	+++

Example	UV	MW	MH+	Syk IC50
245	211, 243	460.5	MW=460.5; M+1=461.2	++++
246	242, 316	460.5	MW=460.5; M+1=461.2	+++
247	216, 238, 303	473.6	MW=473.6, M+1=474.4	+++
248	252	485.6	MW=485.6; M+1=486.4	+++
249	247	485.6	MW=485.6; M+1=486.4	+++
250	246	471.6	MW=471.6; M+1=472.4	+++
251	248, 282	485.6	MW=485.6; M+1=486.4	+++
252	245	485.6	MW=485.6; M+1=486.4	+++
253	239, 274, 296	446.5	MW=446.5; M+1=447.3	++++
254	240, 285	480.6	MW=480.6; M+1=481.4	+
255	246	480.6	MW=480.6; M+1=481.4	++++
256	250	480.6	MW=480.6; M+1=481.4	+++
257	235, 308	480.6	481.4	+++
259	239, 313	480.6	481.4	+++
260	239, 302	453.6	454.4	++
261	240, 301	453.6	454.4	++
262	241, 302	453.6	454.4	++
264	212, 236, 322	416.5	417.4	+++
265	210, 244, 289	416.5	417.3	+++
266	238, 296	429.5	430.3	+++
267	250	393.5	394.3	++
268	250	393.5	394.3	+++
269	252	393.5	394.3	++
270	252	393.5	394.3	+
272	252	393.5	394.3	+
273	251	379.4	380.3	+
274	259	461.5	MW=461.4, M+1= 462.2	+++
275	239, 296	407.5	MW=407.47, M+1= 408.4	+++
276	238, 296	406.5	MW= 406.48, M+1= 407.5	++
277	245, 295	461.5	MW=461.4, M+1=462.4	+++
278	245, 295	461.5	MW=461.4, M+1=462.4	++
279	244	352.4	353.2	++++
280	236, 310	352.4	353.2	+++
281	242, 289	354.5	355.3	+++
282	240, 290	368.5	369.3	+++

Example	UV	MW	MH+	Syk IC50
283	250	407.5	408.4	+++
284		391.4	392.4	+++
285	242, 305	411.4	MW=411.44, M+1=412.2	+++
292		376.5	377.1 377.1 (M+1) 377.3 (M+1) 3771., 378.2	++++
294	245.4	379.5	380.4	++
295	249	379.4	380.4	++
296	240, 287	326.4	327.4	++
297	217, 239, 290	340.4	341.4	+++
298	249	395.4	396.3	+++
299	250	395.4	396.3	++
300	246	394.4	395.3	+++
301	249	406.5	407.3	++
302	240, 288	342.4	343.3	+++
303	240, 290	356.4	357.3	++++
304	240, 283	358.4	359.3	+++
305	241, 287	342.4	343.3	++
306	239, 292	376.4	377.3	++
308	240, 292	358.4	359.2	+++
310a	243, 294	356.4	357.3	++
310b	243, 290	356.4	357.3	+++
311	249	409.5	410.3	+++
312a	247, 295	370.5	371.3	++
312b	242, 289	370.5	371.3	++
314	240	356.4	357.3	++
315	246, 303	382.4	383.1	+++
316	245, 302	340.3	341.1	++
317	249, 298	402.4	403.1	++
318	241, 283	393.5	394.1 394.2 (M+1)	+++
319	243, 303	399.5	399.1	+++
320	245	381.4	382.1	+++
321	247, 301	382.4	383.2	+++
322	249, 285	420.5	421.1	+
323	250, 300	420.5	421.1	++
324	243, 296	468.6	469.2	++
325	244, 297	382.4	383.2	+++
327	245, 299	340.3	341.2	++
328	245, 296	413.5	414.2	++
330	244, 303	357.4	358.2	++
331	249, 292	357.4	358.2	++
332	247, 295	399.5	400.2	+++
333	250	340.3	341.1	++
334	252	382.4	383.1	+++

Example	UV	MW	MH+	Syk IC50
335	224	339.4	340.1	++
336	243, 310	400.4	401.1	++
337	243, 312	358.4	359.1	++
338	243	394.4	395.2	+++
339	242	352.4	353.2	++
340	241, 308	408.5	409.2	++
341	240, 314	425.5	426.2	+++
342	233, 311	426.5	427.2	+++
343	240	400.5	406.1	++
344	244, 314	419.5	420.2	++
345	244, 294	427.5	428.3	+++
346	240, 310	445.5	446.3	++
347	246	427.5	428.3	++
349	247, 292	411.5	412.3	++
350	241, 314	419.5	420.3	++
351	250	419.5	420.3	++
352	243, 284	395.5	MS: 396.4 (M + H)	+++
353	250	408.5	409.3	++
354		367.4	MS: 368.17 (M + H)	++
355		367.4	MS: 368.29 (M + H)	++
356		450.5	451.35 (M+1)	+++
357	251	409.5	410.3	++
358	250	381.4	382.3	++
359	251	367.4	368.3	++
360	247	353.3	354.3	+
361	240, 313	424.5	425.3	+++
362	244, 298	426.5	427.3	++
364	251, 302	490.6	491.3	++
372	207.5, 244.0, 325.9	396.5	397.4	++
374		388.4	Turbo Spray Mass Spec [M+1]=388	++
375		407.3	Turbo Spray MS [M+1]=407	++
376		372.4	Turbo Spray MS [M+1]=373	++
378		396.4	Turbo Spray MS [M+1]=397	++
379		353.4	Turbo Spray MS [M+1]=354	++
380		358.4	Turbo Spray MS [M=1]=359	++
381		342.4	Turbo Spray MS [M+1]=343	++
383		360.4	Turbo Spray [M+1]=361	++
385		328.4	Turbo Spray	++

Example	UV	MW	MH+	Syk IC50
			MS [M+1]=329	
386		314.3	ES (+) MS [M+H]=315 Turbo Spray MS [M+1]=315	++
387		330.3	Turbo Spray MS [M+1]=331	++
389		422.4	Turbo Spray Mass Spec [M+1]=423	++
390		392.4	Turbo Spray MS [M+1]=393	++
391		430.4	Turbo Spray [M+1]=431	++
392		441.3	Turbo Spray=442	++
393		344.4	Turbo Spray MS [M+1]=345	++
394		344.4	Turbo Spray MS [M+1]=345	++
396		330.3	Turbo Spray MS [M+1]=331	++
397		395.2	Turbo Spray MS [M]=395	++
398		346.3	Turbo Spray MS [M+1]=347	++
399		404.5	Turbo Spray MS [M+1]=405	++
400		424.9	Turbo Spray MS [M+1]=425	++
401		408.4	Turbo Spray MS [M+1]=409	++
402		404.5	Turbo Spray MS [M+1]=405	++
404		391.4	Turbo Spray MS [M+1]=392	++
405		420.5	Turbo Spray MS [M+1]=421	++
406		406.4	Turbo Spray MS [M+1]=407	+++
407		406.4	Turbo Spray MS [M+1]=407	++
408	248, 294	385.5	386.4	+
409	240, 283	365.4	366.2	+++
410	243, 302	385.5	386.4	++
411	246, 293	371.4	372.4	++
412	216.9, 244.0	395.5	396.3	+++
413	213.3, 244.0, 333.1	396.5	397.4	+++
414	241.6, 318.8	382.4	383.4, 384.3	++
416	240, 292	300.4	301.3	+++
417	249	339.4	340.3	+++
418	251	353.4	354.3	++
419	252	367.4	368.3	++

Example	UV	MW	MH+	Syk IC50
420	249	367.4	368.3	++
422	250	353.4	354.3	++
423	254	394.4	395.3	+
424	250	353.4	354.3	+++
425	247	364.4	365.4	+++
426	243, 289	300.4	301.4	+++
427	243, 289	314.4	315.4	+++
428	250	353.4	354.3	+++
440	219.2, 239.3, 331.9	369.4	370.4	++++
441	220.4, 325.9	367.5	368.4	++++
442	220.4, 239.9, 331.6	397.5	398.4	++++
443	219.2, 239.3, 331.9	383.5	384.3	++++
444	215.7, 238.1, 327.1	369.4	370.3	++++
445	214.9, 241.7, 324.1	370.4	371.3	++++
447	203.9, 244.0, 303.3	395.5	396.4	++++
448	208.6, 240.4, 283.1, 324.7	384.4	385.4	+++
449	221.6, 336.7	409.5	410.4	+++
450	222.8, 336.7	409.5	410.4	+++
451	221.6, 335.5	409.5	410.4	+++
452	219.2, 239.3, 327.1	381.5	382.4, 383.5	+++
454		439.9	Turbo Spray MS [M+1]=440	+++
455		396.4	Turbo Spray MS [M+1]=396	+++
456		405.5	Turbo Spray MS [M+1]=406	+++
457		359.4	ES (+) MS [M+1]=360	+++
458		426.5	Turbo Spray MS [M+1]=427	+++
459		460.9	Turbo Spray MS [M+1]=447	+++
460		435.5	Turbo Spray MS [M+1]=436	++
462		423.5	Turbo Spray MS [M+1]=424	++
463		462.5	Turbo Spray MS [M+1]=463	++
465	246	367.4	MW=367.4, M+1=368.3	+++
467	238, 284	314.4	415.4	+++
468	240, 290	328.4	329.4	+++
469	248	367.4	368.4	++++
470	248	378.4	379.4	+++
471	246	366.4	367.4	+++

Example	UV	MW	MH+	Syk IC50
473	250	379.4	380.4	+++
478	245	421.4	422.3	+++
479	240	340.4	341.5	+++
481	219.2, 240.4, 331.9	367.5	368.4	++++
482	220.2, 241.4, 330.6	365.4	366.4	++++
483	219.2, 240.4, 333.1	353.4	354.4	++++
484	219.3, 239.4, 326.7	397.5	398.4	++++
485	216.7, 238.7, 327.2	355.4	356.4	++++
499	224.9, 316.2	409.5	410.2, 411.3	+++
500	223.9	383.5	384.4	+++
501	203.9, 241.6	384.4	385.3, 386.4	+++
502	220.4, 333.1	369.4	370.4	+++
503	209.8, 240.4, 283.1, 325.9	384.4	385.4	+++
507	220.4, 240.4	383.5	384.4	+++
508	218.6, 242.3	431.5	432.4	+++
509	219.8, 241.7	381.5	382.4	+++
510	240.3, 290.0	344.4	345.4, 346.5	+++
511	218	383.5	384.4	+++
512	211.3, 242.3, 330.9	432.5	433.4	+++
513	202.8, 246.3	392.5	393.4	+++
514	221.6, 315.2	396.5	397.0, 398.4	+++
515	203.4, 246.6	454.5	455.4	+++
516	222.8, 316.4	423.5	424.4, 425.1	+++
517	208.8, 241.7, 316.7	370.4	371.5	+++
518	240.5, 288.4	328.4	329.5	+++
519	241.1, 286.5	314.4	315.4	+++
520	206.3, 240.4, 311.6	356.4	357.3	+++
521	203.8, 235.5, 290.0	376.4	377.30, 378.42	+++
522	218.0, 311.6	479.5	480.4	+++
523	239.3, 289.0	330.3	331.1, 332.1	+++
524	241.1, 287.7	354.5	355.5	+++
525	241.7, 285.9	328.4	329.4	+++
526	219.2, 282.8	366.4	367.1, 368.2 367.4	+++
527	241.7, 286.5	326.4	327.4	+++
530	241.4, 287.7	340.4	341.4	+++
531	242.8	393.5	394.4	+++
532	240.4, 290.2	399.5	400.2, 401.5	+++
533	204.6, 251.5	393.5	394.4	+++
535	242.3, 285.4	383.4	384.3	+++

Example	UV	MW	MH+	Syk IC50
536	239.3, 285.4	344.4	345.1, 356.1	+++
537	202.8, 238.1, 308.0	370.4	371.3	+++
538	208.6, 240.4, 319.9	384.4	385.3	+++
539	203.9, 249.9	367.4	368.4	+++
540	202.1, 246.0	406.5	407.4	+++
543	215.7, 240.4, 289.0	364.8	365.2, 367.1	+++
546	239.9, 284.7	342.4	343.5	+++
547	238.1, 299.7	370.4	371.4	+++
548	239.7	346.4	347.23, 348.32	+++
549	239.3, 286.6	344.4	345.2, 346.3	++
550	215.5, 241.7, 330.9	433.5	434.5	++
551	249.9	383.4	384.3, 385.3	++
552	247.2	382.4	383.3	++
553	243.6	394.4	395.3, 396.4	++
554	238.1, 286.6	316.4	317.25, 318.83	++
556	239.3	344.4	345.2, 346.3	++
557	240.5, 286.5	344.4	345.4	++
558	220.4, 239.3	339.4	340.4	++
560	239.3	360.4	361.2, 362.2	++
561	238.1, 281.9	382.4	383.5, 384.5	++
562	250.3	411.5	412.4	++
563	208.6, 240.4, 311.6	384.4	385.3	++
564	238.1, 292.6	360.4	361.2, 362.3	++
565	232.6, 287.8	373.4	374.3	+++
566	239.3, 287.8	356.5	357.4	++
567	204.6, 250.9	379.4	380.4	++
569	242.8	384.4	385.2, 386.4	++
570	238.1, 290.2	344.4	345.1, 346.2	++
581	243.6, 292.1	373.4	374.3	++
582	239.3, 285.4	342.4	343.4	++
583	235.7, 285.4	376.4	377.1, 378.2	++
584	240.4, 287.8	383.5	384.14, 385.06	++
585	235.7, 315.2	374.4	375.2	++
586	230.1, 311.2	394.4	395.4, 396.3	++
587	245.4	368.4	369.2, 370.1	++
588		373.5	374.3, 375.3	++
589	202.8, 239.9, 282.2	390.4	391.4	++
590	238.1, 293.8	415.5	416.2, 417.4	++
591	239.3, 292.7	374.4	375.3	++
592	240.4	356.5	357.4	++
593	241.7, 288.4	408.5	409.4	++
594	203.9, 235.7,	357.4	358.3	++

Example	UV	MW	MH+	Syk IC50
	292.6			
595	239.3	358.4	359.2, 360.4	++
598	248.7	395.5	396.4	++

Inhibition of GPVI-Mediated Platelet Function In Vitro

[1205] The ability for candidate molecules to inhibit syk-mediated platelet functions are tested by measuring the inhibition the GPVI-specific agonist Convulxin-induced human platelet calcium-mobilization or aggregation. Calcium-mobilization is assessed in human washed platelets in a 96-well microtiter format. Aggregation is assessed in a 96-well microtiter assay (see generally the procedures in Jantzen, H. M. *et al.* (1999) *Thromb. Hemost. 81*:111-117) or standard cuvette light transmittance aggregometry using human platelet-rich plasma (PRP).

Inhibition of Convulxin-Mediated Platelet Calcium-Mobilization In Vitro

[1206] Inhibition of Convulxin-induced calcium-mobilization was determined in human washed platelets using the FLIRP Calcium 3 Assay Kit (Molecular Devices, Sunnyvale, CA). For preparation of washed platelets, human venous blood is collected from healthy, drug-free volunteers into ACD (85 mM sodium citrate, 111 mM glucose, 71.4 mM citric acid) containing PGI_2 (1.25 ml ACD containing 0.2 μM PGI_2 final; PGI_2 was from Sigma, St. Louis, MO). Platelet-rich plasma (PRP) is prepared by centrifugation at 160 X g for 20 minutes at room temperature. Washed platelets are prepared by centrifuging PRP for 10 minutes at 730 g and resuspending the platelet pellet in CGS (13 mM sodium citrate, 30 mM glucose, 120 mM NaCl; 2 ml CGS/10 ml original blood volume). After incubation at 37 °C for 15 minutes, the platelets are collected by centrifugation at 730 g for 10 minutes and resuspended at a concentration of 3 X 10^8 platelets/ml in Hepes-Tyrode's buffer (10 mM Hepes, 138 mM NaCl, 5.5 mM glucose, 2.9 mM KCl, 12 mM $NaHCO_3$, pH 7.4). This platelet suspension is kept >45 minutes at room temperature before use in calcium mobilization assays.

[1207] For 96-well plate Calcium-mobilization experiments, equal volumes of 3 X 10^8 washed platelets/ml were incubated with equal volumes of Calcium-3 Assay Reagent A resuspended in 1 X Hank's Balanced Salt Solution, pH 7.4, 20 mM Hepes buffer. The total reaction volume of 0.2 ml/well includes 1.5 x 10^8/ml washed platelet/Calcium-3 Assay reagent A mix, 10 μM Eptifibatide (Millennium Pharmaceuticals Inc, Cambridge, MA), serial

dilutions (1:3) of test compounds in 0.75% DMSO. DMSO alone is added to 1 well of each 8 set to allow for a maximal calcium-mobilization reading. After 20 minutes preincubation at room temperature the 96-well microplate reader is loaded into the FlexStation (Molecular Devices, Sunnyvale, Calif). The FlexStation experimental conditions for measuring Calcium mobilization are set up using SOFTMax Pro. The settings used are detailed below. Fluorescence parameters-assay mode: flex, excitation 485 nM, 525 nM with a cut-off of 515 nM; Parameters- PMT sensitivity- 6, pipette height 230 µl, read time 2 minutes and 40 seconds, read intervals 2 seconds, temperature-23-25°C. After 18 seconds of baseline reading, calcium-mobilization is initiated by the addition of Convulxin to a final concentration of 125 ng/ml. Inhibition of calcium-mobilization was calculated as the maximum response observed in the presence of inhibitor, compared to that in the absence of inhibitor. IC_{50}s were derived by non-linear regression analysis.

Inhibition of Convulxin-Mediated platelet Aggregation In Vitro

[1208] For preparation of human platelet-rich plasma for aggregation assays, human venous blood was collected from healthy, drug-free volunteers into 0.38 % sodium citrate (0.013 M, pH 7.0 final). Platelet-rich plasma (PRP) is prepared by centrifugation of whole blood at 160 x g for 20 minutes at room temperature. The PRP layer is removed, transferred to a new tube, and the platelet count is adjusted, if advantageous, to achieve a platelet concentration of ~3 x 10^8 platelets/ml using platelet-poor plasma (PPP). PPP is prepared by centrifugation of the remaining blood sample (after removal of PRP) for 20 minutes at 800 x g. This preparation of PRP can subsequently be used for aggregation assays in either a 96-well plate or standard cuvette aggregometry.

[1209] Inhibition of Convulxin-induced aggregation is determined in 96-well flat-bottom microtiter plates using a microtiter plate shaker and plate reader similar to the procedure described by Frantantoni *et al., Am. J. Clin. Pathol.* 94, 613 (1990). All steps are performed at room temperature. For 96-well plate aggregation using platelet-rich plasma (PRP), the total reaction volume of 0.2 ml/well includes 190 µl of PRP (~3 x 10^8 platelets/ml, see above), and 5 µl of either serial dilution of test compounds in 30% DMSO or buffer (for control wells). After 20 minutes preincubation at room temperature 5 µl of 320 ng/ml Convulxin agonist solution is added to each well to give a final concentration of 8 ng/ml Convulxin. The plates are then agitated for 5 min on a microtiter plate shaker and the 5 minute reading is obtained in the microtitre plate reader (Softmax, Molecular Devices, Menlo Park, Calif.). Aggregation is

calculated from the decrease of OD at 650 nm at t=5 minutes. IC_{50}s were derived by non-linear regression analysis.

