FUSED PYRIDINE, PYRIMIDINE AND TRIAZINE COMPOUNDS AS CELL CYCLE INHIBITORS

FIELD OF THE INVENTION

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cancer.

BACKGROUND OF THE INVENTION

Cyclin-dependent kinases (Cdks) are a family of serine/ threonine protein kinases playing important cellular functions. The cyclins are the regulatory subunits that activate the catalytic Cdks. Cdk1/Cyclin B1, Cdk2/Cyclin A, Cdk2/Cyclin E, Cdk4/Cyclin D, Cdk6/Cyclin D are critical regulators of cell cycle progression. Cdks also regulate transcription, DNA repair, differentiation, senescence and apoptosis (Morgan D.O., *Annu. Rev. Cell. Dev. Biol.* 1997; 13:261-291).

Small molecule inhibitors of Cdks have been developed to treat cancer (de Carcer G et al., *Curr Med Chem.* 2007; 14:969-85). Large amount of genetic evidence support that Cdks play critical roles in the development of most human cancers (*Malumbres M. et al, Nature Rev Cancer,* 2001; 1:222-231). Genetic alterations in Cdks, their substrates or regulators have been shown to be associated with human cancer. Endogenous protein inhibitors of Cdks including p16, p21 and p27 inhibit Cdk activity and their overexpression result in cell cycle arrest and inhibition of tumor growth in preclinical models (Kamb A., *Curr. Top. Microbiolo. Immunol.*, 1998; 227:139-148).

Small molecule inhibitors of Cdks may also be used to treat variety of other diseases that result from aberrant cell proliferation, including cardiovascular disorders, renal diseases, certain infectious diseases and autoimmune diseases. Cell proliferation regulatory pathways including genes involved in the cell cycle G1 and S phase checkpoint (p53, pRb, p15, p16, and Cyclins A, D, E, Cdk 2 and Cdk4) have been associated with plaque progression, stenosis and restenosis after angioplasty. Over-expression of the Cdk inhibitor protein p21 has been shown to inhibit vascular smooth muscle proliferation and intimal hyperplasia following angioplasty (Chang M.W. et al., *J. Clin. Invest.,* 1995; 96:2260; Yang Z-Y. et al., *Proc. Natl. Acad. Sci. (USA)* 1996; 93:9905). A small molecule Cdk2 inhibitor CVT-313 (Ki = 95 nM) was shown to cause in significant inhibition of neointima formation in animal models (Brooks E.E. et al., *J. Biol. Chem.* 1997; 272:29207-29211). Disregulation of cell cycle has been associated with polycystic kidney diseases, which are characterized by the growth of fluid-filled cysts in renal tubules. Treatment with small molecule inhibitors of Cdks yielded effective arrest of cystic disease in mouse models (Bukanov N. O., et al., *Nature,* 2006; 4444:949-952). Infection by a variety of infectious agents, including fungi, protozoan parasites such as *Plasmodium falciparum,* and DNA and RNA viruses may be treated with Cdk inhibitors. Cdks have been shown to be required for replication of herpes simplex virus (HSV) (Schang L.M. et al., *J. Virol.* 1998; 72:5626). Cdks are essential proteins in yeast. Synovial tissue hyperplasia plays important roles in the development of

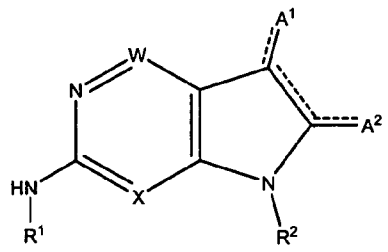
rheumatoid arthritis; inhibition of synovial tissue proliferation may suppress inflammation and prevent joint destruction. It has been shown that over-expression of Cdk inhibitor protein p16 inhibited synovial fibroblast growth (Taniguchi K. et al., *Nat. Med.* 1999; 5:760-767) and joint swelling was substantially inhibited in animal arthritis models.

Selective inhibitors of some Cdks may also be used to protect normal untransformed cells by inhibiting specific phases of cell cycle progression (Chen et al. *J. Natl. Cancer Institute,* 2000; 92:1999-2008). Pre-treatment with a selective Cdk inhibitor prior to the use of a cytotoxic agent that inhibits a different phase of the cell cycle may reduce the side effects associated with the cytotoxic chemotherapy and possibly increase the therapeutic widow. It has been shown that induction of cellular protein inhibitors of Cdks (p16, p27 and p21) conferred strong resistance to paclitaxel- or cisplatin-mediated cytotoxicity on the inhibitor-responsive cells but not on the inhibitor-unresponsive cells (Schmidt, M, *Oncogene,* 2001 20:6164-71).

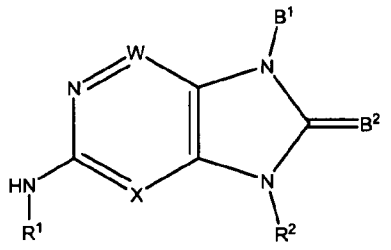
DESCRIPTION OF THE INVENTION

A class of compounds useful in treating cancer is defined by the following Formula I or II

A compound of Formula I or II



I



II

enantiomers, diastereomers, salts and solvates thereof wherein

W and X are independently CH or N;

A^1 and A^2 together with ring carbon atoms to which they are attached combine to form benzene, cyclopentadiene, pyridine, pyridone, pyrimidine, pyrazine, pyridazine, 2H-pyran, pyrrole, imidazole, pyrazole, triazole, furan, oxazole, isoxazole, oxadiazole, thiophene, thiazole, isothiazole or thiadiazole

any of which may be optionally partially saturated, and any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

B^1 and B^2 together with the ring atoms to which they are attached combine to form dihydropyridine, dihydropyridone, dihydropyrimidine, dihydropyrimidone, dihydropyrazine, dihyrdopyridazine, pyrrole, imidazole, pyrazole, triazole, or tetrazole any of which may be optionally partially saturated, and any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^1 is $-Y-(alkylene)_m-R^a$;

Y is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl or heteroaryl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^a is heterocyclo, heteroaryl, $-NR^3R^4$, $-C(=O)NR^3R^4$; $-O-R^5$, $-S(O)_n-R^5$, or $-S(O)_n-NR^3R^4$ any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring;

R^2 is alkyl, cycloalkyl, heterocyclo, aryl, $-S(O)_nR^5$, $-C(=O)R^5$, $-C(=S)R^5$, $-C(=O)OR^5$, $-C(=S)OR^5$, $-C(=O)NR^3R^4$, $-C(=S)NR^3R^4$, $-SO_2NR^3R^4$, any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^3 and R^4 at each occurance are independently

(i) hydrogen or

(ii) alkyl, cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring;

or R^3 and R^4 together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring;

R^{3*} and R^{4*} at each occurance are independently

(i) hydrogen or

(ii) alkyl, alkenyl, alkynyl cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

or R^{3*} and R^{4*} together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more R^x groups as allowed by valance;

R^5 and R^{5*} at each occurance is

(i) hydrogen or

(ii) alkyl, alkenyl, alkynyl cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^x at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, -(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-CN, -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-$S(O)_nR^5$*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-$C(=O)R^5$*, -(alkylene)$_m$-$C(=S)R^5$*, -(alkylene)$_m$-$C(=O)O\ R^5$*, -(alkylene)$_m$-$OC(=O)R^5$*, -(alkylene)$_m$-$C(=S)OR^5$*, -(alkylene)$_m$-$C(=O)NR^3$*R^4*, -(alkylene)$_m$-$C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)R^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)R^5$*, -(alkylene)$_m$-$OC(=O)NR^3$*R^4*, -(alkylene)$_m$-$OC(=S)NR^3$*R^4*, -(alkylene)$_m$-SO_2NR^3*R^4*, -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*, -(alkylene)$_m$-$N(R^3$*$)SO_2NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)OR^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)OR^5$*, or -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*;

n is independently 0, 1 or 2; and

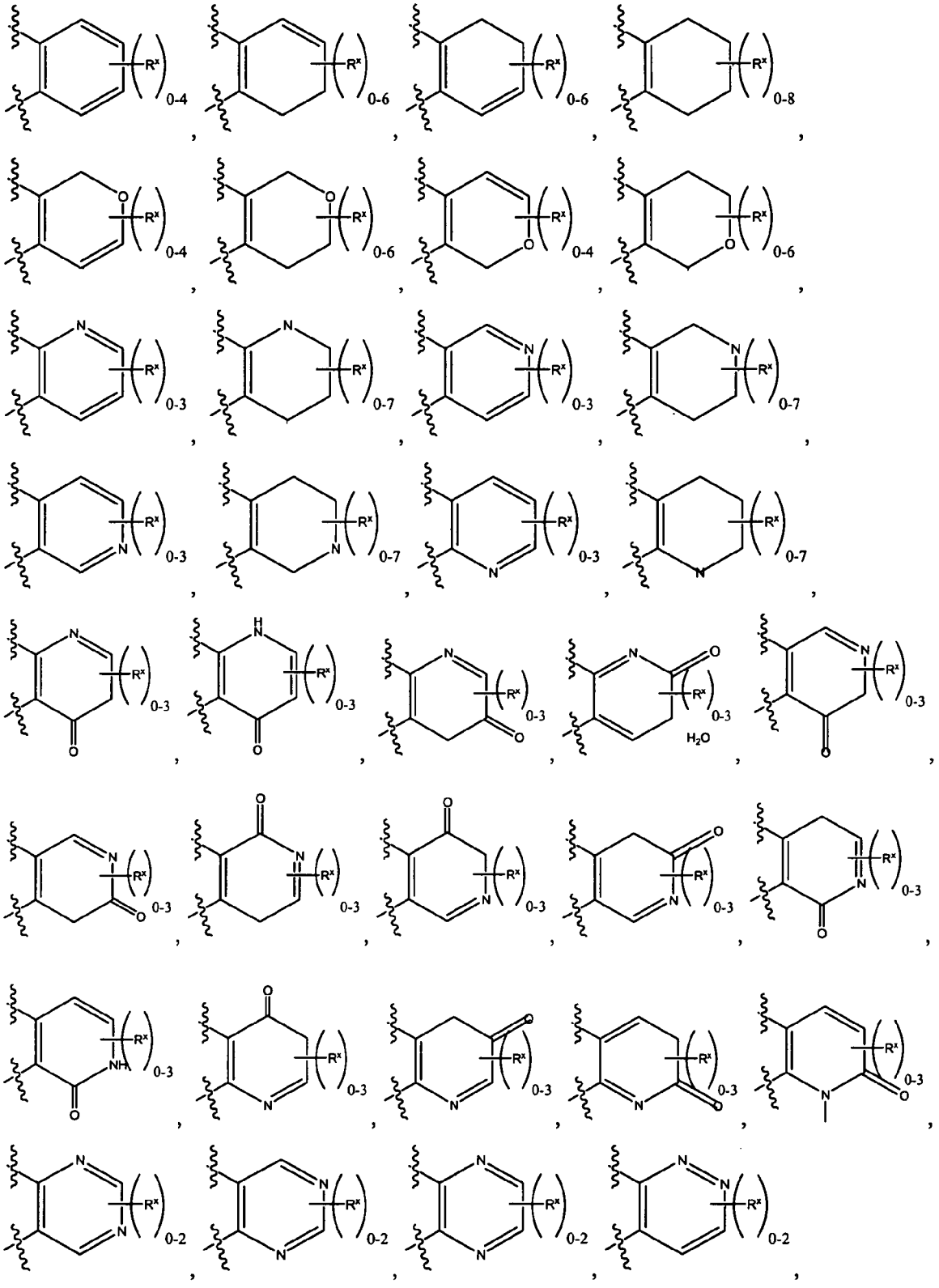
m is independently 0 or 1.