[1210] Inhibition of Convulxin-induced aggregation was also determined for cuvette light transmittance aggregation assays, serial dilutions (1:2) of test compounds were prepared in 30% DMSO in a 96 well V-bottom plate (final DMSO concentration in the cuvette was 0.3%). The test compound (5 µl of serial dilutions in DMSO) was preincubated with PRP for 20 minutes prior to initiation of aggregation reactions, which is performed in a ChronoLog aggregometer by addition of agonist (125-250 ng/ml Convulxin) to 495 µL of PRP at 37°C. The aggregation reaction is recorded for 4 min, and maximum extent of aggregation is determined by the difference in extent of aggregation at baseline, compared to the maximum aggregation that occurs during the 4 minute period of the assay. Inhibition of aggregation was calculated as the maximum aggregation observed in the presence of inhibitor, compared to that in the absence of inhibitor. IC_{50}s were derived by non-linear regression analysis.

Examples of compounds and their syk and PRP IC_{50} values are given in tables 2-5.

Calcium flux assay in Ramos cells induced by BCR cross-linking

[1211] Ramos cells (2G6.4C10, Burkitt's lymphoma, ATCC Item Number: CRL-1923) are sub-cultured at 5 x10^5 cells/ml in fresh medium 3 or 4 days ahead of experiments. Cells are harvest and re-suspend in fresh medium at 8 x 10^6 cells/ml before dye-loading. An equal volume of Calcium 3 loading dye (Molecular Device) is added and mixed into cell suspension. Loading cells are dispensed in a 96 well plate and incubated 30 min. Compounds are then added in the dye-loaded cells and incubated for another 30 min. Spin cell down at 1000 rpm for 3 min before fluorescence measurement in FlexStation. BCR stimulation is carried by the addition of 5 µg/ml antibody (AffiniPure F(ab')$_2$ fragment Donkey anti-human IgM, Jackson ImmunoResearch Laboraotries).

Calcium flux assay in Jurkat cells induced by TCR cross-linking

[1212] The protocol is very similar to B cell calcium flux as described in the previous section. The only differences are that T cells (clone E6-1, Acute T cell Leukemia, ATCC Item Number: Tib-152) and anti-human CD3 (Functional Grade Purified anti-human CD3, clone OKT3, eBioscience, No. 16-0037) replaced B cells and anti-human IgM. Cell density is kept the same but antibody is used at a concentration of 100 ng/ml.

IL-2 secretion in Jurkat cells induced by TCR cross-linking

[1213] Jurkat cell propagation and compound incubation procedures are the same as described in Jurkat calcium flux assay in the previous section. Antibody (anti CD3, OKT3) is coated onto a fresh plate (without cells) at 100 ng/well. Cells are suspended at 8 x 10^6 cells/ml and incubated with compounds for 30 min in a separate plate. At the end of incubation, cells are transferred to the antibody-coated plate and incubated for 16 hours. 100 µl of cell medium after incubation is used for IL-2 measurement after incubation. IL-2 level is determined using an IL-2 ELISA kit (Human IL-2 ELISA kit II, BD Bioscience, No. 550611).

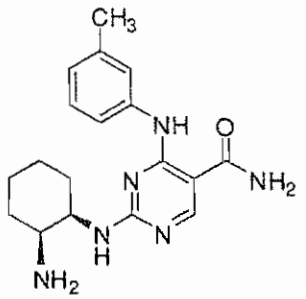
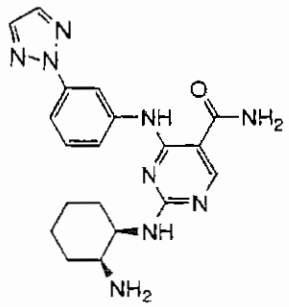
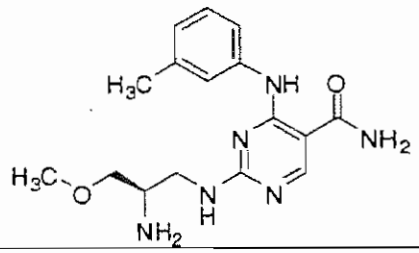
Example 611 Millipore Upstate KinaseProfiler™ screening

[1214] This assay is a direct measurement of the effect of compound on the catalytic activity of JAK3. Purified human JAK3 (GenBank AF513860) sequence (residue 781 – C terminus) was obtained from insect cells. The catalytic hydrolysis of ATP is measured using a radiometric filter binding method. Incubation of kinase with ^{33}[P]ATP and substrate leads to incorporation of ^{33}[P] into the substrate which can then be separated from the other reaction components by filtration. Assays were performed using 10 µM ATP and in the absence or presence of 1, 0.3, or 0.1 µM compound. Activity was expressed as % of inhibition of control.

Example 612 Ambit KinomeScan screening

[1215] This assay is an ATP-site dependent competition binding assay in which human kinases of interest are fused to a proprietary tag (T7 bacteriophage). The amount of kinase bound to an immobilized, active-site directed ligand is measured in the presence and absence of the test compound. Ambit's JAK assays use kinase domains and not full-length proteins. The domain used for JAK1 binding is the pseudo kinase domain while that for JAK3 binding is the catalytic domain (Mazen W Karaman, Sanna Herrgard, Daniel K Treiber, et. al. A Quantitative analysis of kinase inhibitotr selectivity. Nature Biotechnology, 2008, Volume 26, No. 1, Page 127-132).

Table 6b Potency and Specificity of Kinase Inhibtion (IC50 in nM)

Compound	Syk	Jak 1	Jak 2	Jak 3
P142-76 	4	No inhibition at 500nM	No inhibition at 500nM	No inhibition at 500nM
Example 87 	6	No inhibition at 300nM	No inhibition at 300nM	No inhibition at 300nM
Example 596 	43	No inhibition at 300nM	No inhibition at 300nM	No inhibition at 300nM

Example 605 JAK3/STAT6 cellular assay

[1216] Stimulation of Ramos B cells by interleukin 4 (IL4) leads to signaling through JAK1/JAK3 resulting in phosphorylation of STAT6 (signal transducers and activators of transcription). The effect of compounds on inhibition of JAK3 and/or JAK1 can be assessed by measuring the amount of phosphorylated STAT6. This is performed by Western blotting using a specific phospho-STAT6 antibody.

[1217] Ramos B cells were suspended in 10 mM Hepes-buffered RPMI media (2×10^7 cells/ml). Cells (90 µl) were incubated with 10 µl 3.3 µg/ml interleukin 4 (R & D Systems

Inc, cat # 204-IL; final concentration: 0.33 μg/ml). Incubations were for 10 min at 37° C in the absence or presence of 2 μl compound diluted in 30 % DMSO. Reactions were terminated by the addition of an equal volume of 2x lysis buffer (100 mM TRIS-HCl pH 8.0, 2 % Triton-X-100, 5 mM EDTA, 250 mM NaCl, 20 % glycerol, 1.25 mM PMSF, 5 mM sodium orthovandate, 5 mM β-glycerophosphate, mini complete EDTA protease inhibitor cocktail (Sigma)).

[1218] Samples were incubated with 1 μl of the nuclease, benzonase (Novagen, cat # 71205-3) for 1 hour, room temperature and then 50 μl 5x loading buffer (330 mM TRIS pH 6.8, 9.5 % SDS, 34 % glycerol, 0.01 % bromophenol blue, 10 % beta-mercaptoethanol) was added.

[1219] Cell lysates (15 μL) were subjected to SDS-PAGE (Novex 4-12 % TRIS-glycine gels, Invitrogen) under reducing conditions, followed by electroblot-transfer onto nitrocellulose membranes. Membranes were then incubated in Zymed blocking buffer (Invitrogen) for 1 hr at room temperature (RT) then overnight at 4° C with 1:500 anti phosphotyrosine- STAT6 (Cell Signaling Technology, cat # 9364) primary antibody in Zymed blocking buffer. Following 5 x 10 min washes with Tris-buffered saline, 0.25 % NP40 (TBSN), blots were incubated for 1 hr at room temperature in the presence of 1:10,000 HRP-conjugated donkey anti-rabbit secondary antibody (Amersham Biosciences, cat # NA934V) in Zymed blocking buffer. After 4 x 10 min TBSN washes, blots were visualized by ECL (Pierce Western Lightening, Perkin Elmer cat # NEL101). In order to determine total β3 content, blots were stripped, washed 4 x with TBSN, and re-probed with 1:2000 C3A antibody in block buffer overnight at 4° C. After 4 x 10 min TBSN washes, blots were incubated with 1:10,000 goat anti-mouse secondary antibody in blocking buffer, washed 4 more times with TBSN and exposed to Western Lightening reagent. Levels of stimulation over background and the extent of inhibition of compound were were determined by densitometry.

Example 606 Inhibition of JAK kinase activity assay for Ramos B-cell Line Stimulated with IL-4

[1220] These examples illustrate methods for evaluating the *in vitro* and *in vivo* human JAK kinase activities of the inventive compounds can be determined by various procedures known in the art, such as a test for their ability to inhibit the activity of human plasma JAK kinase. The potent affinities for human JAK kinase inhibition exhibited by the inventive

compounds can be measured by an IC_{50} value (in nM). The IC_{50} value is the concentration (in nM) of the compound required to provide 50% inhibition of human JAK kinase activity. The smaller the IC_{50} value, the more active (potent) is a compound for inhibiting JAK kinase activity.

[1221] An *in vitro* assay for detecting and measuring inhibition activity against JAK kinase is as follows:

[1222] The activity of the compounds for JAK kinases is confirmed in cellular assays designed to test for JAK inhibition. Briefly, JAK inhibition is tested in human Ramos B-cells activated with cytokine Interleukin-4 (IL-4). Twenty to 24 hours post stimulation, the cells are stained for upregulation of CD23 and analyzed by FACS. Stimulation of the B-cells with IL-4 leads to the activation of the JAK/STAT pathway through phosphorylation of the JAK kinase JAK1 and JAK3, which in turn phosphorylate and activate transcription factors STAT-5 and STAT-6. The low-affinity IgE receptor (CD23) is upregulated by activated STAT-5.

[1223] For the assay, human Ramos B-cells (ATCC, Catalog No. CRL-1596) are cultured in RPMI 1640 medium (Cellgro, Catalog No. 10-040-CM) containing 10% fetal bovine serum (JRH, Catalog No. 12106-500M) according to the propagation protocol supplied with the cells, and maintained at a density of approximately 3.5 X 10^5 cells/ml. The day before the assay, the cells are diluted to 3.5 X 10^5 cells/ml to insure they are in the logorithmic growth phase. The cells are spun down, and suspended in RPMI 1640 medium (Cellgro, MediaTech, Inc., Herndon, Va., Cat No. 10-040-CM) containing 5-10% fetal bovine serum (FBS), heat inactivated (JRH Biosciences, Inc, Lenexa, Kans., Cat No. 12106-500M) according to ATCC propagation protocol. Cells are maintained at a density of 3.5 X 10^{4-5} cells/ml. The day before the experiment, Ramos B-cells are diluted to 3.5 X 10^5 cells/mL to ensure that they are in a logarithmic growth phase and aliquots dispensed into a 96-well tissue culture plate. Cells are incubated with test compound (dissolved in DMSO) or DMSO (control) for 1 hr at 37° C. and then stimulated with IL-4 (Pepotech, Catalog No. 200-04) for 20-24 hours (final concentration is 50 Units/ml).

[1224] Cells are spun down and suspended in RPMI with 5% serum. 5X10^4 cells are used per point in a 96-well tissue culture plate. Cells are pre-incubated with compound or DMSO (Sigma-Aldrich, St. Louis, Mo., Cat No. D2650) vehicle control for 1 hour in a 37° C. incubator. Cells are then stimulated with IL-4 (Peprotech Inc., Rocky Hill, N.J., Cat No. 200-04) for a final concentration of 50 units/mL for 20-24 hours. Cells are then spun down and

stained with anti-CD23-PE(BD Pharmingen, San Diego, Calif., Cat No. 555711) and analyzed by FACS. Detection is performed using a BD LSR I System Flow Cytometer, purchased from Becton Dickinson Biosciences of San Jose, Calif.

[1225] Proliferation is measured using CellTiter-Glo.RTM. Luminescent Cell Viability Assay (Promega), which determines the number of viable cells in culture based on quantitation of the ATP present, as an indicator of metabolically active cells. The substrate is thawed and allowed to come to room temperature. After mixing the Cell Titer-Glo reagent and diluent together, 100 µL is added to each well. The plates are mixed on an orbital shaker for two minutes to induce lysis and incubated at room temperature for an additional ten minutes to allow the signal to equilibrate. Detection is performed using a Wallac Victor2 1420 multilabel counter purchased from Perkin Elmer, Shelton, Conn.

[1226] On day two, A549 cells are pre-incubated with a 2,4-pyrimidinediamine test compound or DMSO (control) (Sigma-Aldrich, St. Louis, Mo., Catalog No. D2650) for 1 hour. The cells are then stimulated with IFNγ (75 ng/mL) (Peprotech Inc., Rocky Hill, N.J., Cat. No. 300-02) and allowed to incubate for 24 hours. The final test compound dose range is 30 µM to 14 nM in 200 µL F12K media containing 5% FBS, 0.3% DMSO.

[1227] On day three, the cell media is removed and the cells are washed with 200 µL PBS (phosphate buffered saline). Each well is trypsinized to dissociate the cells, then neutralized by addition of 200 µL complete F12K media. Cells are pelleted and stained with an APC conjugated mouse anti-human ICAM-1 (CD54) (BD Pharmingen, San Diego, Calif., Catalog #559771) antibody for 20 minutes at 4° C. Cells are washed with ice cold FACS buffer (PBS+2% FBS) and surface ICAM-1 expression is analyzed by flow cytometry. Detection is performed using a BD LSR I System Flow Cytometer, purchased from BD Biosciences of San Jose, Calif. Events are gated for live scatter and the geometric mean is calculated (Becton-Dickinson CellQuest software version 3.3, Franklin Lakes, N.J.). Geometric means are plotted against the compound concentration to generate a dose response curve.

Example 607: Inhibition of Syk-mediated signal transduction through the B cell receptor in non-Hodgkin's lymphoma cell lines

[1228] Cells were pre-treated for 1 hour without or with compound (0.02 to 2uM) prior to stimulation of B cell receptor singling by incubation of cells with 3µg/ml anti-mu antibody for 10 minutes at 37°C. Ca^{2+} flux was measured using the Calcium 3 loading dye and the

FlexStation (Molecular Device). B cell receptor signaling was assayed by intracellular phospho-Flow Cytometry, following protocols supplied by BD Pharmingen (San Jose, CA). Syk activation was measured by induction of BLNK tyrosine phosphorylation at amino acid position 84 (pBLNK Y84) and induction of ERK1/2 tyrosine phosphorylation at amino acid position 204 (pERK Y204). Activation of the Src family member Lyn was measured by induction of Syk tyrosine phosphorylation at amino acid position 352 (pSyk Y352). Data are presented as μM IC_{50}s. Each compound effectively inhibited B cell receptor-induced Ca^{2+} fluxing and activation of Syk, but not the Src family member Lyn.

Table 7A:

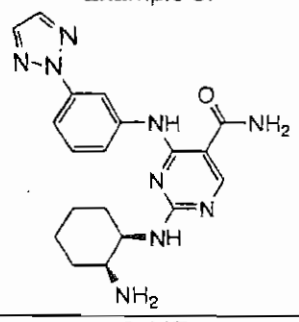
	Ramos
	Example 87 
Ca^{2+}	0.117
pBLNK Y84	0.5-0.75
pERK Y204	0.02-0.125
pSyk Y352	0.75-2

Table 7B:

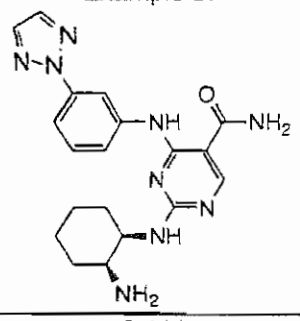
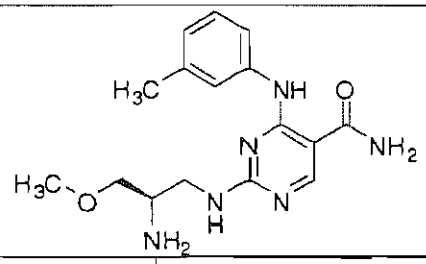
	SUDHL-6
	Example 87 
Ca^{2+}	0.111
pBLNK Y84	0.1-0.3
pERK Y204	0.1
pSyk Y352	>2

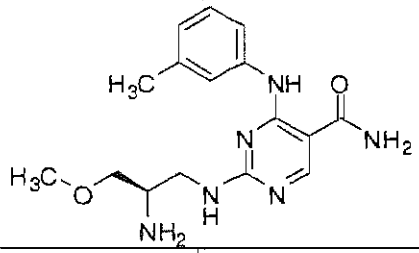
Table 7C:

Ramos
Example 596



Ca^{2+}	0.123
pBLNK Y84	0.5-0.75
pERK Y204	0.02-0.125
pSyk Y352	>2

Table 7D:

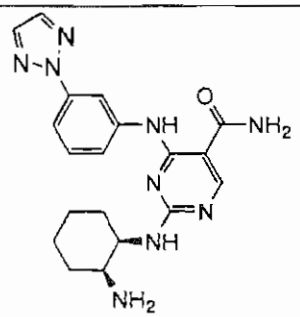
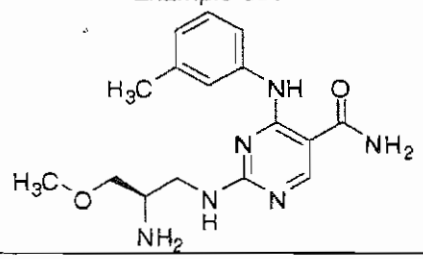
SUDHL-6	
Example 596 	
Ca^{2+}	0.057
pBLNK Y84	0.1-0.3
pERK Y204	0.1
pSyk Y352	>2

Example 608: Syk inhibition exerts an anti-proliferative effect on non-Hodgkin's lymphoma cell lines

[1229] Cells were incubated with increasing concentrations of each compound, then evaluated at 72 hours for extent of proliferation using the MTT assay (company, city, state) following the manufacturer supplied protocol. Data are presented as μM IC50 values, representing the mean plus/minus standard deviation from 5 or 6 independent experiments. Each compound inhibited proliferation of SUDHL-4 and -6 cell lines, which rely on Syk for survival and growth signals, in the low μM range. Toledo cells which do not require Syk, was noticeably less sensitive to the anti-proliferative effects of Syk inhibition.