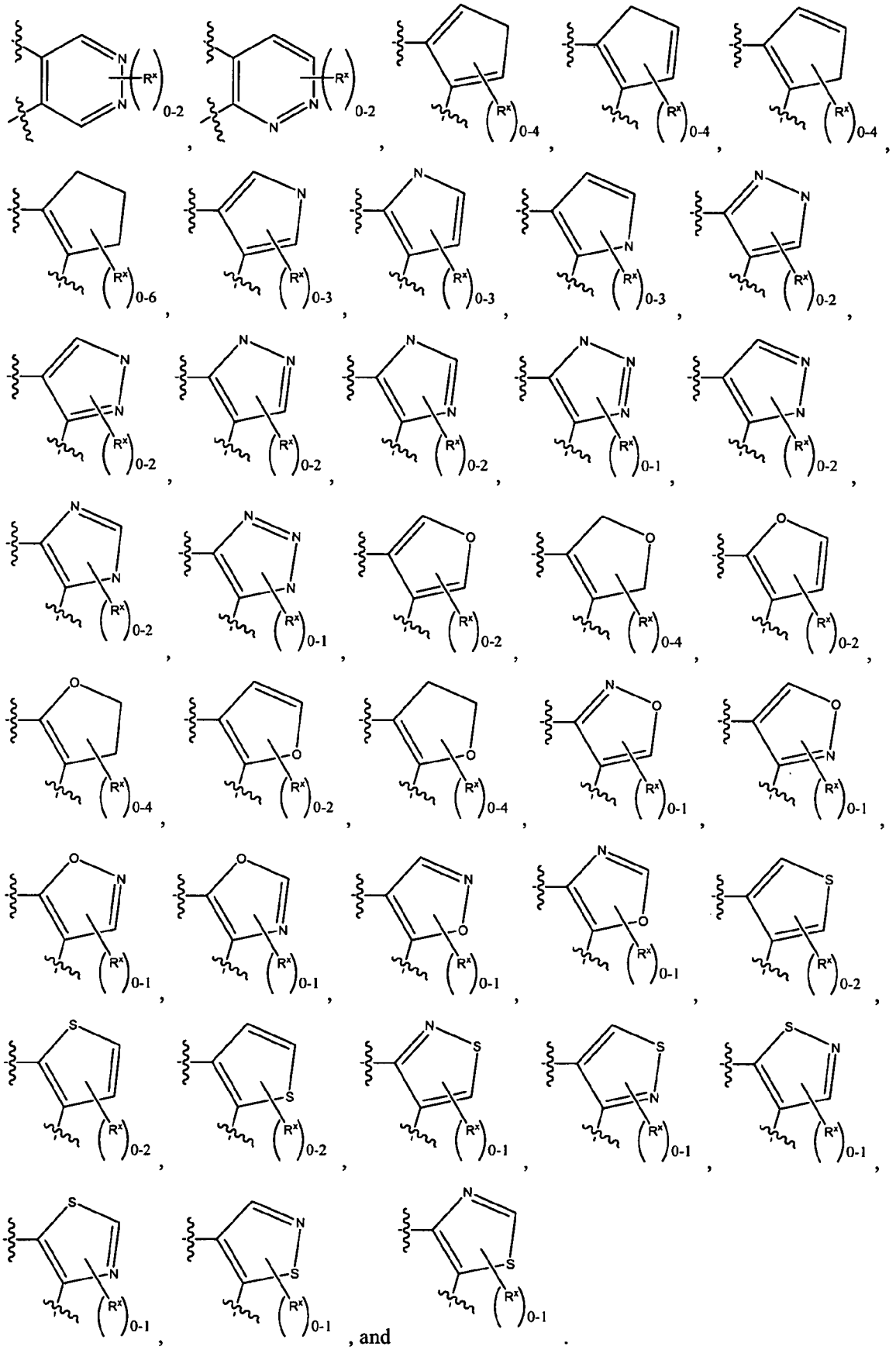
Compounds of this invention are selective inhibitors of cyclin dependent kinase Cdk4, which is to say that they inhibit Cdk4 with higher potency than they inhibit tyrosine kinases and other serine-threonine kinases including other cyclin-dependent kinases such as Cdk1. Cdk6 is structurally and functionally similar to Cdk4.

Compounds of the present invention also inhibit Cdk6 at similar concentrations to those to inhibit Cdk4. Preferred embodiments of the present invention are compounds of the formula 1 inhibit Cdk4 at least about 100-fold more potently than they inhibit Cdk1.

The compounds of the present invention are useful for treating cancer including leukemia and solid cancer of the lung, breast, prostate, and skin such as melanoma, and other diseases with abnormal cell proliferation including but not limited to psoriasis, HSV, HIV, restenosis, and atherosclerosis.

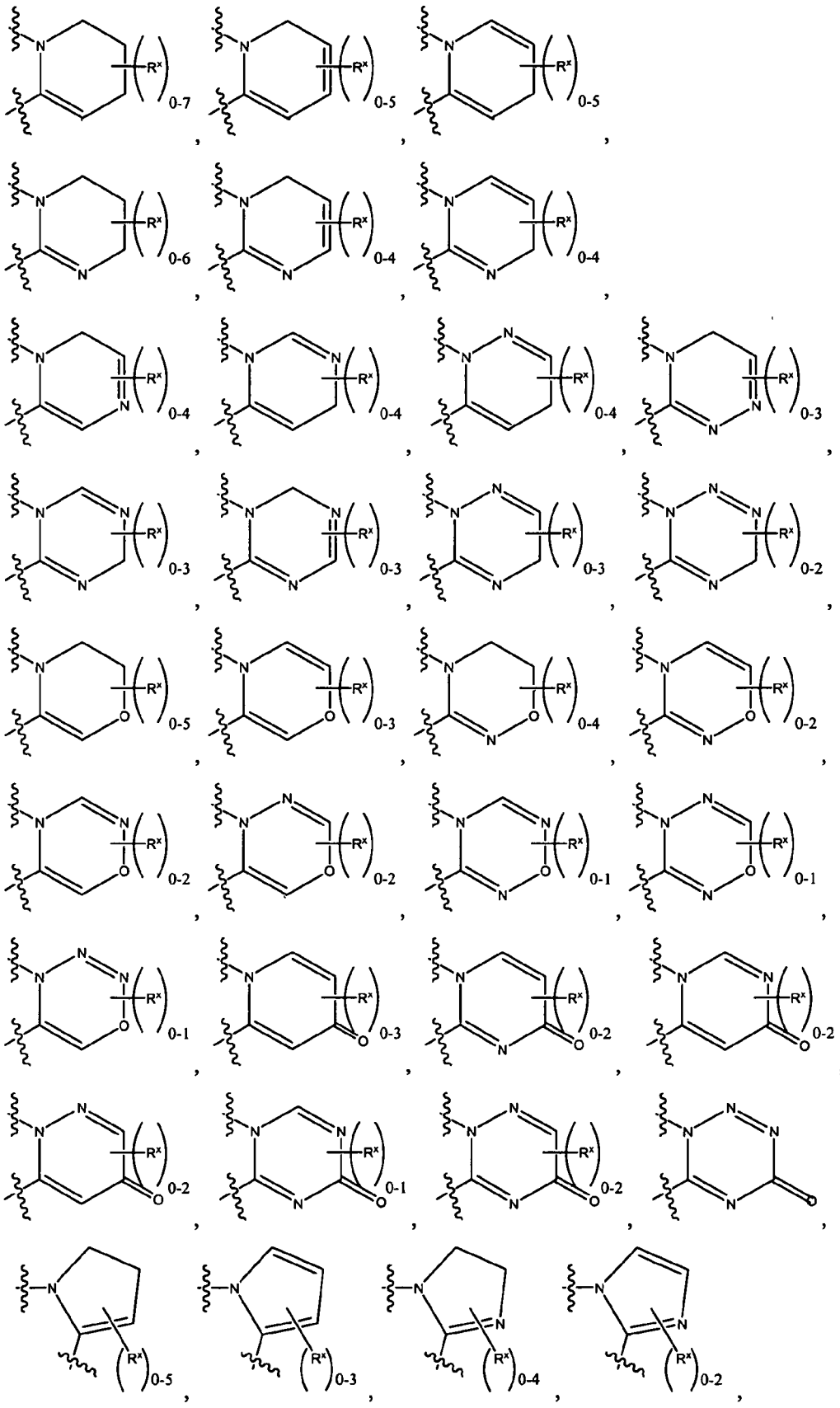
Preferred compounds within the scope of Formula I include compounds wherein A^1 and A^2 together with the ring atoms to which they are attached combine to form

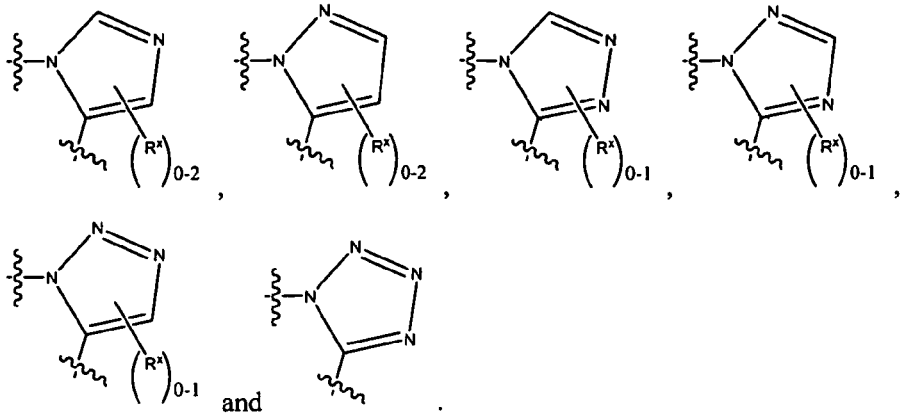




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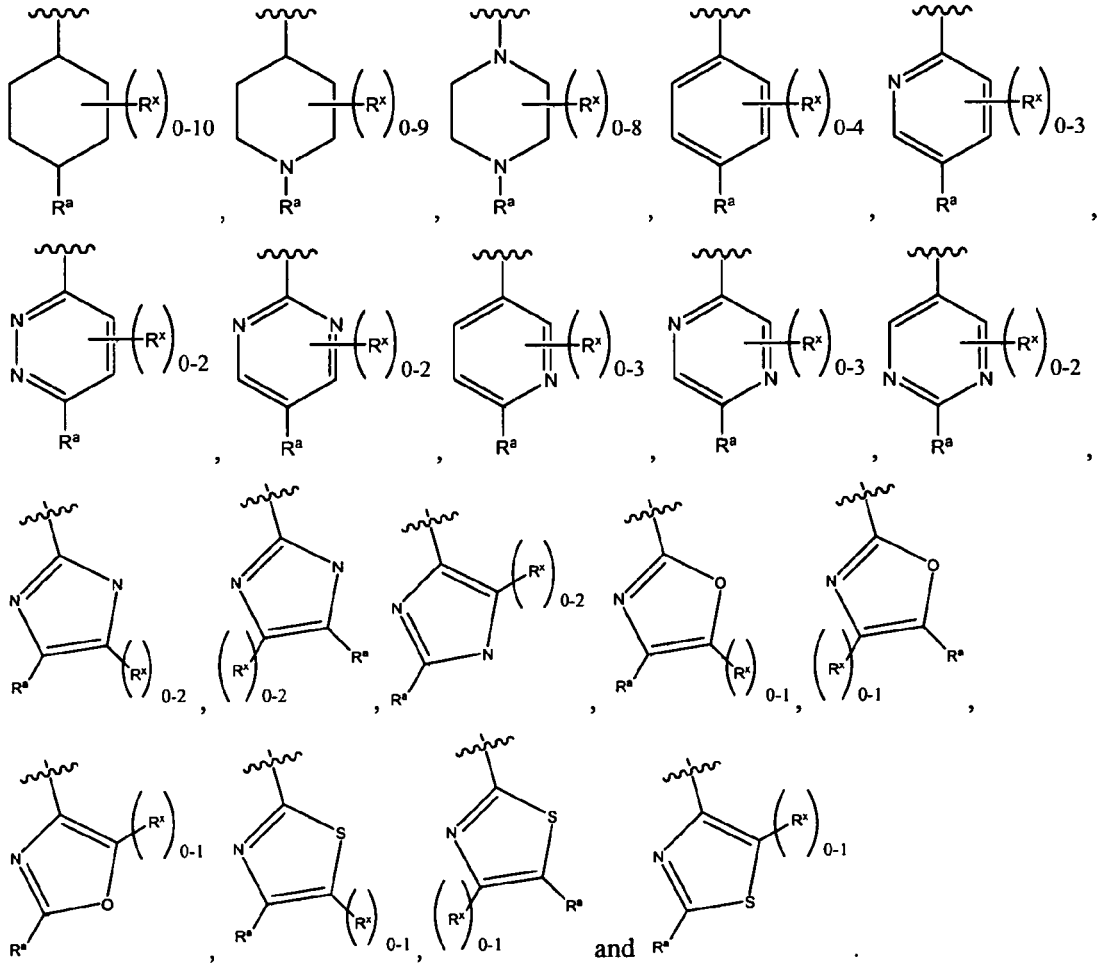
Preferred compounds within the scope of Formula II include compounds wherein B^1 and B^2 together with the ring atoms to which they are attached combine to form





Preferred compounds within the scope of Formula I and II include compounds where Y is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, phenyl, pyridinyl, pyrimidinyl, cyclopentadienyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl.