Table 8

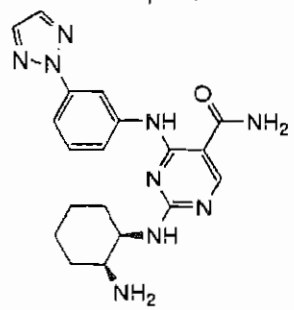
	SUDHL-4	SUDHL-6	Toledo
Example 87	1.8±0.7 (5)	1.1±0.4 (5)	9.3±4.0 (5)

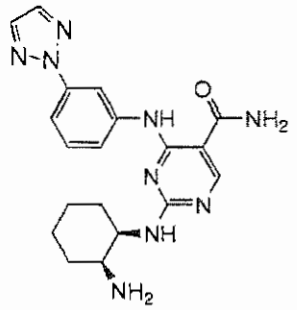
			
Example 596 	5.4±1.8 (5)	2.6±1.4 (5)	38±19 (5)

Example 609: Syk inhibition induces apoptosis in non-Hodgkin's lymphoma cell lines

[1230] Data represent two independent experiments to evaluate the effect of Syk and Syk/JAK inhibition on survival of diffuse large non-Hodgkin's lymphoma B cell lines. SUDHL-4 and SUDHL-6 cells lines rely on Syk-mediated B cell receptor signaling for survival, while Toledo cells do not. Cells were incubated with compounds at the indicated concentrations and times; induction of apoptosis was measured by flow cytometry using the Caspase 3 Detection Kit (Sigma-Aldrich, Saint Luis, MO). Data are presented as the percent of total cells positive for the apoptosis marker, caspase 3. As expected, Syk inhibition resulted in the induction of apoptosis in SUDHL-4 and -6 cell lines, but not the Toledo cell line.

Table 9A:

SUDHL-4			
Example 87 			
	24h	48h	72h
1uM	8.7	10.7	9.9
3uM	18.5	32.3	32.6
10uM	34.5	59.4	75.3

SUDHL-6			
	Example 87 		
	24h	48h	72h
1uM	11	20.2	20.4
3uM	22.5	54.9	71
10uM	12.1	27.3	38.7

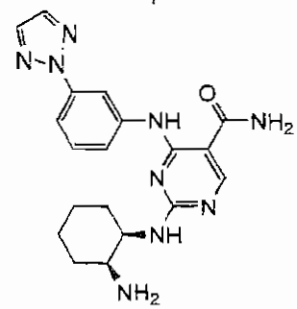
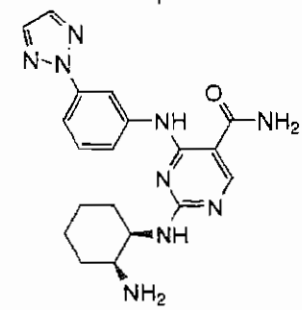
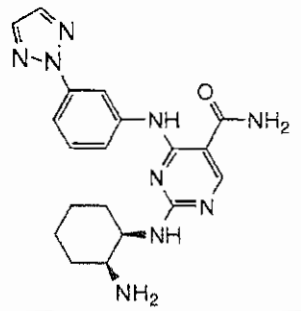
Toledo			
	Example 87 		
	24h	48h	72h
1uM	0.6	0.3	1.2
3uM	0.8	0	1.8
10uM	1	3.3	4.3

Table 9B

SUDHL-4			
	Example 87 		
	24h	48h	72h
1uM	6.6	7.2	7.6
3uM	13.6	19.7	23.4
10uM	20.4	43.9	57.4

SUDHL-6

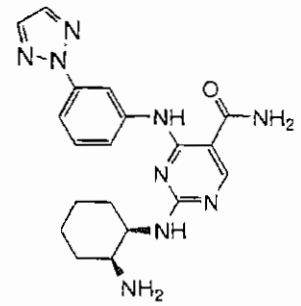
Example 87



	24h	48h	72h
1uM	12.9	21.9	15
3uM	19.9	39.5	34.6
10uM	12.5	19.9	23.5

Toledo

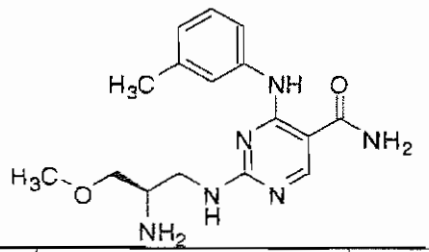
Example 87



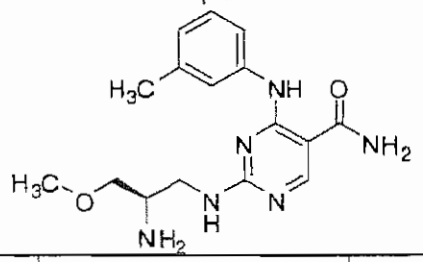
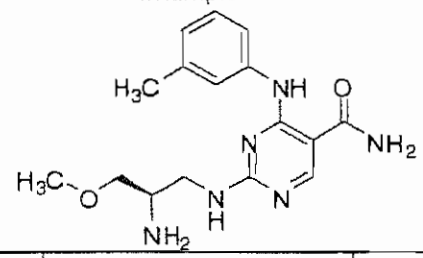
	24h	48h	72h
1uM	0	0.2	0.5
3uM	0	0.1	0.2
10uM	0	0.9	2.5

Table 9C:

EXAMPLE 596



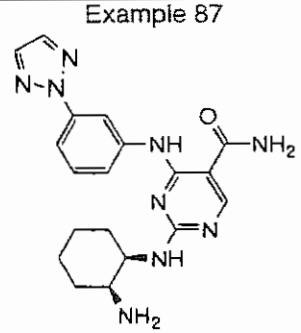
	24h	48h	72h
1uM	1.1	0.9	5.8
3uM	4.9	3.5	5.2
10uM	12.4	16.7	15.5

SUDHL-6			
	Example 596 		
	24h	48h	72h
1uM	8.3	11.6	10.6
3uM	15.1	23.7	17.8
10uM	17.8	37.3	32.4
Toledo			
	Example 596 		
	24h	48h	72h
1uM	0	0.1	0.2
3uM	0	0	0.1
10uM	0	0.2	0.7

Example 610: Inhibition of mouse primary B cell activation by Syk inhibitors

[1231] Mouse primary splenocytes were pre-treated for 1 hour with increasing concentrations of each compound (0.05-2μM) prior to addition of control or goat anti-mouse IgD serum. Anti-IgD induced B cell activation was measured 16 hours later by flow cytometry, staining for the activation markers CD80/86 and CD69. Data represent IC_{50} ranges for the inhibition of B cell activation.

Table 10:

	CD69	CD80/86
Example 87 	<0.05	0.05-0.125

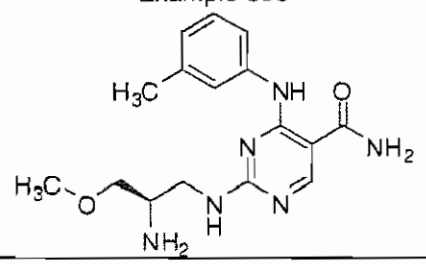
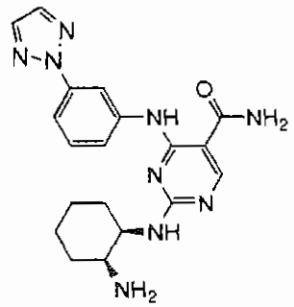
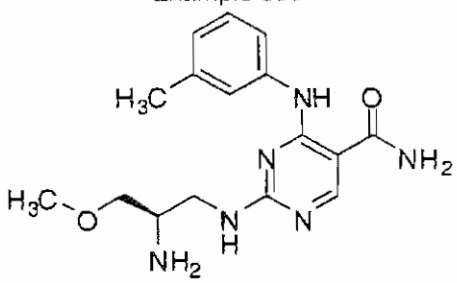
Example 596 	<0.05	0.125-0.25

Table 11:

	CD69	CD80/86
Example 87 	<0.05	0.125-0.25
Example 596 	0.125-0.25	0.125-0.25

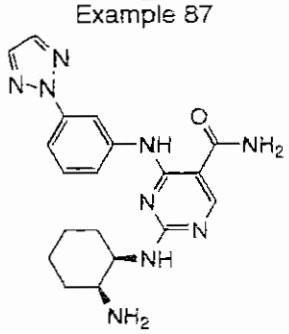
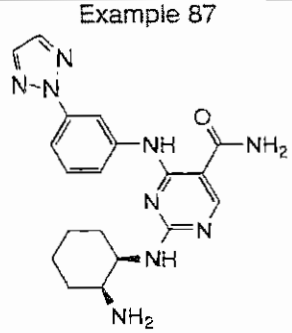
Example 611: Mouse model of immune-mediated thrombocytopenia

[1232] Immune-mediated thrombocytopenia is caused by antibodies directed against platelet surface glycoproteins, antibodies against drug-containing complexes on the platelet surface, or by antibody-coated cells or immune complexes that interact with the platelet surface. Select compounds were evaluated for their ability to inhibit platelet clearance in a mouse model of antibody-mediated thrombocytopenia. In this model, a rapid clearance of circulating platelets (approximately 50%) results from the intravenous administration of a rat anti-mouse GPIIb (clone MWReg30) antibody (BD Biosciences, Pharmingen). To evaluate capacity for inhibition of platelet clearance, compounds were suspended into 0.5% methycellulose in water and administered via oral gavage (100 ul/mouse) at a time prior to antibody injection when the compound would achieve maximum plasma concentration (typically 1 - 2 hours based on separate pharmacokinetic experiments for individual

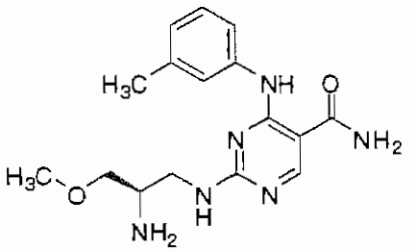
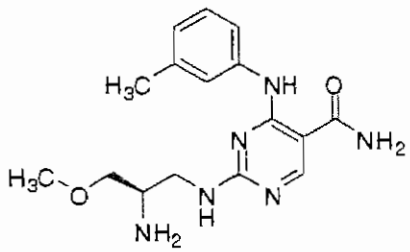
compounds). At 4 and 8 hours after injection of antibody, terminal blood samples were obtained from groups of vehicle and test article treated mice (n=5 -10 mice/group) via cardiac puncture. Blood was anticoagulated using trisodium citrate or EDTA. Whole blood samples were measured for platelet counts on a hematology analyzer (Hemavet, Drew Scientific). Remaining blood was processed for plasma and compound concentrations measured by mass spectrometry.

[1233] Platelet clearance was determined by measuring the difference in platelet number between the average non-antibody treatment group and animals administered the rat anti-mouse GPIIb antibody. Inhibition of platelet clearance was determined by comparing the difference between platelet clearance of vehicle and compound treated animals.

Table 12.

COMPOUND DOSE	AVERAGE PEAK PLASMA CONCENTRATION (μM)	AVERAGE INHIBITION OF PLATELET CLEARANCE (4 HRS)	AVERAGE INHIBITION (%) OF PLATELET CLEARANCE (8 HRS)
Example 87  30 MG/KG/DAY		27% *	12%
Example 87  10 MG/KG/DAY		7%	13%

* DENOTES STATISTICALLY SIGNIFICANT REDUCTION IN CLINICAL INFLAMMATION SCORE COMPARED TO VEHICLE CONTROL BY 2-TAILED, UNPAIRED, STUDENTS T-TEST

Compound dose	Average Peak Plasma Concentration (μM)	Average Inhibition (%) of inflammation score
Example 596  100 mg/kg/day	10.2 μM	88% *
EXAMPLE 596  30 mg/kg/day	4.4 μM	27% *

* denotes statistically significant reduction in clinical inflammation score compared to vehicle control by 2-tailed, unpaired, Students t-Test

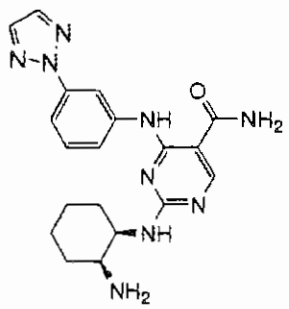
Example 612: Mouse model of collagen antibody induced arthritis

[1234] The inhibitory activity of select compounds was investigated in a mouse model of collagen antibody induced arthritis (CAIA). Collagen induced arthritis is mediated by autoantibodies to type II collagen and complement, thus arthritis can be induced by administration of polyclonal antibodies or a mixture of monoclonal antibodies to type II collagen. The CAIA model (Chondrex, Inc., Redmond, WA) uses a mixture of 4 clones which recognize individual epitopes clustered within an 83 amino acid peptide fragment of type II collagen. These epitopes share common amino acid sequences with many different species of type II collagen including chicken, mouse, rat, bovine, porcine, monkey and human. The model utilizes a monoclonal antibody cocktail followed by bacterial lipopolysaccharide (LPS) to induce a severe and consistent arthritis in mice within 7 days. This model was developed based on the hypothesis that bacterial toxins absorbed through the

gastrointestinal tract play a synergistic and pathologic role with autoantibodies to type II collagen in triggering arthritis in patients with Rheumatoid Arthritis.

[1235] For these experiments, the monoclonal antibody cocktail (Lot # OC-708) was injected intravenously via tail vein at a dose of 4 mg/mouse (40 mg/ml) on day 0 followed by intraperitoneal injection of LPS diluted into normal saline at a dose of 25 ug/mouse in 8 week old, female Balb/C mice (Charles River, Inc.). Dosing of test articles was started just before or after the IV injection of antibody cocktail. Compounds were suspended into 0.5% methylcellulose in water and administered via oral gavage (100 ul/mouse) daily for the duration of the 7 – 10 day study. Clinical inflammation scores were obtained daily. Inhibition of clinical inflammation scores was determined based on the difference between vehicle and test article treated mice at the end of the experiment. Plasma concentrations represent peak concentration at 1 hour post last dose on the day of study termination.

Table 13.

COMPOUND DOSE	AVERAGE PEAK PLASMA CONCENTRATION (μM)	AVERAGE INHIBITION (%) OF INFLAMMATION SCORE
Example 87  30 mg/kg/day	7.8 μM	44% *

* denotes statistically significant reduction in clinical inflammation score compared to vehicle control by 2-tailed, unpaired, Students t-Test

Example 613: Inhibition of IL-4 induced JAK1/3 to Stat-6 phosphorylation in Ramos B cells

[1236] Ramos B cells were pre-treated for 1 hour with increasing concentrations of compound, as indicated prior to addition of IL-4. Cells were incubated with IL-4 for 10 minutes, and then subjected to intracellular flow cytometry to measure the percent inhibition of IL-4 induced Stat-6.

Example 614: Inhibition of IL-4 induced JAK1/3 to Stat-6 phosphorylation in Ramos B cells

[1237] Ramos B cells were pre-treated for 1 hour with increasing concentrations of compound, as indicated prior to addition of IL-4. Cells were incubated with IL-4 for 10 minutes, and then subjected to intracellular flow cytometry to measure the percent inhibition of IL-4 induced Stat-6.

Example 615 Primary Human T-cell Proliferation Assay Stimulated with IL-2

[1238] Primary human T-cells derived from peripheral blood and pre-activated through stimulation of the T-cell receptor and CD28 proliferate in vitro in response to the cytokine Interleukin-2 (IL-2). This proliferative response is dependent on the activation of JAK-1 and JAK-3 tyrosine kinases, which phosphorylate and activate the transcription factor Stat-5.

[1239] Human primary T cells are prepared as follows. Whole blood is obtained from a healthy volunteer, mixed 1:1 with PBS, layered on to Ficoll Hypaque (Amersham Pharmacia Biotech, Piscataway, N.J., Catalog #17-1440-03) in 2:1 blood/PBS:ficoll ratio and centrifuged for 30 min at 4° C. at 1750 rpm. The lymphocytes at the serum: ficoll interface are recovered and washed twice with 5 volumes of PBS. The cells are resuspended in Yssel's medium (Gemini Bio-products, Woodland, Calif., Catalog #400-103) containing 40 U/mL recombinant IL2 (R and D Systems, Minneapolis, Minn., Catalog #202-IL (20 μg)) and seeded into a flask pre-coated with 1 μg/mL anti-CD3 (BD Pharmingen, San Diego, Calif., Catalog #555336) and 5 μg/mL anti-CD28 (Immunotech, Beckman Coulter of Brea Calif., Catalog #IM1376). The primary T-cells are stimulated for 3 to 4 days, then transferred to a fresh flask and maintained in RPMI with 10% FBS and 40 U/mL IL-2.

[1240] Primary T-cells are washed twice with PBS to remove the IL-2 and resuspended in Yssel's medium at 2X 10^6 cells/mL. 50 μL of cell suspension containing 80 U/mL IL-2 is added to each well of a flat bottom 96 well black plate. For the unstimulated control, IL-2 is omitted from the last column on the plate. Compounds are serially diluted in dimethyl sulfoxide (DMSO, 99.7% pure, cell culture tested, Sigma-Aldrich, St. Louis, Mo., Catalog No. D2650) from 5 mM in 3-fold dilutions and then diluted 1:250 in Yssel's medium. 50 μL of 2X compound is added per well in duplicate and the cells are allowed to proliferate for 72 hours at 37° C.

[1241] Proliferation is measured using CellTiter-Glo.RTM. Luminescent Cell Viability Assay (Promega), which determines the number of viable cells in culture based on quantitation of the ATP present, as an indicator of metabolically active cells. The substrate is

thawed and allowed to come to room temperature. After mixing the Cell Titer-Glo reagent and diluent together, 100 µL is added to each well. The plates are mixed on an orbital shaker for two minutes to induce lysis and incubated at room temperature for an additional ten minutes to allow the signal to equilibrate. Detection is performed using a Wallac Victor2 1420 multilabel counter purchased from Perkin Elmer, Shelton, Conn.

Example 616 A549 Epithelial Line Stimulated with IFNγ

[1242] A549 lung epithelial cells up-regulate ICAM-1 (CD54) surface expression in response to a variety of different stimuli. Therefore, using ICAM-1 expression as readout, compound effects on different signaling pathways can be assessed in the same cell type. IFNγ up-regulates ICAM-1 through activation of the JAK/Stat pathway. In this example, the up-regulation of ICAM-1 by IFNγ is assessed.

[1243] The A549 lung epithelial carcinoma cell line originated from the American Type Culture Collection. Routine culturing is with F12K media (Mediatech Inc., Lenexa, Kans., Cat. No. 10-025-CV) with 10% fetal bovine serum, 100 I.U. penicillin and 100 ng/mL streptomycin (complete F12k media). Cells are incubated in a humidified atmosphere of 5% CO_2 at 37° C. Prior to use in the assay, A549 cells are washed with PBS and trypsinized (Mediatech Inc., Cat. No. 25-052-CI) to lift the cells. The trypsin cell suspension is neutralized with complete F12K media and centrifuged to pellet the cells. The cell pellet is resuspended in complete F12K media at a concentration of 2.0X 10^5/mL. Cells are seeded at 20,000 per well, 100 µL total volume, in a flat bottom tissue culture plate and allowed to adhere overnight.

[1244] On day two, A549 cells are pre-incubated with a 2,4-pyrimidinediamine test compound or DMSO (control) (Sigma-Aldrich, St. Louis, Mo., Catalog No. D2650) for 1 hour. The cells are then stimulated with IFNγ (75 ng/mL) (Peprotech Inc., Rocky Hill, N.J., Cat. No. 300-02) and allowed to incubate for 24 hours. The final test compound dose range is 30 µM to 14 nM in 200 µL F12K media containing 5% FBS, 0.3% DMSO.