Preferred compounds within the scope of Formula I and II further include compounds where R^1 is selected from

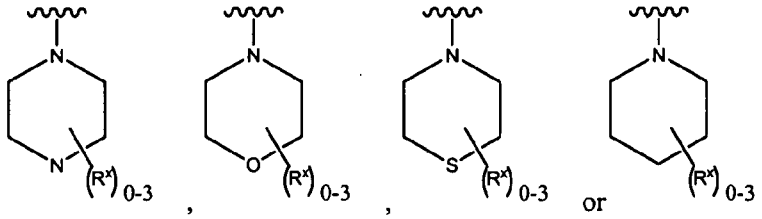


Preferred compounds within the scope of Formula I and II further include comounds where R^a is selected from

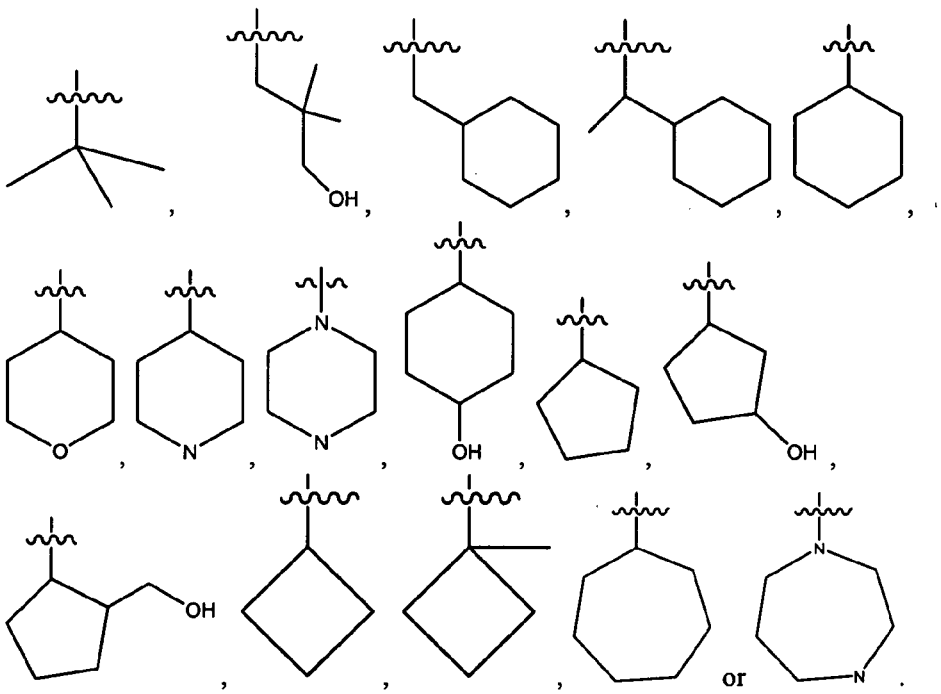
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

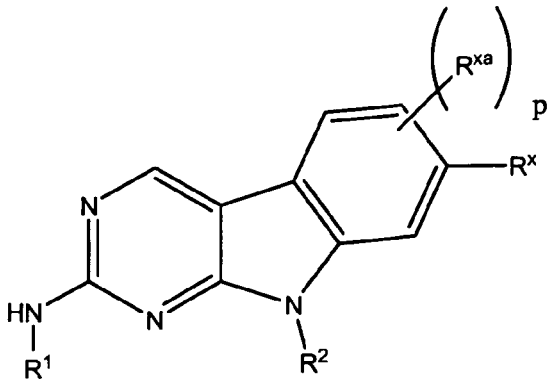
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



Preferred compounds within the scope of Formula I and II further include compounds where R^2 is



Preferred compounds within the scope of Formula I include compounds of the following formula IA



IA

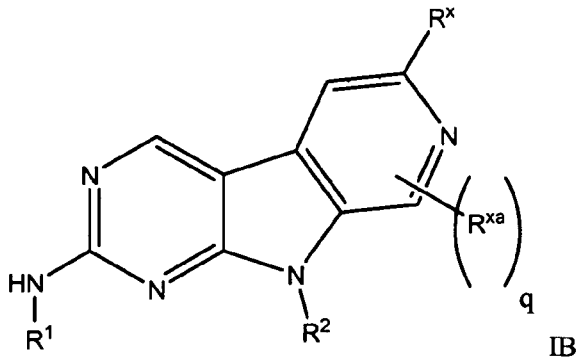
wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, -(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-$S(O)_nR^5$*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-$C(=O)R^5$*, -(alkylene)$_m$-$C(=S)R^5$*, -(alkylene)$_m$-$C(=O)OR^5$*, -(alkylene)$_m$-$OC(=O)R^5$*, -(alkylene)$_m$-$C(=S)OR^5$*, -(alkylene)$_m$-$C(=O)NR^3$*R^4*, -(alkylene)$_m$-$C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)R^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)R^5$*, -(alkylene)$_m$-$OC(=O)NR^3$*R^4*, -(alkylene)$_m$-$OC(=S)NR^3$*R^4*, -(alkylene)$_m$-SO_2NR^3*R^4*, -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*, -(alkylene)$_m$-$N(R^3$*$)SO_2NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)OR^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)OR^5$*, or -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*;

m is 0 or 1 ; and
p is zero to three.

Preferred compounds within the scope of Formula IA include compounds having any of the preferred Y, R^1, R^a and/or R^2 substituents previously listed above.

Preferred compounds within the scope of Formula I include compounds having the following Formula IB



IB

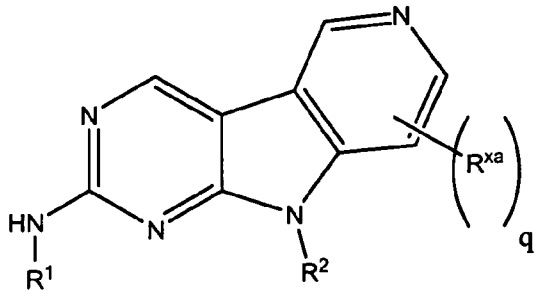
wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, —(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-$S(O)_nR^5$*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-$C(=O)R^5$*, -(alkylene)$_m$-$C(=S)R^5$*, -(alkylene)$_m$-$C(=O)OR^5$*, -(alkylene)$_m$-$OC(=O)R^5$*, -(alkylene)$_m$-$C(=S)OR^5$*, —(alkylene)$_m$-$C(=O)NR^3$*R^4*, -(alkylene)$_m$-$C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)R^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)R^5$*, -(alkylene)$_m$-$OC(=O)NR^3$*R^4*, -(alkylene)$_m$-$OC(=S)NR^3$*R^4*, -(alkylene)$_m$-SO_2NR^3*R^4*, -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*, -(alkylene)$_m$-$N(R^3$*$)SO_2NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)OR^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)OR^5$*, or -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*;

m is 0 or 1 ; and
q is zero to two.

Preferred compounds within the scope of Formula IB include compounds having any of the preferred Y, R^1, R^a and/or R^2 substituents previously listed above.