[1245] On day three, the cell media is removed and the cells are washed with 200 µL PBS (phosphate buffered saline). Each well is trypsinized to dissociate the cells, then neutralized by addition of 200 µL complete F12K media. Cells are pelleted and stained with an APC conjugated mouse anti-human ICAM-1 (CD54) (BD Pharmingen, San Diego, Calif., Catalog #559771) antibody for 20 minutes at 4° C. Cells are washed with ice cold FACS buffer

(PBS+2% FBS) and surface ICAM-1 expression is analyzed by flow cytometry. Detection is performed using a BD LSR I System Flow Cytometer, purchased from BD Biosciences of San Jose, Calif. Events are gated for live scatter and the geometric mean is calculated (Becton-Dickinson CellQuest software version 3.3, Franklin Lakes, N.J.). Geometric means are plotted against the compound concentration to generate a dose response curve.

Example 617 U937 IFNγICAM1 FACS Assay

[1246] U937 human monocytic cells up-regulate ICAM-1 (CD54) surface expression in response to a variety of different stimuli. Therefore, using ICAM-1 expression as readout, compound effects on different signaling pathways can be assessed in the same cell type. IFNγ up-regulates ICAM-1 through activation of the JAK/Stat pathway. In this example, the up-regulation of ICAM-1 by IFNγ is assessed.

[1247] The U937 human monocytic cell line is obtained from ATCC of Rockville, Md., catalog number CRL-1593.2, and cultured in RPMI-1640 medium containing 10% (v/v) FCS. U937 cells are grown in 10% RPMI. The cells are then plated at a concentration of 100,000 cells per 160 µL in 96 well flat bottom plates. The test compounds are then diluted as follows: 10 mM test compound is diluted 1:5 in DMSO (3 µL 10 mM test compound in 12 µL DMSO), followed by a 1:3 serial dilution of test compound in DMSO (6 µL test compound serially diluted into 12 µL DMSO to give 3-fold dilutions). Then 4 µL of test compound is transferred to 76 µL of 10% RPMI resulting in a 10X solution (100 µM test compound, 5% DMSO). For control wells, 4 µL of DMSO is diluted into 76 µL 10% RPMI.

[1248] The assay is performed in duplicate with 8 points (8 3-fold dilution concentrations from 10 µL) and with 4 wells of DMSO only (control wells) under stimulated conditions and 4 wells of DMSO only under unstimulated conditions.

[1249] The diluted compound plate is mixed 2X using a multimek (Beckman Coulter of Brea, Calif.) and then 20 µL of the diluted compounds is transferred to the 96 well plate containing 160 µL of cells, which are then mixed again twice at low speeds. The cells and compounds are then pre-incubated for 30 minutes at 37° C with 5% CO_2.

[1250] The 10X stimulation mix is made by preparing a 100 ng/mL solution of human IFNγ in 10% RPMI. The cells and compound are then stimulated with 20 µL of IFNγ stimulation mix to give a final concentration of 10 ng/mL IFNγ, 10 µM test compound, and

0.5% DMSO. The cells are kept under conditions for stimulation for 18-24 hours at 37° C with 5% CO_2.

[1251] The cells are transferred to a 96 well round bottom plate for staining and then kept on ice for the duration of the staining procedure. Cells are spun down at 1000 rpm for 5 minutes at 4° C., following which the supernatant is removed. Following removal of the supernatant, 1 µL APC conjugated mouse anti-human ICAM-1 antibody is added per 100 µL FACS buffer. The cells are then incubated on ice in the dark for 30 minutes. Following incubation, 150 µL of FACS buffer is added and the cells are centrifuged at 1000 rpm for 5 minutes at 4° C., following which the supernatant is removed. After removal of the supernatant, 200 µL of FACS buffer is added and the cells are resuspended. After suspension, the cells are centrifuged at 1000 rpm for 5 min at 4° C. Supernatant is then removed prior to resuspension of the cells in 150 µL FACS buffer.

[1252] Detection is performed using a BD LSR I System Flow Cytometer, purchased from BD Biosciences of San Jose, Calif. The live cells are gated for live scatter and the geometric mean of ICAM-APC is measured (Becton-Dickinson CellQuest software version 3.3, Franklin Lakes, N.J.). Both % live cells and ICAM-1 expression is analyzed. The assays for the test compounds is carried out in parallel with a control compound of known activity. The EC_{50} for the control compound is typically 40-100 nM.

Example 618 Analysis of B cell signaling:

[1253] The human non-Hodgkin's lymphoma B cell lines SUDHL-4 (#ACC 495), SUDHL-6 (#ACC572), and Karpas-422 (#ACC32) were obtained from DSMZ (Braunschweig, Germany); Toledo (#CRL-2631) and Ramos (#CRL-1596) were obtained from the American Type Culture Collection (ATCC; Manassas, VA). All cells were maintained in RPMI media (Invitrogen, Carlsbad, CA) supplemented with 10% fetal calf serum (ATCC) and penicillin/streptomycin (Invitrogen), and maintained in a 37°C humidified tissue culture incubator. Antibodies used in these studies include polyclonal goat F(ab)'2 anti-human IgG (H+L) and anti-human IgM (BioSource, Camarillo, CA); rabbit anti-human Syk, rabbit anti-human phospho-Syk (Y525/526), rabbit anti-human phospho- Syk (Y352), anti-human BLNK, anti-human phospho-BLNK (Y84) were obtained from Cell Signaling Technologies, Inc. (Danvers, MA). The following antibodies were obtained from Becton Dickenson (San Jose, CA) for phospho-flow cytometry: Alexa fluor 488-conjugated mouse anti-human phospho-STAT6 (Y641), Phycoerythrin (PE)-conjugated mouse anti-human

phospho-Zap70 (Y319)/Syk(Y352), and Fluorescein isothiocyanate (FITC)-conjugated mouse anti-human phospho-ERK1/2 (T202/Y204).

[1254] Phospho-flow cytometry was performed essentially as described elsewhere (Irish, Czerwinski et al. Blood 108(9): 3135-42 (2006). 0.5x106 cells in growth media were stimulated with 1μg/ml anti-μ or anti-γ antibody for 10 minutes. Induced signaling was terminated immediately following the indicated time by the addition of paraformaldehyde (Electron Microscopy Sciences, Hatfield, PA) to a final concentration of 1%. Cells were incubated with paraformaldehyde for 5 minutes at room temperature, washed once with phosphate buffered saline (PBS), then resuspended and incubated overnight at 4°C in pre-chilled methanol (-80°C) (company, address). Fixed and permeablized cells were subsequently washed once in PBS, a second time in PBS containing 1% bovine serum albumin (BSA) (Sigma-Aldrich, St. Louis, MO), and then stained with the indicated antibodies diluted 1:20 in PBS + 1% BSA. After 30 minutes, cells were washed once in PBS and subjected to flow cytometry using the FACS Calibur (Becton Dickenson). For Western blot analyses, 106 cells were stimulated for 30 minutes with 2μg/ml of the indicated BCR-specific antibodies. Signaling was terminated by resuspending the cells in lysis buffer and incubated on ice for 1 hour. Cell debris were removed by centrifugation, and the cleared protein lysates were resolved by 10% SDS-PAGE and probed with the indicated antibodies following recommendations made by the manufacturers. Where indicated, cells were pre-treated for 1 hour at 37°C with Syk inhibitors or vehicle control (0.5% DMSO) at several concentrations prior to stimulation with anti-BCR antibody.

Example 619 Selective inhibition of Syk activity.

[1255] Compounds were tested for their ability to inhibit purified Syk. example 596 and example **87** (two compounds from a Syk-specific series as shown in **Table 1b**) and P420-89 (from a series with dual Syk and JAK inhibitory activities) were found to suppress Syk kinase activity with IC50s of 43nM, 6nM, and 31nM, respectively. The selectivity of these compounds for Syk was determined by screening each against a panel of 270 independent purified kinases at 300nM (Millipore). The percent inhibition relative to vehicle control was calculated, and the numbers were converted into a heat-map; no inhibition is represented as green, increasing blending with red indicates increasing percent inhibition with yellow representing 50% inhibition and red representing 100% inhibition (**Figure 9**). As depicted in **Figure 9A**, example 596 and example 87 were highly Syk specific (first and second rows,

respectively) whereas P420-89 inhibited multiple kinases (third row). The subset of kinases that were inhibited by ≥80% by any of the three compounds are shown in Figure 9B. example 596 inhibited Syk and MLK-1 (first row). At 300nM example **87** inhibited 10 different kinases (second row). When re-tested at 50nM (approximately 10x above its Syk IC50 value of 6nM), however, Syk was the only kinase that remained inhibited (third row). P420-89 inhibited Syk, JAK2 and JAK3, along with several other kinases (fourth row).

[1256] Employing the Milipore panel of purified kinases EXAMPLE 87 (IC_{50} = 1nM) inhibited 98% of purified Syk kinase activity at 50nM. IC50 values were determined for those kinases that were inhibited by >80% at 300nM in the Millipore kinase panel.

Kinase	IC50 (nM)
Syk(h)	1
MLK1	60
Fgr(h)	81
Yes(h)	123
Flt3(h)	139
PAK5	166
Lyn(h)	199
cSRC(h)	244
Lck(h)	300

[1257] By contrast, multi-kinase inhibitor P420-89 is more akin to Rigel's R788. At 300nM, P420-89 inhibited Syk by 88%, along with >80% inhibition of 32 additional kinases. Among these were JAK 2 and 3 (93% and 85% inhibited, respectively), Flt-3 (83-92% inhibited), and cKit (95-97% inhibited), all targets for therapeutic manipulation of lymphocyte function.

Example 620 Calcium flux assay and Selective inhibition of Syk in non-Hodgkin's lymphoma B cell lines.

[1258] Ramos cells were cultured (maintaining approximately 0.5 x106 cells/ml) in growth medium 3 to 4 days ahead of experiments. Cells were harvested and re-suspended in fresh medium at 8x106 cells/ml before dye-loading. An equal volume of Calcium 3 loading dye (Molecular Device, Sunneyvale, CA) was added to the cell suspensions. Loaded cells were dispensed in a 96 well plate and incubated for 20 minutes. Syk inhibitors were then added to

the loaded cells and incubated for another 30 minutes. B cells were stimulated with 5μg/ml anti-μ antibody. Changes in intracellular $Ca2^+$ concentration was measured using the FlexSTATion (Molecular Devices, Sunnyvale, CA).

[1259] The selectivity and potency of Syk inhibition in B cells was initially interrogated by Western blot, measuring BCR-mediated induction of pSyk Y525/526 and pBLNK Y84, both measures of Syk kinase activity, and the induction of pSyk Y352, a measure of Src kinase activity. SUDHL-6 B cells were stimulated with anti-BCR specific antibody for 30 minutes in the presence or absence of each Syk inhibitor or vehicle control. Treatment with 0.16 or 1μM of each compound reduced BCR-induced Syk autophorphorylation (Y525/526) by roughly 40% and 60%, respectively, as estimated by densitometry (data not shown). An expanded range of concentrations was used to further evaluate the effect of these compounds on BCR induced Syk and Src kinase activity. As shown in **Figure 10, A-C**, each compound inhibited Syk activity (pBLNK Y84) with IC50 values ranging from 0.16 to 1μM, while no effect on Src activity (pSyk Y352) was observed as high as 2.5μM.

[1260] The ability of each compound to suppress signaling events more distal to the BCR was also measured. Cells were again stimulated by anti-BCR antibody in the presence or absence of various concentrations of each Syk inhibitor. The induction of pSyk Y352 was measured as a specificity control, while that of pERK1/2/Y204 was used as a measure of more distal Syk-dependent signaling (Jiang, Craxton et al. J Exp Med 188(7): 1297-306 (1998). **Figure 13C** shows representative FACS plots depicting the effect of the most specific and potent Syk inhibitor of the three, example 87, on BCR signaling. At 125nM, ERK1/2 activation was completely suppressed, whereas the stimulated cells still stained positive for Syk Y352. This experiment was repeated, in which the effect of all three compounds on Src and Syk activity were determined (**Figure 11A**). Concentrations of less than 125nM were sufficient to suppress BCR induced Syk signaling to ERK1/2. By contrast, much higher concentrations were required to cause a modest suppression of Src activity; an effect on Src that was not observed by Western blot (**Figure 10, A-C**). None of these Syk inhibitors suppressed PMA-induced ERK1/2 tyrosine phosphorylation, demonstrating these compounds do not inhibit signaling events down-stream of PKC.

[1261] Whereas example 596 and example 87 specifically inhibited Syk in purified and cellular assays, **P420-89** additionally demonstrated activity against purified JAK kinases. These compounds were tested for inhibition of IL-4 signaling to STAT-6 via JAK1/3 in B

cells, a signaling pathway that does not require Syk. The Syk specific compounds did not suppress IL4 signaling at concentrations as high as 2μM. Conversely, **P420-89** did suppress IL4 signaling, with an IC50 around 125nM (**Figure 11B**).

[1262] This shows that selective inhibition of Syk suppressed BCR-induced Ca2+ flux in B cells with IC50 values around 100nM. This suggests that by inhibiting Syk, these compounds suppress the signaling pathway, blocking the cellular response.

[1263] Selective inhibition of Syk is sufficient to suppress BCR signaling without affecting Src (**Figures 10, 11 and 13**) or JAK (**Figure 11B**). example 87, suppressed proliferation of NHL cell lines with equal potency to the multi-kinase inhibitor, P420-89 (**Table, Figure 18C**). Additionally, example 87 and P420-89 equally induced apoptosis in these cells (**Figure 12B**). This data demonstrates the role of Syk signaling in the survival of NHL cell lines, and demonstrates that inhibition of kinases other than Syk is not required to achieve this effect.

Example 621 Caspase 3 and proliferation assays: Syk Inhibition Disrupts Proliferation and Survival of non-Hodgkin's Lymphoma B Cell Lines.

[1264] Induction of apoptosis was measured using the PE-conjugated monoclonal active caspase-3 antibody apoptosis kit (Becton Dickenson) following the supplied protocol. Cells were suspended in growth media (0.5x106 cells/ml) and treated with the indicated concentrations of each Syk inhibitor or vehicle control for 24, 48, or 72 hours prior to FACS analysis. The MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole) assay (company name) was used as a measure of cell viability and growth, following protocols supplied by the manufacturer. Cells were treated with the indicated concentrations of each Syk inhibitor or vehicle control for 72 hours.

[1265] SUDHL-4 and SUDHL-6 cells were previously classified as "BCR-type" (Monti, Savage et al. Blood 105(5): 1851-61 (2005); Polo, Juszczynski et al. Proc Natl Acad Sci U S A 104(9): 3207-12 (2007) and sensitive to Syk inhibition by R406 (Chen, Monti et al. 2008). The Toledo and Karpas-422 cell lines that lack BCR and BLNK expression, respectively (Gabay, Ben-Bassat et al. Eur J Haematol 63(3): 180-91 (1999); Sprangers, Feldhahn et al. Oncogene 25(36): 5056-62 (2006), having therefore adapted to survive independent of BCR signals, were insensitive to R406 (Chen, Monti et al. 2008). The proliferation of these cell lines when cultured in the presence or absence of various concentrations of each Syk inhibitor for 72 hours was tested. As presented in the Table in **Figure 18C**, each compound

suppressed proliferation of the Syk-dependent SUDHL cell lines with IC50 values in the low μM range. Toledo cells required much higher concentrations to affect proliferation. Dual suppression of Syk and JAK kinases by P420-89 did not appear to have a greater anti-proliferative effect relative to Syk inhibition alone.

[1266] Selective inhibition of Syk was sufficient to induce apoptosis in "BCR-type" NHL cell lines. Cells were incubated with 1 or 3μM of the Syk specific inhibitor example 87 for 72h. As demonstrated in **Figure 12A**, SUDHL-4 and -6 cells each underwent apoptosis, whereas the Toledo and Karpas-422 cells did not (**Figure 12A**). In replicate experiments, the specific inhibition of Syk by example 596 and example 87 induced apoptosis only in the SUDHL and Ramos cell lines. By comparison, P420-89, which potently inhibits Syk and JAK kinases, induced apoptosis in all the "BCR-type" cell lines, as well as in Karpas-422 and JJN-3, a multiple myeloma cell line that lacks BCR, and BLNK expression (Sprangers, Feldhahn et al. Oncogene 25(36): 5056-62 (2006). The Toledo cells remained insensitive to all three compounds (**Figure 12B**). In a separate experiment, the SUDHL-6 and Toledo cells were found to be equally sensitive to induction of apoptosis by 72h treatment with 1μM PMA. These data demonstrate the specific requirement of Syk in the survival of certain NHL cell lines.

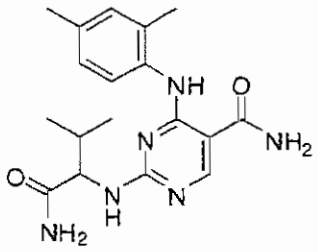
Example 622 Xenograft studies and Tumor and plasma concentration analysis.

[1267] Syk Inhibition Protects Against Tumor Formation in a Xenograft Mouse Model. Mice were received (company) and acclimated in-house at least three days prior to use. Ramos cells (3x106) were injected subcutaneously into the hind flank area of conscious mice using a 27 gauge needle in an injection volume of less than 0.5ml. Following injection, mice were randomized into treatment groups (n = 15) and dosed twice daily by oral gavage with vehicle or 10, 15, or 20mg/kg of the Syk inhibitor example 87. Body weights were obtained at least once per week and caliper measurements of tumors were determined twice per week beginning when palpable tumorrs were formed until the end of the study. Tumor volume was assessed by caliper measurement using a formula [maximum length x width x height x $\pi/6$]. Twice daily dosing of vehicle or example 87 continued until the vehicle or any treatment group exhibited tumors that exceeded 1.5 grams in size. At the time of termination (5 weeks post Ramos innoculation) the mice were anesthetized with a ketamine cocktail. A blood sample was obtained for CBC and plasma concentration determination via cardiac puncture and the mice were euthanized via cervical dislocation. Tumors were then be excised and

weighed. One half of the tumor was snap frozen in liquid nitrogen for determination of concentration of example 87 in the tumor tissue and the other half was placed in 10% buffered formalin for histological investigation.

[1268] The effect of Syk inhibition on Ramos tumor formation in a xenograft mouse model was assessed. Mice were dosed twice daily with 10, 15, or 20mg/kg example 87 or vehicle control beginning the day of tumor cell inoculation. Caliper measurements were initiated when tumors began to form, approximately thee weeks post-tumor inoculation, and repeated every third day until termination of the study. The study was terminated when tumor weights began reaching approximately 1.5mg, at which time tumors were excised and weighed. Tumor and plasma samples were subjected to pharmacokinetic analysis.

[1269] Each tumor sample was homogenized in 3 ml of saline per gram of tumor using the Kontes® Microtube Pellet Pestle® Rods and Motor (Kimble Chase, Vineland, NJ). Plasma and tumor samples were analyzed for example 87 concentration using a liquid chromatography tandem mass spectrometer (LC/MS/MS). In brief, plasma and tumor samples were processed in a 96-well Captiva™ filter plate (0.2 μm, Varian, Inc., Palo Alto, CA). Aliquots of plasma and homogenized tumor samples were precipitated with acetonitrile containing 200 ng/mL of:



Compound A,

the internal standard. The mixture was vortexed and refrigerated at 4°C for 30 minutes to allow complete protein precipitation. The mixture was filtered into a 96-well collection plate. The filtrate was injected onto a Sciex API3000 LC/MS/MS equipped with a turbo-ion spray source. example 87 and Compound A were separated on a Phenomenex Luna 5μ HILIC column (4.6 x 100 mm, 5mm; Phenomenex, Torrance, CA). A mobile phase gradient mixture of 10% mobile phase A (0.1% formic acid in water) and 90% mobile phase B (0.1% formic acid in 90% acetonitrile, 10% water) to 65% mobile phase B was programmed over 1.1 minutes followed by a gradient of mobile phase B from 65% to 90% over 0.01 minutes.

The peak areas of the m/z 394/360 product ion of example 87 were measured against those of the m/z 357/295 product ion of Compound A (internal standard) in positive ion mode. The analytical range was 2 to 5000 ng/ml.

[1270] Pharmacokinetic analysis revealed that at steady-state, tumor concentrations of example 87 followed the concentration-time profiles seen with plasma in the 10, 15, and 20 mg/kg dose groups. Nonlinear increases in Cmax, AUC (0-8), and tumor Cmin were observed as the dose was increased, but a dose-proportional increase in plasma Cmin was noted. Mean Cmax and AUC (0-8) in plasma was at least 2-fold greater than that in tumor for all doses examined; however, mean nadir concentrations (Cmin) were higher in tumor than in plasma (**Table 14A**), indicating accumulation of example 87 in the tumor compartment.

Table 14A

Determined from plasma

Dosing regiment	Tmax (hr)	Cmin (ng/mL)	Cmax (ng/mL)	AUC (0-8) (ng*hr/mL)
10 mg/kg BID	1.50	17.6	179	738
15 mg/kg BID	1.50	26.6	343	1671
20 mg/kg BID	4.00	39.5	570	3191

Determined from tumor

Dosing regiment	Tmax (hr)	Cmin (ng/mL)	Cmax (ng/mL)	AUC (0-8) (ng*hr/mL)
10 mg/kg BID	8.00	24.5	55.2	353
15 mg/kg BID*	4.00	67.8	163	475
20 mg/kg BID	4.00	125	252	1453

Table 14B

Dosing regimen	tumor/plasma ratio		
	AUC based	Cmax based	Cmin based
10 mg/kg BID	0.478	0.308	1.39
15 mg/kg BID*	0.284	0.475	2.55
20 mg/kg BID	0.455	0.442	3.15

Note: Nadir (0), 1.5, 4, and 8h samples were taken on the da of harvest following the AM dose. The second dose was not administered on the day of harvest; therefore, pharmacokinetic values above were determined after a single AM dose at steady-state.

*Only one tumor sample was available for the 8h time-point and may have been an outlier (tumor concentrations at 8h - 608ng/ml); therefore, pharmacokinetic parameters were determined between 0 to 4h for the 15mg/kg BID EXAMPLE 87 dose group. As a result, AUC (0-8) and AUC based tumor/plamsa ration for this dose group may be underestimated.

The difference between plasma and tumor C_{min} became more prominent as the dose was increased, as indicated by the increase in tumor/plasma ratios determined from C_{min} (**Table 14B**). Tumor/plasma ratios determined from C_{max} and AUC (0-8) were similar across the various dose groups. Tumor concentrations were sustained above 60, 170, and 640nM over the entire dosing interval at steady-state for example 87 at 10, 15, and 20 mg/kg, respectively.

[1271] Mice dosed with all three concentrations of example 87 were protected from Ramos tumor growth in vivo. This was first evident from caliper measurements (data not shown), which revealed a reduced rate of tumor growth in the presence of the Syk inhibitor. Upon study completion, mice were euthanized and tumors excised and weighed; data presented in **Figure 18A**. Consistent with caliper measurements, a statistically significant reduction in average tumor weight was achieved in all dosing groups, relative to vehicle control. These data reveal that sub-micromolar concentrations of example 87 can prevent tumor formation by an aggressive NHL cell line in mice.

[1272] Mice dosed with the Syk inhibitor did not present with reduced numbers in any subset of white blood cells. In fact, the only effect observed was an increase in the number of lymphocytes in mice treated with 15mg/kg example 87, which was not repeated in mice dosed with 10 or 20mg/kg (**Figure 18B**). The relative percent of each cell subtype analyzed was also unaffected by the Syk inhibitor (data not shown). On average, mice treated with vehicle control had a 9.45% increase in body weight. Mice treated with 10, 15, and 20mg/kg example 87, on the other hand, had on average 0.27% increase, 1.67% decrease, and 2.27% decrease in body weight, respectively, over the course of the study. There was no relationship, however, between % change in body weight and tumor growth ($R2 = 0.27$). These data suggest that the inhibition of tumor growth was indeed mediated by suppression of Syk activity.

[1273] The Syk-specific inhibitor example 87 was also tested for activity in a Ramos tumor mouse xenograft model. At all the concentrations tested, statistically significant reductions in tumor growth were observed in mice dosed BID with example 87. The lowest concentration tested was 10mg/kg, achieving tumor concentrations ranging from 64 to 140nM over the course of the day. Suppression of tumor growth at these concentrations *in vivo* is consistent with concentrations of <125nM found to suppress BCR-induced Ca2+ flux and distal BCR signaling to pERK Y204 (**Figures 11 and 13**). The selective pharmacological inhibition of Syk results in effects on the proliferations and survival of NHL cell lines. These data

suggest that the selective targeting of Syk may similarly have clinical benefit in a variety of B-cell proliferative disorders.

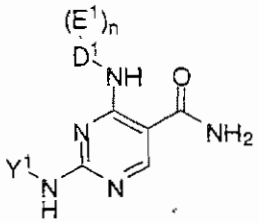
[1274] As detailed herein, Syk has been implicated experimentally in B cell development, proliferation, and survival. Moreover, Syk is implicated as an oncogene. Expression of constitutively active Syk in adoptively transferred bone marrow cells induces leukemia in mice, and over-activity of Syk is associated with a variety of lymphomas in humans Given the role of Syk in B cell biology, its selective inhibition may be sufficient to provide clinical benefit in B cell proliferative disorders, while reducing toxicities that may arise due to suppression of other off-target kinases.

[1275] The present invention provides a number of embodiments. It is apparent that the examples may be altered to provide other embodiments of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments, which have been represented by way of example.

[1276] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety. From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

WHAT IS CLAIMED IS:

1. A compound having formula (I):

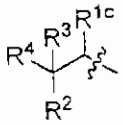


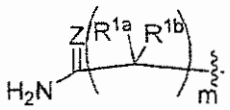
(I)

or a tautomer thereof or a pharmaceutically acceptable salt thereof,

wherein:

Y^1 is selected from the group consisting of:



and  ;

Z is O or S;

D^1 is selected from the group consisting of:

(a) phenyl substituted with a group, R^5, wherein the phenyl is further optionally substituted with from 1 to 2 substituents, R^{7a}, independently selected from the group consisting of $C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkoxy, halo, $C_{1\text{-}8}$alkylsulfonyl and heterocyclyl;

R^5 is selected from the group consisting of:

(i) heteroaryl;

(ii) heterocyclyl;

(iii) $C_{1\text{-}8}$alkyleneheterocyclyl;

(iv) phenyleneheteroaryl

(v) phenyleneheterocyclyl

(vi) –L-phenyl;

(vii) –L-heterocyclyl; and

(viii) acetoxy;

L is selected from the group consisting of –CO-, -O-, $-SO_2-$, -CONH- and –$CONHCH_2$-;

each R^5 is optionally further substituted with from 1 to 2 substituents independently selected from the group consisting of C_{1-8}alkyl, hydroxyC_{1-8}alkyl-, aminoC_{1-8}alkyl, C_{1-8}alkylamino, C_{1-8}alkylcarbonyl, aminocarbonyl, cyano, hydroxy, oxo, halo, haloC_{1-8}alkyl, aminosulfonyl, C_{3-8}cycloalkyl and aryl;

(b) naphthyl substituted a substituent , R^{7b}, selected from the group consisting of halogen, C_{1-8}alkylcarbonyl, C_{1-8}alkylsulfonyl, aminosulfonyl, heterocyclylcarbonyl and aminocarbonyl;

(c) C_{3-8}cycloalkyl, optionally substituted with from 1 to 2 substituents, R^{7c}, independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, halo, C_{1-8}alkylsulfonyl and heterocyclyl;

(d) heteroaryl; optionally substituted with from 1 to 2 substituents, R^{7d}, independently selected from the group consisting of: C_{1-8} alkyl, amino, hydroxyl, oxo, halo, C_{1-8} alkoxy, hydroxyC_{1-8}alkyl-, aminoC_{1-8}alkyl, C_{1-8}alkylcarbonyl, haloC_{1-8}alkyl, C_{3-8}cycloalkyl, C_{1-8}aminocycloalkyl, aminoC_{1-8}alkylenecarbonyl, aminocarbonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenecarbonyl, C_{1-8}alkoxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkoxycarbonyl, C_{1-8} alkoxycarbonylamino, aryl, arylC_{1-8} alkoxycarbonylamino, C_{1-8}alkylsulfonyl, aminoC_{1-8}alkylenesulfonyl, aminosulfonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenesulfonyl, C_{1-8}alkoxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkoxysulfonyl, aminosulfonyl, and C_{1-8}alkylheterocyclyl; and

(e) heterocyclyl; with from 1 to 2 substituents, R^{7e}, independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, halo, C_{1-8}alkylsulfonyl and heterocyclyl;

each E^1 is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, C_{1-8}alkylthio, aminocarbonyl, C_{1-8}alkoxycarbonylC_{1-8}alkylene, C_{1-8}alkoxycarbonyl$C_{1-8}C_{1-8}$alkoxy, C_{1-8}alkoxycarbonylamino, oxo, halo, cyano, haloC_{1-8}alkyl, haloC_{1-8}alkoxy, aminosulfonyl, heteroarylsulfinyl; amino, hydroxyl, C_{1-8}arylalkylene, phenyl, aminoC_{1-8}alkyl, aminoC_{3-8}cycloalkyl, heterocyclyl, heteroaryl and heterocyclylC_{1-8}alkylene;

each R^{1a}, R^{1b} and R^{1c} is independently selected from the group consisting of: H, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, C_{1-8}haloalkyl, amino, C_{1-8}alkylamino, C_{1-8} alkoxycarbonylaminoC_{1-8} alkylene, C_{3-8}cycloalkyl, heteroaryl, C_{1-8} alkylC_{3-8}cycloalkyl, C_{1-8}alkylthioC_{1-8} alkyl, C_{1-8}alkylsulfonylC_{1-8} alkylene, aminocarbonyl, C_{1-8}alkoxyC_{1-8}alkyl, haloC_{1-8}alkyl, aryl and heterocyclyl; wherein the aryl is optionally substituted by hydroxyl, C_{1-8}alkoxy, halo or haloC_{1-8}alkyl; or taken together with R^3 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or hetercycloalkyl ring;

R^2 is selected from the group consisting of H, amino, C_{1-8}alkylamino, hydroxycarbonylamino C_{1-8}alkoxycarbonylamino ,arylC_{1-8}alkoxycarbonylamino and hydroxyl;

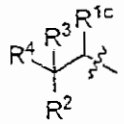
R^3 is selected from the group consisting of H, C_{1-8}alkyl, C_{1-8}alkylamino, amino aminoC_{1-8}alkyl, carboxy, C_{1-8}alkylaminoC_{1-8}alkyl, C_{1-8}alkoxyC_{1-8}alkyl, hydroxyC_{1-8}alkyl; carboxyC_{1-8}alkyl, C_{3-8}cycloalkylC_{1-8}alkyl, aryloxyC_{1-8}alkyl, arylC_{1-8}alkyl, heteroarylC_{1-8}alkyl, and hydroxyC_{1-8}alkoxy and hydroxyC_{1-8}alkoxy; or may be combined with R^{1c} or R^4 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring;

R^4 is H or alkyl or may be combined with R^3 and the atoms to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring;

the subscript n is 0, 1, 2, 3 or 4; and

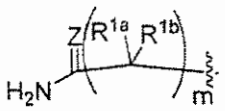
the subscript m is an integer of 1, 2 or 3; and the wavy line indicates the point of attachment to the rest of the molecule.

2. The compound of claim 1 wherein Y^1 is:



.

3. The compound of claim 1 wherein Y^1 is:



.

4. The compound of any of the preceding claims wherein Z is S.

5. The compound of any of the preceding claims wherein Z is O.

6. The compound of any of claims 1 to 3 wherein Z is S.

7. The compound of any of the preceding claims wherein D^1 is phenyl.

8. The compound of claim 7, wherein R^5 is heteroaryl.

9. The compound of claim 7, wherein R^5 is heterocyclyl.

10. The compound of claim 7, wherein R^5 is C_{1-8}alkyleneheterocyclyl.

11. The compound of claim 7, wherein R^5 is phenyleneheteroaryl.

12. The compound of claim 7, wherein R^5 is phenyleneheterocyclyl.

13. The compound of claim 7, wherein R^5 is –L-phenyl.

14. The compound of claim 7, wherein R^5 is–L-heterocyclyl.

15. The compound of claim 13 or 14, wherein L is –CO-.

16. The compound of claim 13 or 14, wherein L is -O-.

17. The compound of claim 13 or 14, wherein L is -SO_2-.

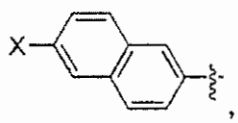
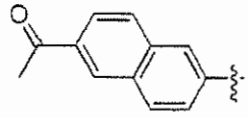
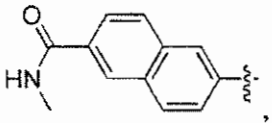
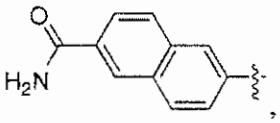
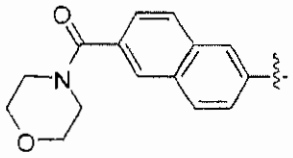
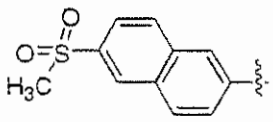
18. The compound of claim 13 or 14, wherein L is -CONH-.

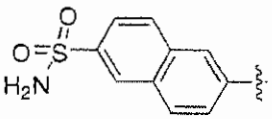
19. The compound of claim 13 or 14, wherein L is –$CONHCH_2$-.

20. The compound of claim 7, wherein R^5 is acetoxy.

21. The compound of any of claims 1 to 3 wherein D^1 is naphthyl.

22. A compound f any of claims 1 to 3, wherein D^1- is selected from the group consisting of:







and


; and

X is halogen.

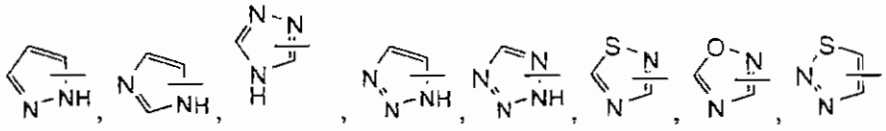
23. The compound of any of claims 1 to 3 wherein D^1 is $C_{3\,8}$cycloalkyl.

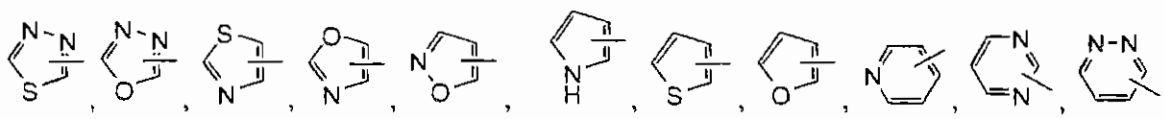
24. The compound of claim 1 to 3, wherein D^1 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

25. The compound of any of claims 1 to 3 wherein D^1 is heteroaryl.

26. The compound of any of claims 1 to 3 wherein D^1 is heterocyclyl.

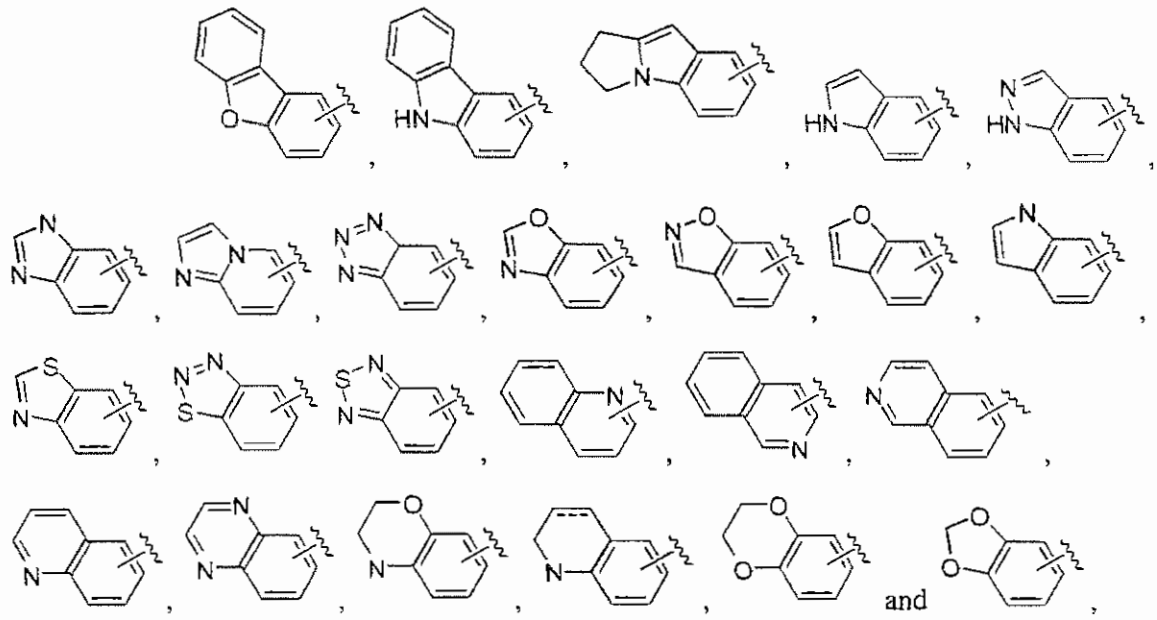
27. The compound of any of the preceding claims wherein the heteroaryl group, alone or when part of a group containing a heteroaryl moiety is selected from the group consisting of:





and  ; each of which is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of: C_{1-8} alkyl, amino, hydroxyl, oxo, halo, C_{1-8} alkoxy, hydroxyC_{1-8}alkyl-, aminoC_{1-8}alkyl, C_{1-8}alkylcarbonyl, haloC_{1-8}alkyl, C_{3-8}cycloalkyl, C_{1-8}aminocycloalkyl, aminoC_{1-8}alkylenecarbonyl, aminocarbonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenecarbonyl, C_{1-8}alkoxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkoxycarbonyl, C_{1-8} alkoxycarbonylamino, aryl, arylC_{1-8} alkoxycarbonylamino, C_{1-8}alkylsulfonyl, aminoC_{1-8}alkylenesulfonyl, aminosulfonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenesulfonyl, C_{1-8}alkoxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkoxysulfonyl, aminosulfonyl, and C_{1-8}alkylheterocyclyl.