Preferred compounds within the scope of Formula I include compounds having the following Formula IC



IC

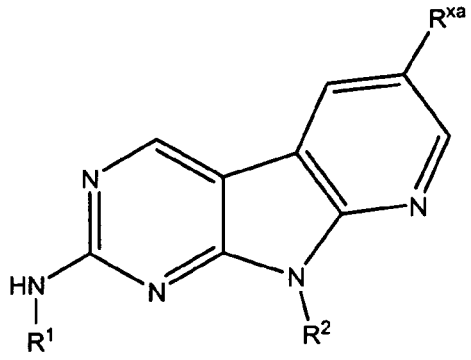
wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, -(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-$S(O)_nR^5$*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-$C(=O)R^5$*, -(alkylene)$_m$-$C(=S)R^5$*, -(alkylene)$_m$-$C(=O)OR^5$*, -(alkylene)$_m$-$OC(=O)R^5$*, -(alkylene)$_m$-$C(=S)OR^5$*, -(alkylene)$_m$-$C(=O)NR^3$*R^4*, -(alkylene)$_m$-$C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)R^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)R^5$*, -(alkylene)$_m$-$OC(=O)NR^3$*R^4*, -(alkylene)$_m$-$OC(=S)NR^3$*R^4*, -(alkylene)$_m$-SO_2NR^3*R^4*, -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*, -(alkylene)$_m$-$N(R^3$*$)SO_2NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)OR^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)OR^5$*, or -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*;

m is 0 or 1 ; and
q is zero to two.

Preferred compounds within the scope of Formula IC include compounds having any of the preferred Y, R^1, R^a and/or R^2 substituents previously listed above.

Preferred compounds within the scope of Formula I include compounds having the following Formula ID



ID

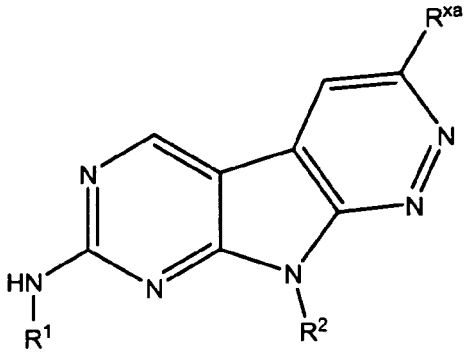
wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, —(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-$S(O)_nR^5$*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-$C(=O)R^5$*, -(alkylene)$_m$-$C(=S)R^5$*, -(alkylene)$_m$-$C(=O)OR^5$*, -(alkylene)$_m$-$OC(=O)R^5$*, -(alkylene)$_m$-$C(=S)OR^5$*, —(alkylene)$_m$-$C(=O)NR^3$*R^4*, -(alkylene)$_m$-$C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)R^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)R^5$*, -(alkylene)$_m$-$OC(=O)NR^3$*R^4*, -(alkylene)$_m$-$OC(=S)NR^3$*R^4*, -(alkylene)$_m$-SO_2NR^3*R^4*, -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*, -(alkylene)$_m$-$N(R^3$*$)SO_2NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)OR^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)OR^5$*, or -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*;

m is 0 or 1 ; and
q is zero to two.

Preferred compounds within the scope of Formula ID include compounds having any of the preferred Y, R^1, R^a and/or R^2 substituents previously listed above.

Preferred compounds within the scope of Formula I include compounds having the following Formula IE



IE

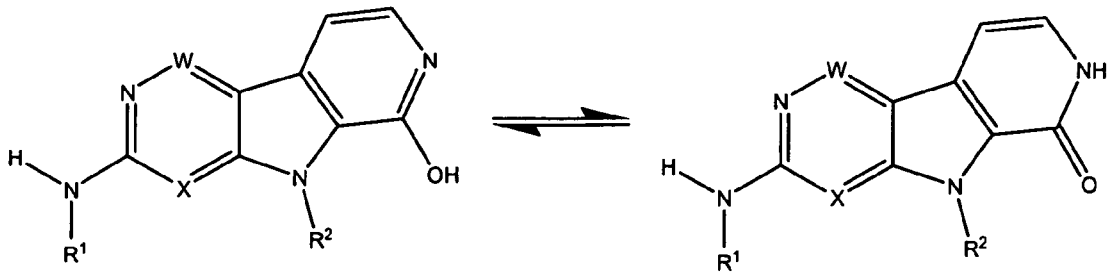
wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, —(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-$S(O)_nR^5$*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-$C(=O)R^5$*, -(alkylene)$_m$-$C(=S)R^5$*, -(alkylene)$_m$-$C(=O)OR^5$*, -(alkylene)$_m$-$OC(=O)R^5$*, -(alkylene)$_m$-$C(=S)OR^5$*, —(alkylene)$_m$-$C(=O)NR^3$*R^4*, -(alkylene)$_m$-$C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)R^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)R^5$*, -(alkylene)$_m$-$OC(=O)NR^3$*R^4*, -(alkylene)$_m$-$OC(=S)NR^3$*R^4*, -(alkylene)$_m$-SO_2NR^3*R^4*, -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*, -(alkylene)$_m$-$N(R^3$*$)SO_2NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)OR^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)OR^5$*, or -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*;

m is 0 or 1 ; and
q is zero to two.

Preferred compounds within the scope of Formula IE include compounds having any of the preferred Y, R^1, R^a and/or R^2 substituents previously listed above.

Certain compounds within the scope of the present invention exist as keto-enol tautomers. For example compounds such as the following:



The current invention further provides a method of treating disorders or conditions consisting of abnormal cell proliferation, such as cancer, atherosclerosis, postsurgical vascular stenosis, restenosis, and endometriosis; infections, including viral infections such as DNA viruses like herpes and RNA viruses like HIV, and fungal infections; autoimmune diseases such as psoriasis, inflammation like rheumatoid arthritis, lupus, type 1 diabetes, diabetic nephropathy, multiple sclerosis, and glomerulonephritis, organ transplant rejection, including host versus graft disease, in a mammal, including human, comprising administering to said mammal an amount of a compound of formula I or II, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

This invention further provides compounds of Formula I and II that are useful for treating abnormal cell proliferation such as cancer. The invention provides a method of treating a abnormal cell proliferation disorder such as myeloid disorders, lymphoid disorders, Hodgkin's hairy cells, leukemia, cancers of the breast, lung, colon, ovary, cervix, prostrate, testis, esophagus, stomach, skin, bone, pancreas, thyroid, biliary passages, buccal cavity and pharyns (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, glioblastoma, neuroblastoma, keratocanthoma, epidermoid carcinoma, large cell carcinoma, adenocarcinoma, adenocarcinoma, adenoma, adenocarcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma, and kidney carcinoma, comprising administering a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, to a subject with one or more above disorders.