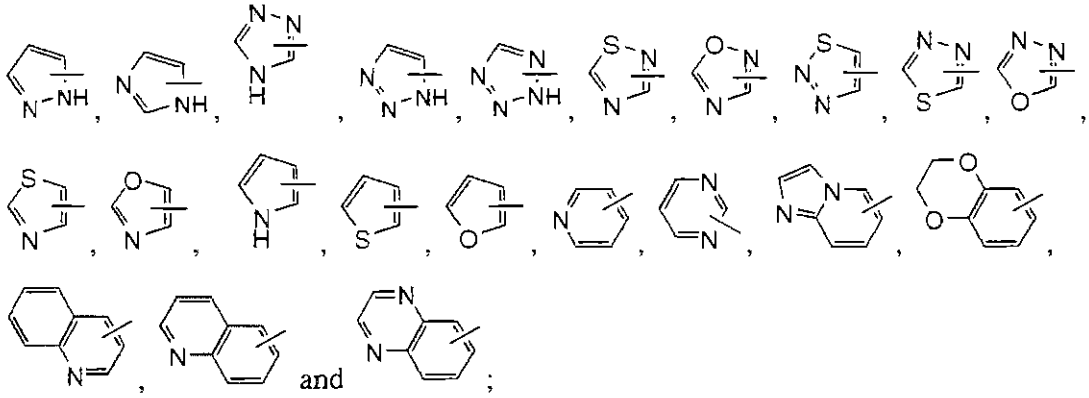
28. The compound of any of the preceding claims wherein the heteroaryl group, alone or when part of a group containing a heteroaryl moiety is selected from the group consisting of:



optionally substituted with from 1 to 3 R^{7d} substituents independently selected from the group consisting of: C_{1-8} alkyl, C_{1-8}alkylcarbonyl, C_{1-8}aminocycloalkyl, aminoC_{1-8}alkylenecarbonyl, aminocarbonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenecarbonyl, C_{1-8}alkoxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkoxycarbonyl, aminocarbonyl, amino, C_{1-8} alkoxycarbonylamino, aryl, arylC_{1-8} alkoxycarbonylamino, hydroxyl, C_{1-8} alkoxy, C_{1-8}alkylsulfonyl, aminoC_{1-8}alkylenesulfonyl, aminosulfonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenesulfonyl, C_{1-8}alkoxyC_{1-8}alkylenesulfonyl,

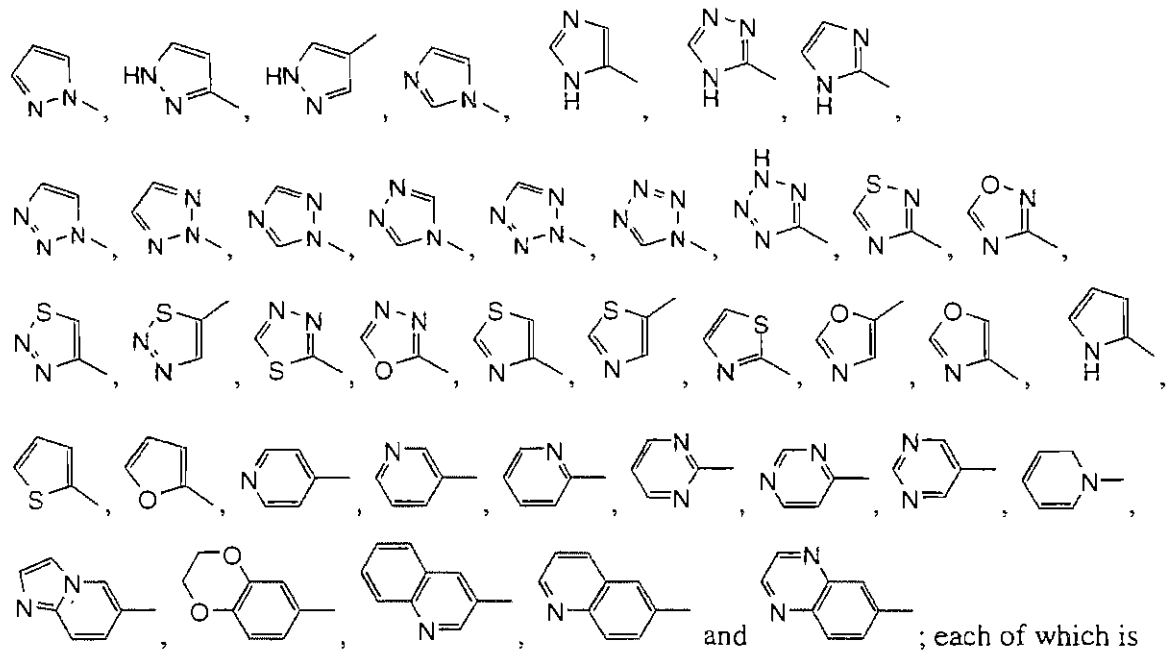
hydroxy$C_{1\text{-}8}$alkylenesulfonyl, hydroxy$C_{1\text{-}8}$alkoxysulfonyl, aminosulfonyl, oxo, halo, phenyl and $C_{1\text{-}8}$alkylheterocyclyl; and the wavy line indicates the point of attachment to the rest of the molecule.

29. A compound of any of claims 1 to 3, wherein R^5 is selected from the group consisting of



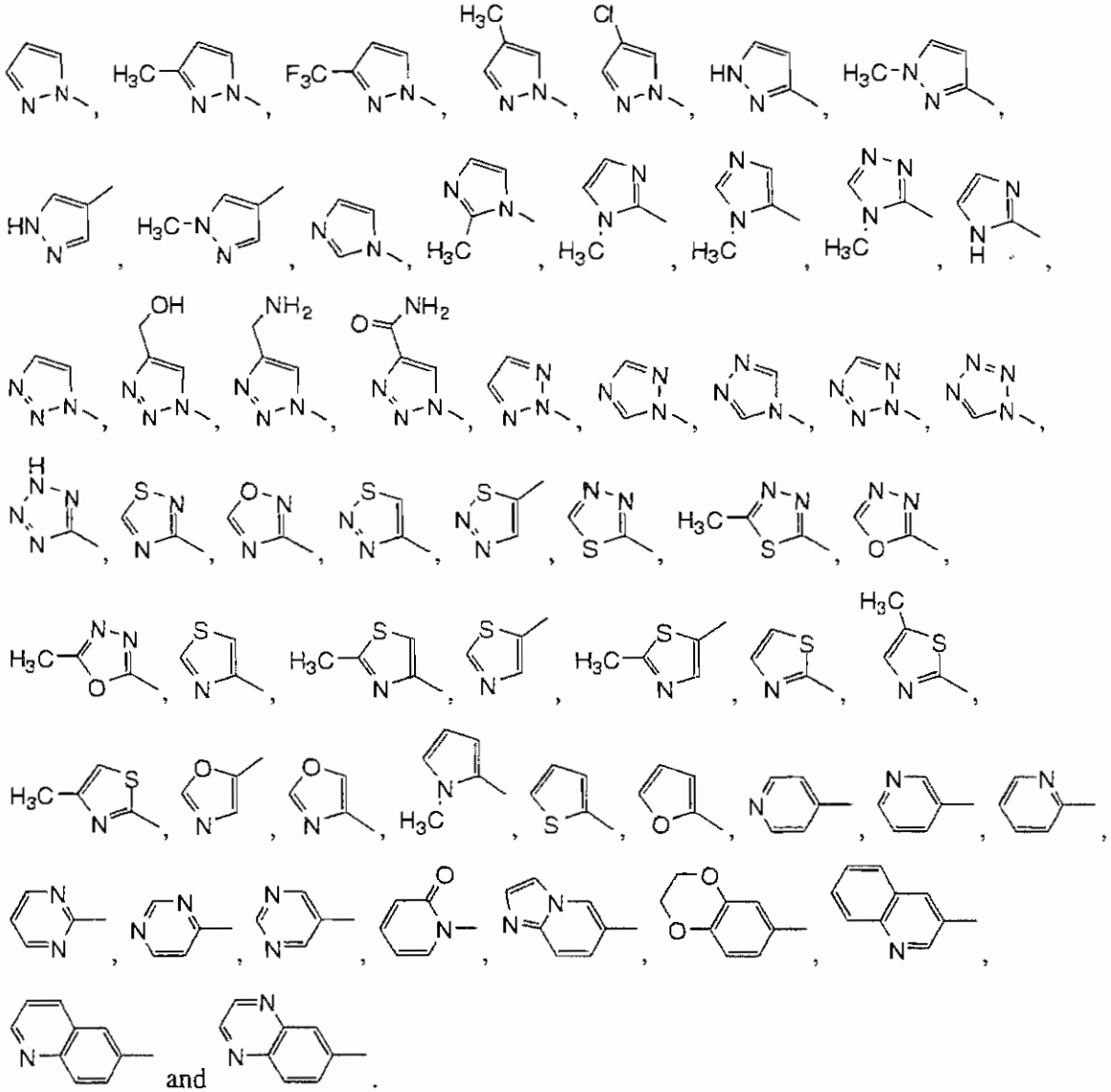
each of which is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of $C_{1\text{-}8}$alkyl, hydroxy$C_{1\text{-}8}$alkyl-, amino$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkylcarbonyl, aminocarbonyl, hydroxy, oxo, halo, halo$C_{1\text{-}8}$alkyl, aminosulfonyl and $C_{3\text{-}8}$cycloalkyl.

30. A compound of claim 29 wherein R^5 is selected from the group consisting of



; each of which is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of $C_{1\text{-}8}$alkyl, hydroxy$C_{1\text{-}8}$alkyl-, amino$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkylcarbonyl, aminocarbonyl, hydroxy, oxo, halo, halo$C_{1\text{-}8}$alkyl, aminosulfonyl and $C_{3\text{-}8}$cycloalkyl.

31. A compound of claim 29 wherein R^5 is selected from the group consisting of

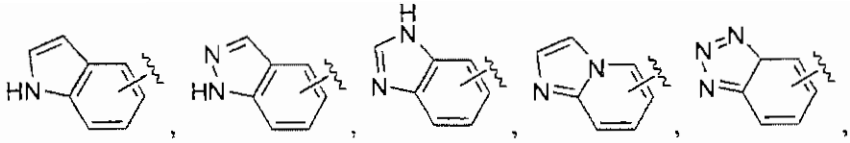


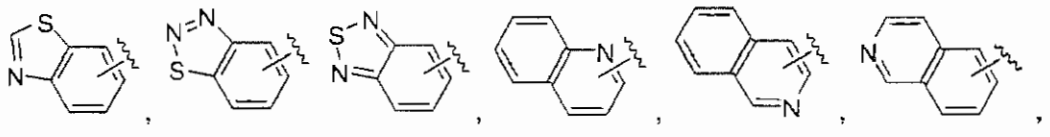
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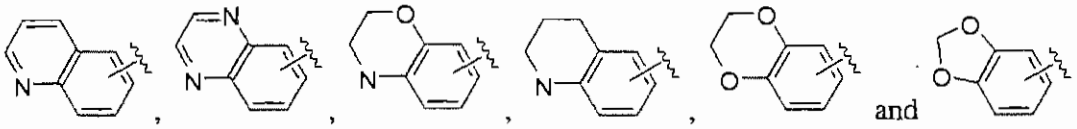
.

32. The compound of any of claims 1 to 3, wherein: D^1 is bicyclic heteroaryl.

33. The compound of claim 32, wherein D^1 is selected from the group consisting of:

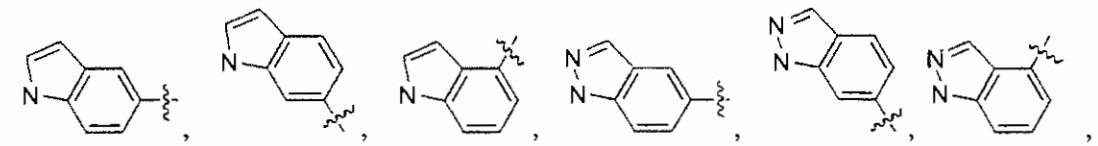


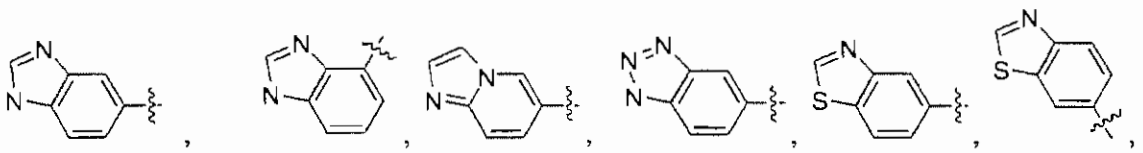


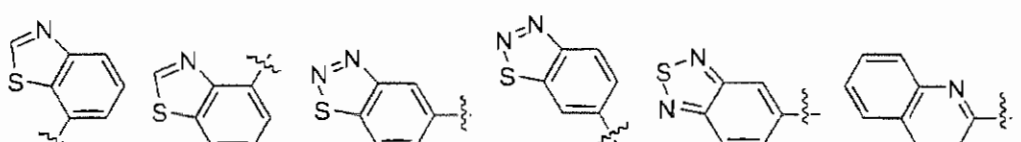

and

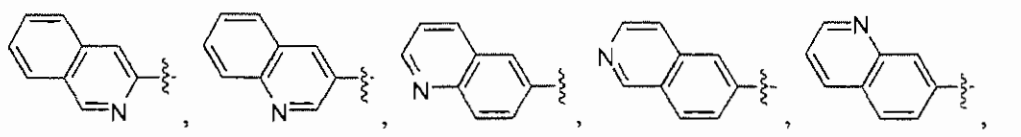
optionally substituted with from 1 to 3 R^{7d} substituents independently selected from the group consisting of: C_{1-8} alkyl, C_{1-8}alkylcarbonyl, aminoC_{1-8}alkylenecarbonyl, aminocarbonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenecarbonyl, C_{1-8}alkoxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkylenecarbonyl, hydroxyC_{1-8}alkoxycarbonyl, aminocarbonyl, amino, C_{1-8} alkoxycarbonylamino, arylC_{1-8} alkoxycarbonylamino, hydroxyl, C_{1-8} alkoxy, C_{1-8}alkylsulfonyl, aminoC_{1-8}alkylenesulfonyl, aminosulfonyl, C_{1-8}alkyleneaminoC_{1-8}alkylenesulfonyl, C_{1-8}alkoxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkylenesulfonyl, hydroxyC_{1-8}alkoxysulfonyl, aminosulfonyl, oxo, halo, phenyl and C_{1-8}alkylheterocyclyl; and the wavy line indicates the point of attachment to the rest of the molecule.

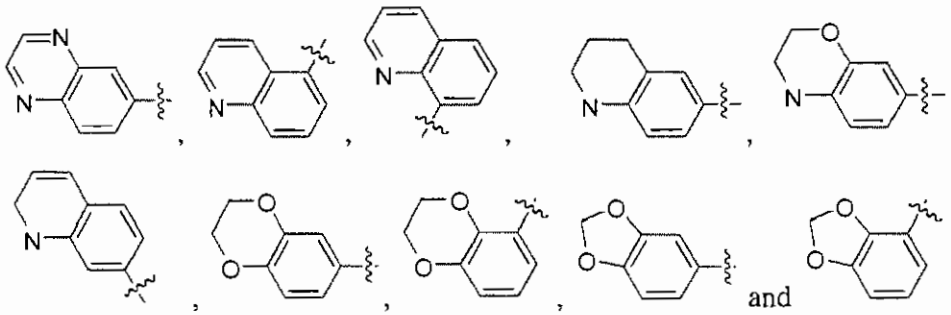
34. A compound of claim 33, wherein D^1 is selected from the group consisting of:







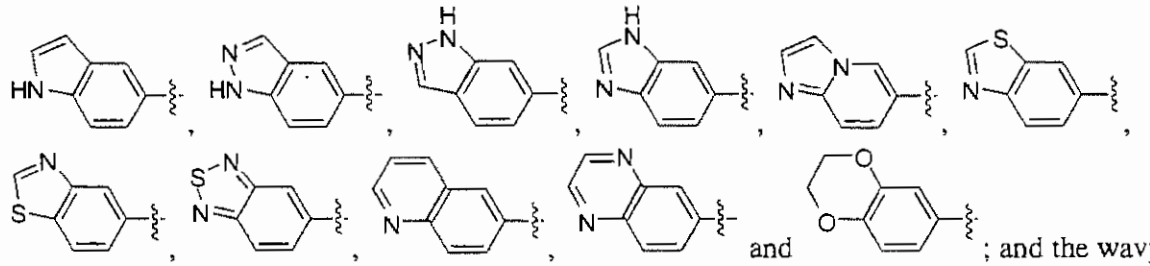




and

; and the wavy line indicates the point of attachment to the rest of the molecule.

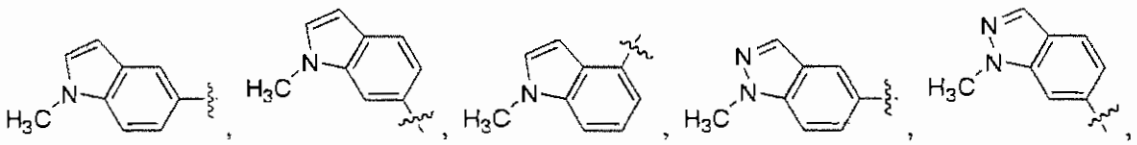
35. The compound of claim 34, wherein D^1 is selected from the group consisting of:

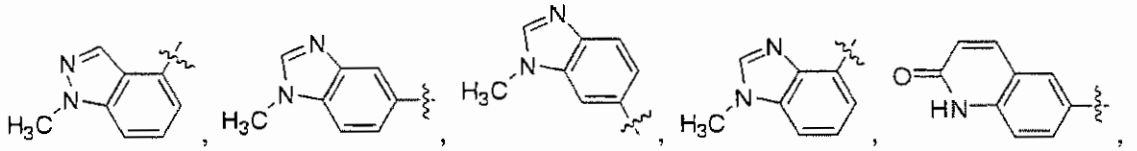


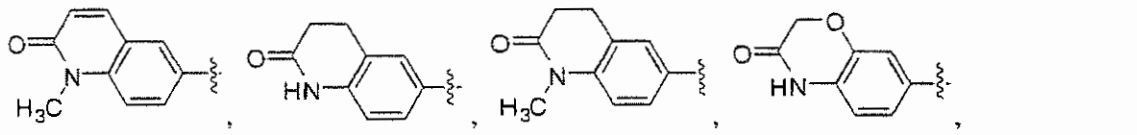
and

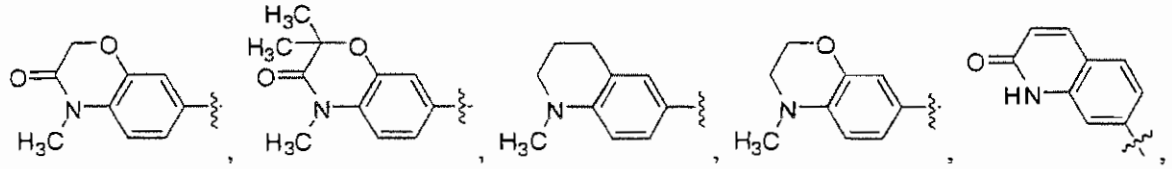
; and the wavy line indicates the point of attachment to the rest of the molecule.

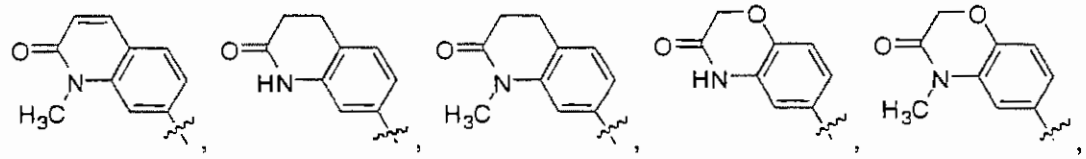
36. A compound of claim 34, wherein D^1 is selected from the group consisting of:

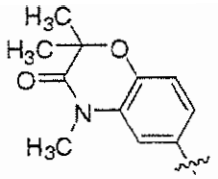
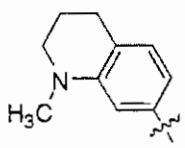
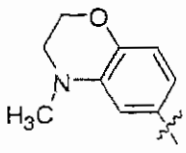




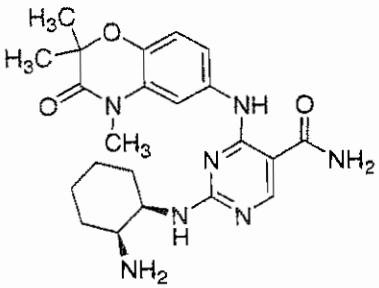
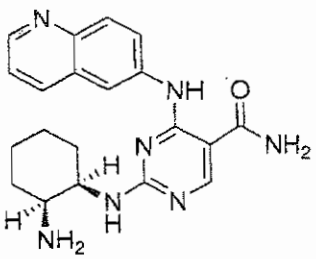
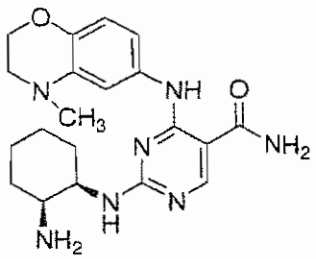






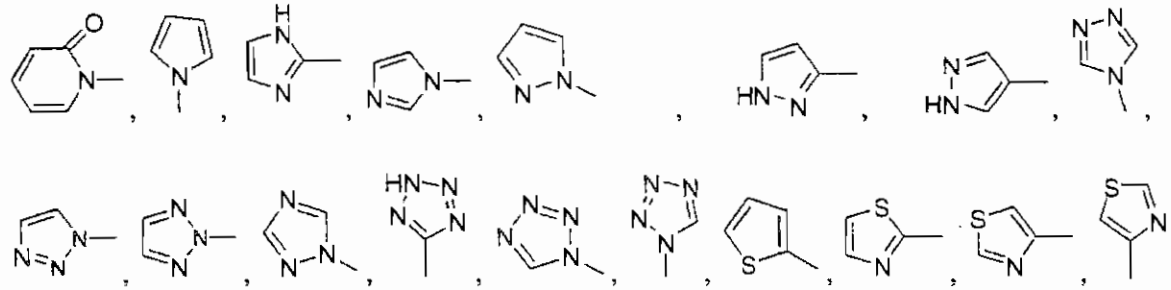


and ; and the wavy line indicates the point of attachment to the rest of the molecule.

37. A compound of claim 36, selected from the group consisting of:

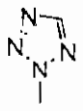
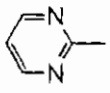


and .

38. The compound of any of claims 1 to 3, wherein each E^1 is independently selected from the group consisting of $C_{1\text{-}8}$alkyl, heteroaryl, heterocyclyl, halo, $C_{1\text{-}8}$haloalkyl, $C_{1\text{-}8}$alkoxy, $C_{1\text{-}8}$acyl, amino$C_{1\text{-}8}$alkyl, aminosulfonyl, $C_{1\text{-}8}$alkylsulfonyl and acylamino.

39. The compound of claim 38 wherein each E^1 is independently selected from the group consisting of

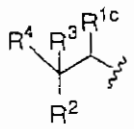


40. The compound of claim 38 wherein each E^1 is independently selected from the group consisting of

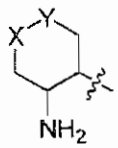
 and .

41. The compound of any of the preceding claims, wherein R^2 is amino.

42. The compound of claim 2, wherein: the moiety:

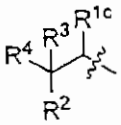


is

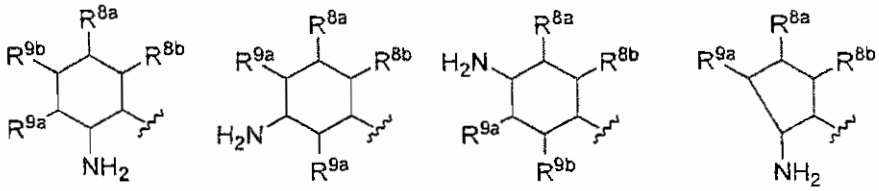
;

wherein X and Y is each independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

43. The compound of claim 2, wherein the moiety:



is selected from the group consisting of:

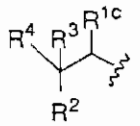


, , or ;

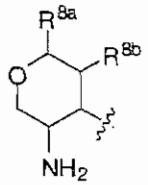
wherein each R^{8a} and R^{8b} is independently H, hydroxyl, halo or if on adjacent carbon atoms, may be combined with the atoms to which they are attached to form a fused benzene ring; and

each R^{9a} and R^{9b} is independently H, hydroxyl, halo or, if on adjacent carbon atoms, may be combined with the atoms to which they are attached to form a fused benzene ring; and the wavy line indicates the point of attachment to the rest of the molecule.

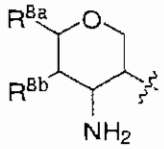
44. The compound of claim 2, wherein: the moiety:



is



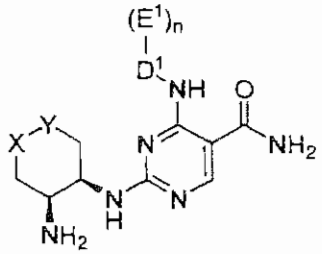
or



;

wherein each R^{8a} and R^{8b} is independently H or may be combined with the atoms to which they are attached to form a fused benzene ring; and the wavy line indicates the point of attachment to the rest of the molecule.

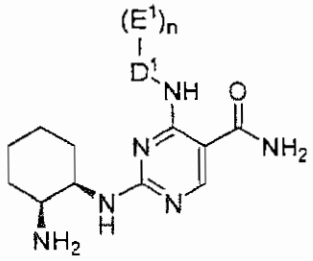
45. The compound of claim 2 wherein the compound has the formula:



;

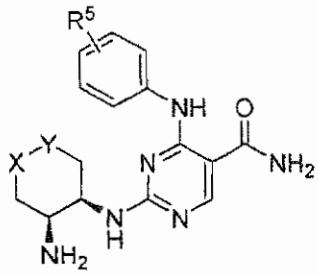
wherein each X and Y is independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

46. The compound of claim 2 wherein the compound has the formula:



,

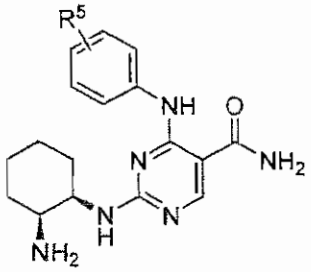
47. The compound of claim 2 wherein the compound has the formula:



;

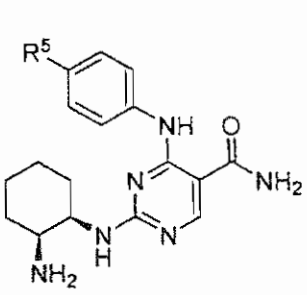
wherein each X and Y is independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

48. The compound of claim 2 wherein the compound has the formula:

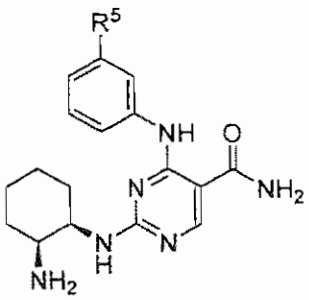


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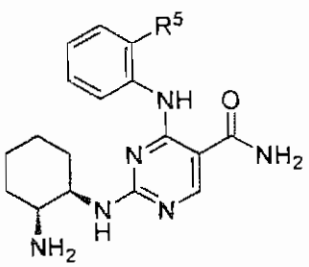
49. The compound of claim 2 wherein the compound has the formula:



,

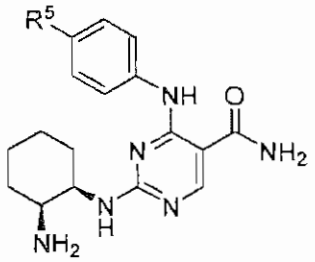


and



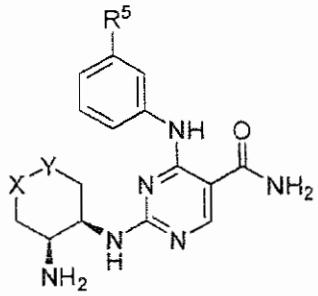
.

50. The compound of claim 2 wherein the compound has the formula selected from the group consisting of:



..

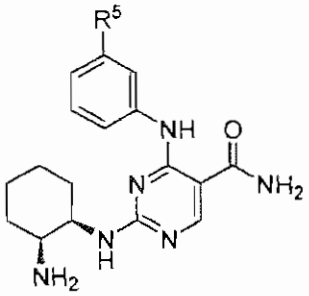
51. The compound of claim 2 wherein the compound has the formula selected from the group consisting of:



;

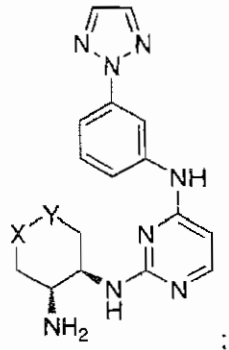
wherein each X and Y is independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

52. The compound of claim 2 wherein the compound has the formula selected from the group consisting of:



..

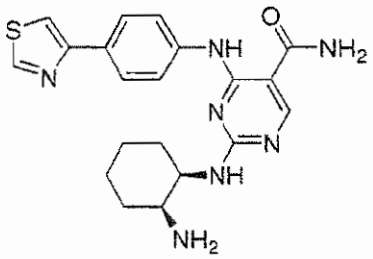
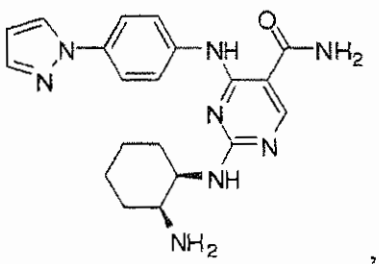
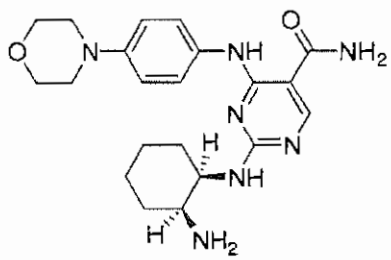
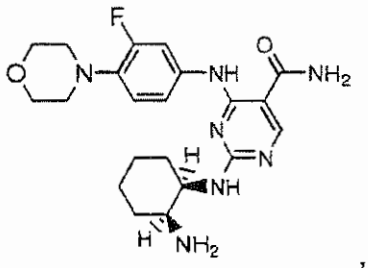
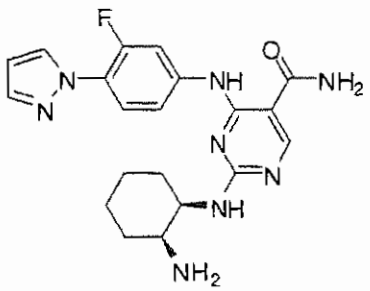
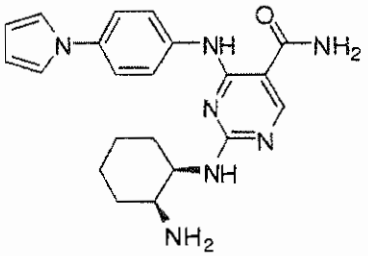
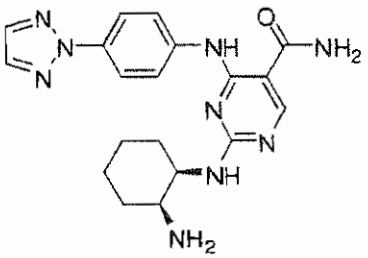
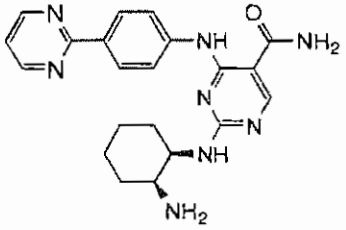
53. The compound of claim 2 wherein the compound has the formula:



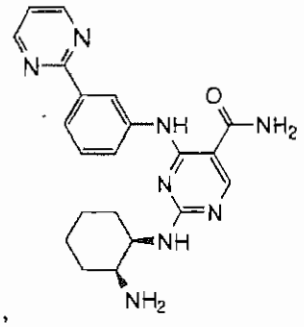
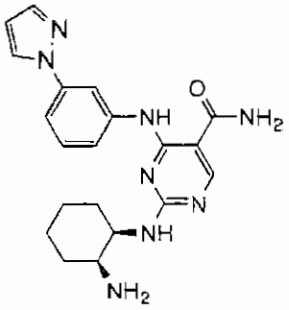
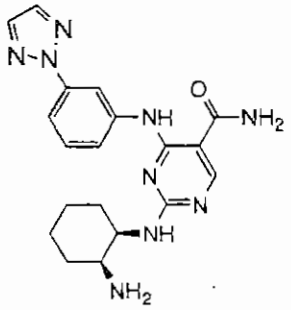
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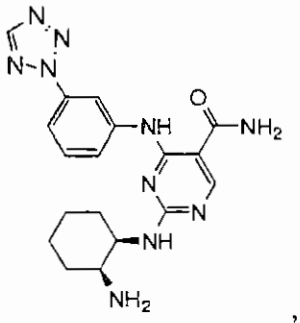
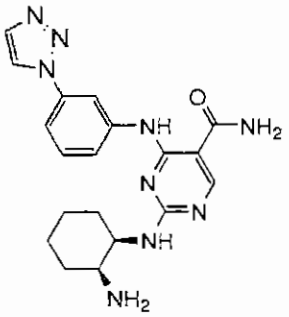
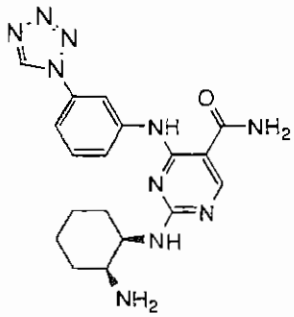
wherein each X and Y is independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S.

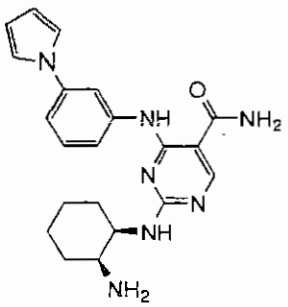
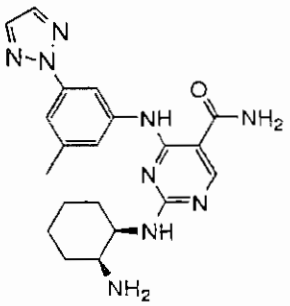
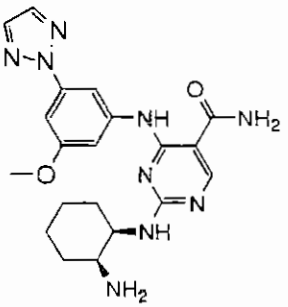
54. The compound of claim 46, selected from the group consisting of:

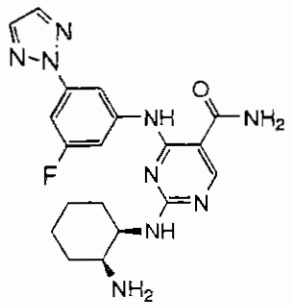
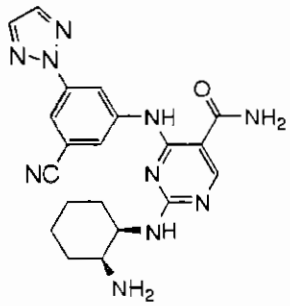
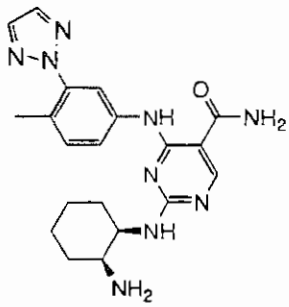

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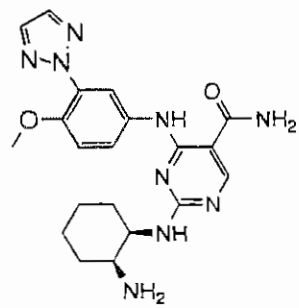
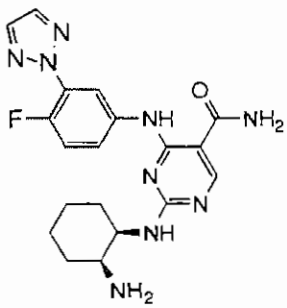
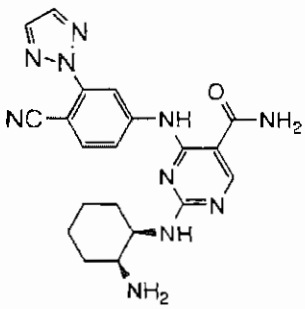
55. The compound of claim 46, selected from the group consisting of:

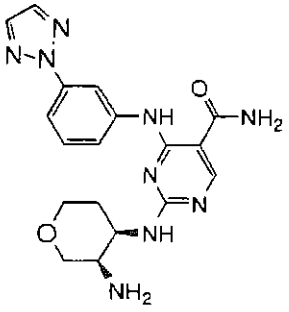
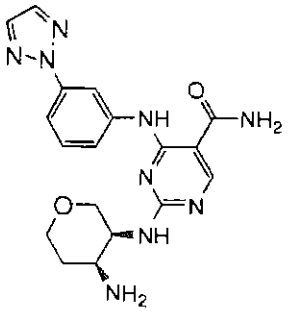
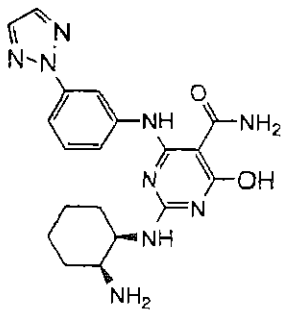

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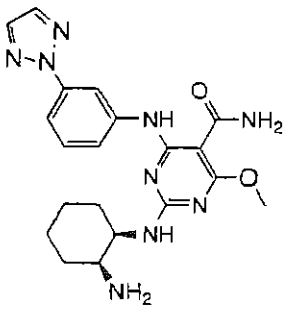
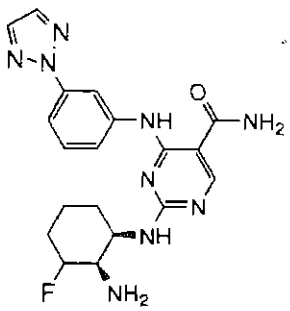
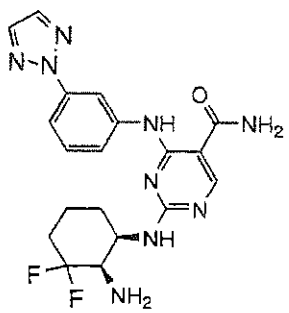