Embodiment of this invention is also a method of treating subjects with diseases caused by vascular smooth muscle cell proliferation. The method comprises administering to a subject with such a disorder an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

This invention further provides a method of treating a subject suffering from gout comprising administering to said subject in need of treatment an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, sufficient to treat the condition.

The present invention further provides a method of treating a subject with kidney disease, such as polycystic kidney disease, comprising administering to said subject in need of treatment an amount of a compound of formula I and II, or a pharmaceutically acceptable salt thereof, sufficient to treat the condition.

DEFINITIONS

The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer, pancreatic cancer, cervical cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer. The terms "treating," "treatment," and "therapy" as used herein refer to curative therapy, prophylactic therapy, and preventative therapy.

The term "mammal" as used herein refers to any mammal classified as a mammal, including humans, cows, horses, dogs and cats. In a preferred embodiment of the invention, the mammal is a human.

The term "treatment" includes therapeutic treatment as well as prophylactic treatment (either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals).

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. For example, effective neoplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkylene" embraces bridging divalent alkyl radicals such as methylene, ethylene, propylene, isopropylene and the like. The term "lower alkyl substituted with R^{2}" does not include an acetal moiety.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Most preferred lower alkenyl radicals are radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

Alkyl, alkylenyl, alkenyl, and alkynyl radicals may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said "aryl" group may have 1 or more substituents such as lower alkyl, hydroxyl, halo,

haloalkyl, nitro, cyano, alkoxy, lower alkylamino, and the like. Phenyl substituted with -O-CH_2-O- forms the aryl benzodioxolyl substituent.

The term "heterocyclyl" (or "heterocyclo") embraces saturated, and partially saturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Heterocyclic rings comprise monocyclic 6-8 membered rings, as well as 5-16 membered bicyclic ring systems (which can include bridged fused and spiro-fused bicyclic ring systems). It does not include rings containing -O-O-,-O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino, lower alkylamino, and the like.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl, dihydrothiazolyl, and the like.

Particular examples of partially saturated and saturated heterocyclyl include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

The term heterocyclyl, (or heterocyclo) also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl].

The term "heteroaryl" denotes aryl ring systems that contain one or more heteroatoms selected from the group O, N and S, wherein the ring nitrogen and sulfur atom(s) are optionally oxidized, and nitrogen atom(s) are optionally quarternized. Examples include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-

1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$).

The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" where sulfamyl radicals are independently substituted with one or two alkyl radical(s). More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, and N-ethylaminosulfonyl.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-.

The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$.

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals independently substituted with one or two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The terms "heterocyclylalkylenyl" and "heterocyclylalkyl" embrace heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkyl radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH_3S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups, which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups, which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C_1-C_3-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups, which have been independently substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl

substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with alkylaminoalkoxy radicals. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminomethoxyethoxy, N-methylaminoethoxyethoxy, N,N-dimethylaminoethoxyethoxy, N,N-diethylaminomethoxymethoxy and the like.

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH_2 groups.

The term "halosulfonyl" embraces sulfonyl radicals substituted with a halogen radical. Examples of such halosulfonyl radicals include chlorosulfonyl and fluorosulfonyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C_1-C_3-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

The term "heteroaryloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heteroarylalkoxy" embraces oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having optionally substituted heteroaryl radicals attached to lower alkoxy radical as described above.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C_3-C_6 rings. More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "5-6-membered cycloalkylalkyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals

include cyclohexylmethyl. The cycloalkyl in said radicals may be additionally substituted with halo, alkyl, alkoxy and hydroxy.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Preferred cycloalkenyl groups include C_3-C_6 rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of an angiogenesis mediated disease state, including those described previously. The compounds of the present invention are useful in the manufacture of an anti-cancer medicament.

The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of the current invention in association with a least one pharmaceutically acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating angiogenesis related disorders in a subject having or susceptible to such disorder, the method comprising treating the subject with a therapeutically effective amount of a compound of the current invention.

COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of the current invention may also be

administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anticancer or cytotoxic agent.

Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline

SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of α-carotene, α-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium,

didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprabin, elliptinium acetate, Tsumura EPMTC, the epothilones, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanlne derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a,

interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Alternatively, the present compounds may also be used in co-therapies with VEGFR inhibitors including

N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-1-phthalazinamine;

4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide;

N-[2-(diethylamino)ethyl]-5-[(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide;

3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide;

N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine;

3-[5,6,7,13-tetrahydro-9-[(1-methylethoxy)methyl]-5-oxo-12H-indeno[2,1-a]pyrrolo[3,4-c]carbazol-12-yl]propyl ester N,N-dimethyl-glycine;

N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide;

N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-4-quinazolinamine

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine

N-(3-((((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((3-(1,3-oxazol-5-yl)phenyl)amino)-3-pyridinecarboxamide;

2-(((4-fluorophenyl)methyl)amino)-N-(3-((((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-[3-(Azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide.

6-fluoro-N-(4-(1-methylethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

2-((4-pyridinylmethyl)amino)-N-(3-(((2S)-2-pyrrolidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-(3-(1,1-dimethylethyl)-1H-pyrazol-5-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3,3-dimethyl-2,3-dihydro-1-benzofuran-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-((((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

2-((4-pyridinylmethyl)amino)-N-(3-((2-(1-pyrrolidinyl)ethyl)oxy)-4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(4-(pentafluoroethyl)-3-(((2S)-2-pyrrolidinylmethyl)oxy)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-((3-azetidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-(4-piperidinyloxy)-5-(trifluoromethyl)phenyl)-2-((2-(3-pyridinyl)ethyl)amino)-3-pyridinecarboxamide;

N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;
2-(1H-indazol-6-ylamino)-N-[3-(1-methylpyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;
N-[1-(2-dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(1H-indazol-6-ylamino)-nicotinamide;
2-(1H-indazol-6-ylamino)-N-[3-(pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;
N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;
N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;
N-[4-(tert-butyl)-3-(3-piperidylpropyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide;
N-[5-(tert-butyl)isoxazol-3-yl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide; and
N-[4-(tert-butyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide.

Other compounds described in the following patents and patent applications can be used in combination therapy: US 6,258,812, US 2003/0105091, WO 01/37820, US 6,235,764, WO 01/32651, US 6,630,500, US 6,515,004, US 6,713,485, US 5,521,184, US 5,770,599, US 5,747,498, WO 02/68406, WO 02/66470, WO 02/55501, WO 04/05279, WO 04/07481, WO 04/07458, WO 04/09784, WO 02/59110, WO 99/45009, WO 00/59509, WO 99/61422, US 5,990,141, WO 00/12089 and WO 00/02871.