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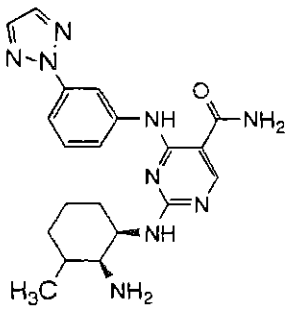
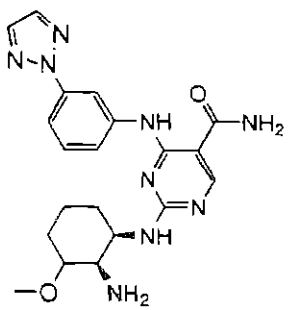
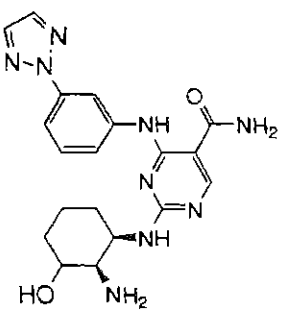

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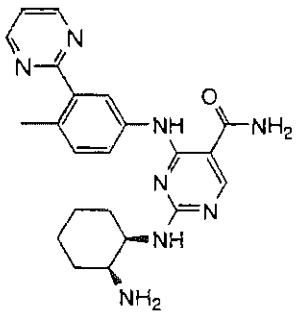
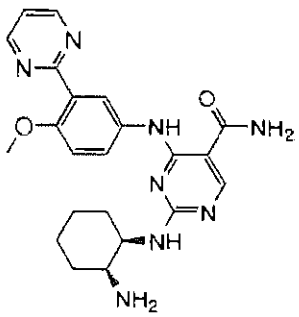
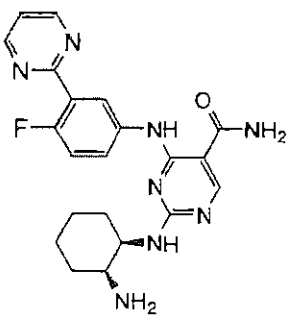

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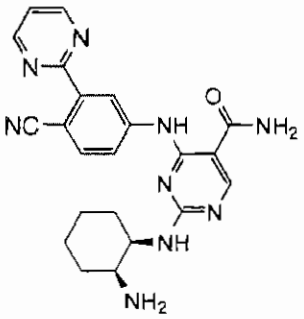
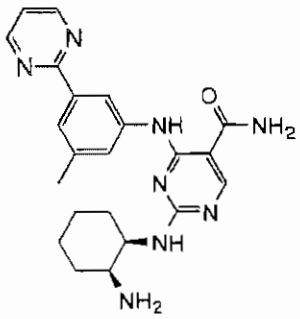
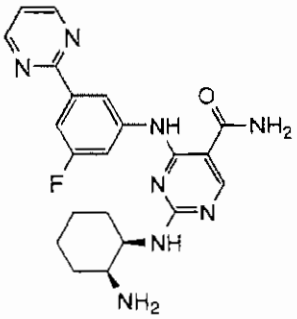

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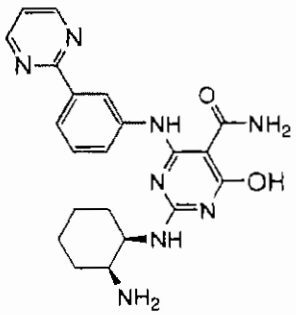
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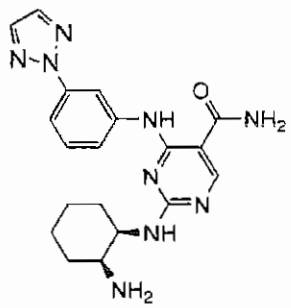
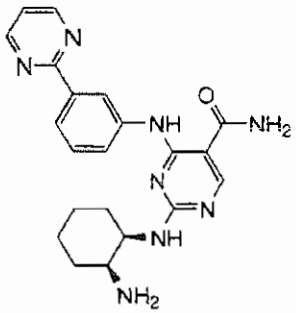
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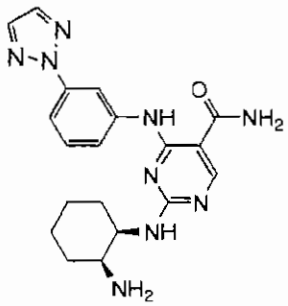


56. A compound of claim 54, having the formula:

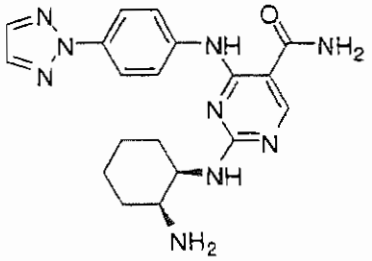



or

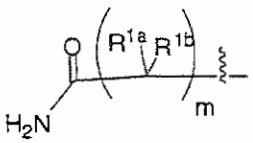
57. A compound of claim 54, having the formula:



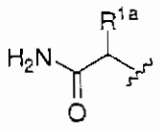
58. A compound of claim 54, having the formula:



59. The compound of claim 3, wherein the moiety:



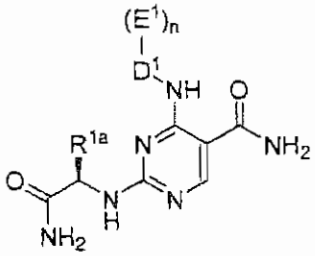
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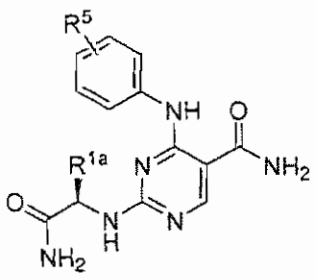
;

and the wavy line indicates the point of attachment to the rest of the molecule.

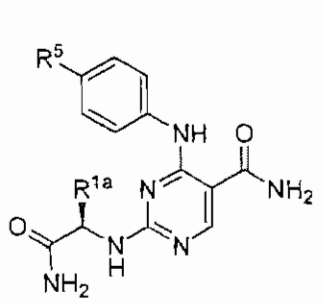
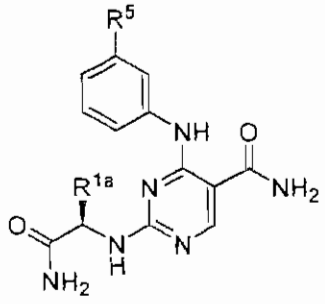
60. The compound of claim 59 wherein a compound having the formula:

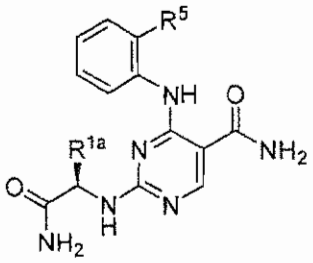


61. The compound of claim 59 wherein the compound has the formula:



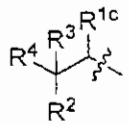
62. The compound of claim 59 wherein the compound has a formula selected from the group consisting of:



and

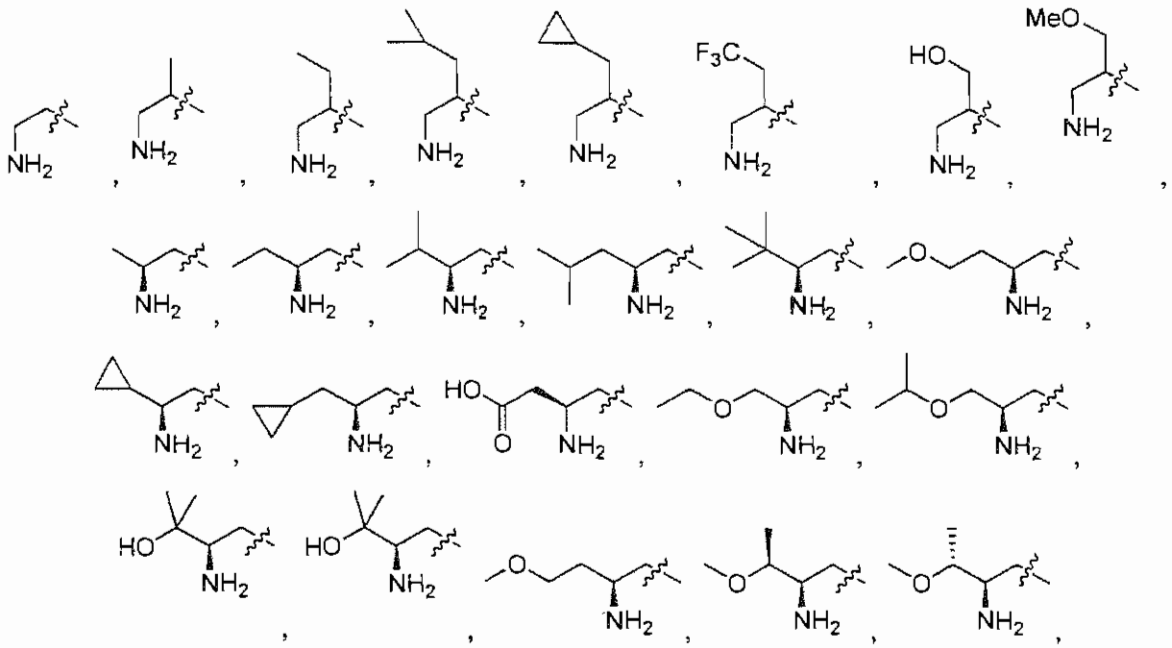


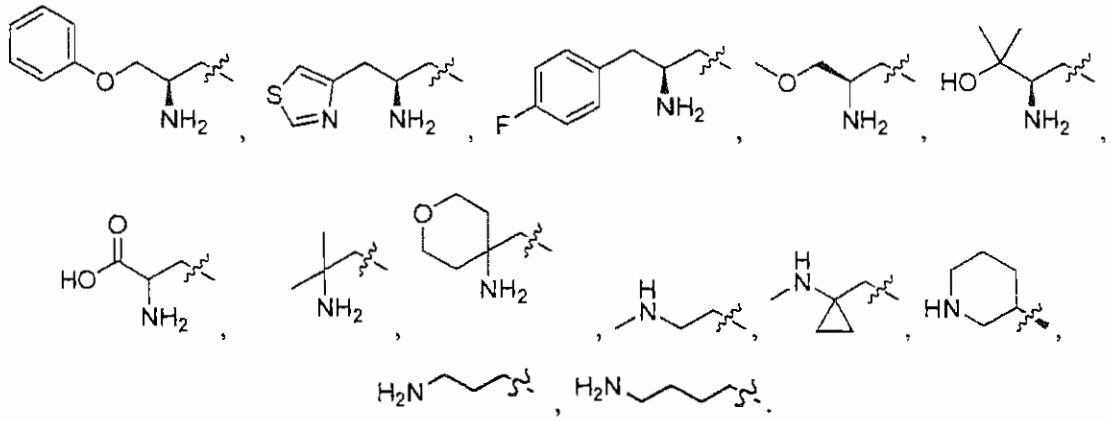
63. The compound of claim 59 wherein R^{1a} is selected from the group consisting of $C_{1\text{-}8}$alkyl, $C_{3\text{-}8}$cycloalkyl, aryl, heteroaryl and heterocyclyl.

64. The compound of claim 2, wherein the moiety:

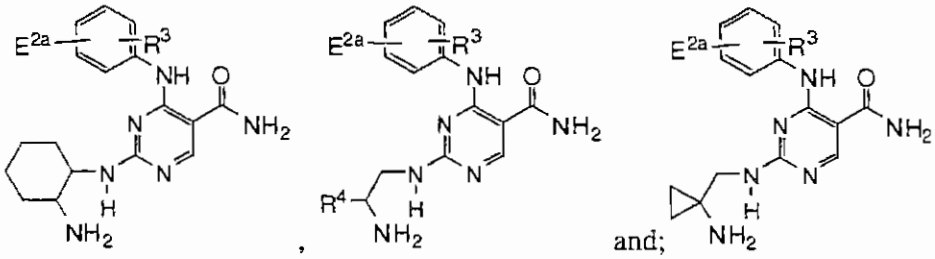


is selected from the group consisting of:





65. A compound having the structure selected from the group consisting of formula IIa-c:



IIa IIb IIc

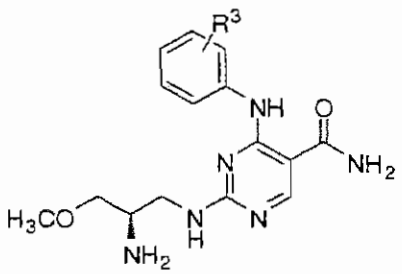
or a tautomer thereof or a pharmaceutically acceptable salt thereof, wherein:

E^{2a} is selected from the group consisting of $C_{1\text{-}8}$ alkoxy, $C_{1\text{-}8}$alkyl$C_{3\text{-}8}$cycloalkylcarbonylamino, $C_{1\text{-}8}$alkoxy$C_{1\text{-}8}$alkylenecarbonylamino-, $C_{1\text{-}8}$alkoxycarbonylamino and $C_{1\text{-}8}$alkylcarbonylamino;

R^3 is selected from the group consisting of H, halo, $C_{1\text{-}8}$alkyl and $C_{1\text{-}8}$alkoxy; and

R^4 is selected from the group consisting of H, $C_{1\text{-}8}$alkyl and $C_{1\text{-}8}$alkoxy $C_{1\text{-}8}$alkylene.

66. A compound having formula (IId):

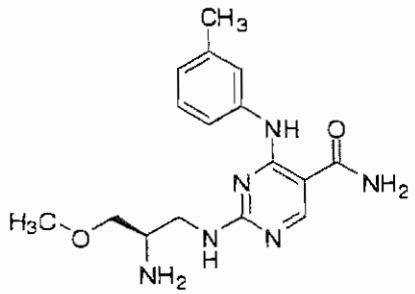


(IId)

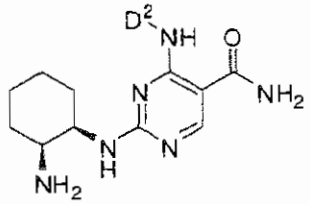
or a tautomer thereof or a pharmaceutically acceptable salt thereof,

wherein R^3 is H or C_{1-8}alkyl.

67. A compound having formula:



68. A compound having formula (IIe):

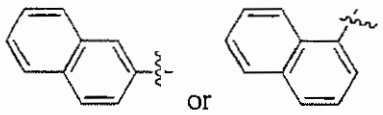


(IIe)

wherein: D^2 is a bicyclic aryl group.

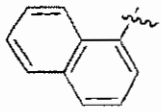
69. The compound of claim 68, wherein: D^2 is naphthyl, optionally substituted with from 1 to 2 substituents, E^{2b}, independently selected from the group consisting of halo, C_{1-8}alkoxy and C_{1-8}alkylaminocarbonyl.

70. A compound of claim 68, wherein D^2 is



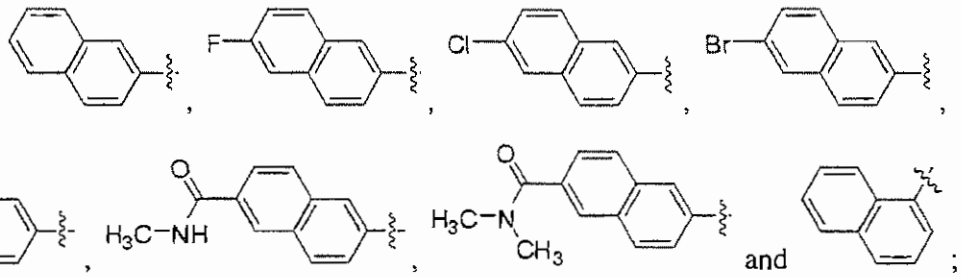
and the wavy line indicates the point of attachment to the rest of the molecule.

71. A compound of claim 68, wherein D^2 is


;

and the wavy line indicates the point of attachment to the rest of the molecule..

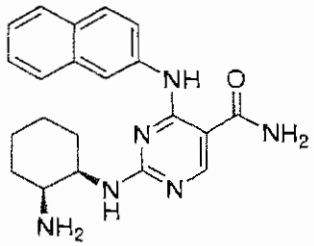
72. A compound of claim 68, wherein D^2 is selected from the group consisting of:



and ;

and the wavy line indicates the point of attachment to the rest of the molecule.

73. A compound of claim 68, having the formula



.

74. A compound having a structure found in the Examples.

75. A compound having a structure found in the Tables.

76. A compound having a structure found in the Figures.

77. A composition comprising a compound of any of the preceding claims in combination with a pharmaceutically acceptable carrier or diluent.

78. A method for inhibiting syk or JAK kinase or a signal transduction pathway mediated at least in part by syk kinase activity comprising the step of contacting a cell with a compound of any one of the preceding claims.

79. A method for treating a condition or disorder mediated at least in part by syk kinase activity in a subject comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of a composition of claim 77.

80. The method of claim 79, wherein the condition or disorder is selected from the group consisting of cardiovascular disease, inflammatory disease and autoimmune disease and cell proliferative disorder.

81. The method of claim 79, wherein said cardiovascular disease is selected from the group consisting of restenosis, thrombosis, immune thrombocytopenic purpura, heparin induced thrombocytopenia, dilated cardiomyopathy, sickle cell disease, atherosclerosis, myocardial infarction, vascular inflammation, unstable angina and acute coronary syndromes.

82. The method of claim 79, wherein said inflammatory disease is selected from the group consisting of allergy, asthma, rheumatoid arthritis, B Cell mediated diseases such as Non Hodgkin's Lymphoma, anti phospholipid syndrome, lupus, psoriasis, multiple sclerosis and end stage renal disease.

83. The method of claim 79, wherein said cardiovascular disease is selected from the group consisting of thrombosis, immune thrombocytopenic purpura, and heparin induced thrombocytopenia.

84. The method of claim 79, wherein said inflammatory disease is rheumatoid arthritis or Non Hodgkin's Lymphoma.

85. The method of claim 79, wherein said sickle cell disease is selected from the group consisting of sickle cell anemia, sickle-hemoglobin C disease, sickle beta-plus thalassemia, and sickle beta-zero thalassemia.

86. The method of claim 79, wherein said immune-related disease is selected from the group consisting of a T-cell mediated disease, an autoimmune disease, host versus graft rejection, graft versus host rejection, a Type IV hypersensitivity reaction and allograft rejection.

87. The method of claim 79, wherein said autoimmune disease is selected from the group consisting of hemolytic anemia, immune thrombocytopenic purpura, multiple sclerosis, Sjogren's syndrome. diabetes, rheumatoid arthritis, lupus and psoriasis.

88. The method of claim 79, wherein said wherein said cell proliferative disorder is leukemia, a lymphoma, myeloproliferative disorders, hematological malignancies, and chronic idiopathic myelofibrosis.

89. The method of claim 79, wherein said disorder is acute myeloid leukemia, chronic lymphocytic leukemia, or non-Hodgkin's lymphoma.

90. A kit comprising a composition of claim 77, packaging and instructions for use.