In some embodiments, the combination comprises a composition of the present invention in combination with at least one anti-angiogenic agent. Agents are inclusive of, but not limited to, *in vitro* synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

Exemplary anti-tumor agents include HERCEPTIN™ (trastuzumab), which may be used to treat breast cancer and other forms of cancer, and RITUXAN™ (rituximab), ZEVALIN™ (ibritumomab tiuxetan), and LYMPHOCIDE™ (epratuzumab), which may be used to treat non-Hodgkin's lymphoma and other forms of cancer, GLEEVAC™ which may be used to treat chronic myeloid leukemia and gastrointestinal stromal tumors, and BEXXAR™ (iodine 131 tositumomab) which may be used for treatment of non-Hodgkins's lymphoma.

Exemplary anti-angiogenic agents include KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™ or VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as ERBITUX™ (IMC-C225), and VECTIBIX™ (panitumumab) IRESSA™ (gefitinib), TARCEVA™ (erlotinib), anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically

binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents. The pharmaceutical compositions of the present invention can also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor "c-Met" as well as small molecules inhibitors of the c-Met kinase activity.

Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., US Publication No. 2003/0162712; US Patent No. 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, Wiley, US Patent No. 6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., US Publication No. 2002/0042368), specifically binding anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (US Patent Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

Additional anti-angiogenic/anti-tumor agents include: SD-7784 (Pfizer, USA); cilengitide.(Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, USA); TLC ELL-12, (Elan, Ireland); anecortave acetate, (Alcon, USA); alpha-D148 Mab, (Amgen, USA); CEP-7055,(Cephalon, USA); anti-Vn Mab, (Crucell, Netherlands) DAC:antiangiogenic, (ConjuChem, Canada); Angiocidin, (InKine Pharmaceutical, USA); KM-2550, (Kyowa Hakko, Japan); SU-0879, (Pfizer, USA); CGP-79787, (Novartis, Switzerland, EP 970070); ARGENT technology, (Ariad, USA); YIGSR-Stealth, (Johnson & Johnson, USA); fibrinogen-E fragment, (BioActa, UK); angiogenesis inhibitor, (Trigen, UK); TBC-1635, (Encysive Pharmaceuticals, USA); SC-236, (Pfizer, USA); ABT-567, (Abbott, USA); Metastatin, (EntreMed, USA); angiogenesis inhibitor, (Tripep, Sweden); maspin, (Sosei, Japan); 2-methoxyestradiol, (Oncology Sciences Corporation, USA); ER-68203-00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz-93, (Tsumura, Japan); TAN-1120, (Takeda, Japan); FR-111142, (Fujisawa, Japan, JP 02233610); platelet factor 4, (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist, (Borean, Denmark); cancer therapy, (University of South Carolina, USA); bevacizumab (pINN), (Genentech, USA); angiogenesis inhibitors, (SUGEN, USA); XL 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb, alpha5beta3 integrin, second generation, (Applied Molecular Evolution, USA and MedImmune, USA); gene therapy, retinopathy, (Oxford BioMedica, UK); enzastaurin hydrochloride (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA and Sanofi-Synthelabo, France); BC 1, (Genoa Institute of Cancer Research, Italy); angiogenesis inhibitor, (Alchemia, Australia); VEGF antagonist, (Regeneron, USA); rBPI 21 and BPI-derived antiangiogenic, (XOMA, USA); PI 88, (Progen, Australia); cilengitide

(pINN), (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); cetuximab (INN), (Aventis, France); AVE 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin, (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA); ANGIOSTATIN, (Boston Childrens Hospital, USA); 2-methoxyestradiol, (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenesis, (EntreMed, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol, (EntreMed, USA); anginex, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); tumor necrosis factor-alpha inhibitors, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S-3APG , (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alpha5 beta1, (Protein Design, USA); KDR kinase inhibitor, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sankyo, Japan); combretastatin A4 prodrug, (Arizona State University, USA); chondroitinase AC, (IBEX, Canada); BAY RES 2690, (Bayer, Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetrathiomolybdate, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, vascular endothelium growth factor, (Xenova, UK); irsogladine (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); squalamine (pINN), (Genaera, USA); RPI 4610, (Sirna, USA); cancer therapy, (Marinova, Australia); heparanase inhibitors, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VGA 1102, (Taisho, Japan);

VEGF receptor modulators, (Pharmacopeia, USA); VE-cadherin-2 antagonists , (ImClone Systems, USA); Vasostatin, (National Institutes of Health, USA);vaccine, Flk-1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan); TumStatin, (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1), (Merck & Co, USA); Tie-2 ligands, (Regeneron, USA); and, thrombospondin 1 inhibitor, (Allegheny Health, Education and Research Foundation, USA).

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as VEGF antagonists, other kinase inhibitors including p38 inhibitors, KDR inhibitors, EGF inhibitors (such as panitumumab), CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, NSAID's, $\alpha_v\beta_3$ inhibitors, phosphatidylinitisol 3-kinase inhibitors, AKT/PCK inhibitors, proteasome inhibitors (such as Velcade™), Trail receptor agonists (such as AMG 655), Trail (such as AMG 951), XIAP inhibitors, BCI2 inhibitors, Aurora kinase inhibitors, Raf kinases inhibitors, ubiquitin ligase inhibitors, HGF inhibitors (such as AMG 102), and c-Met inhibitors (such as compounds described WO 06/116713 and U.S. Serial No. 11/879,034).

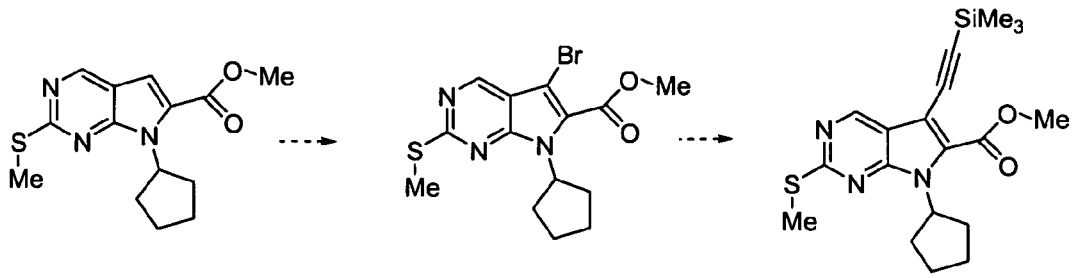
Also included in the family of compounds of the current are the pharmaceutically acceptable salts and solvates thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the current invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of the current invention include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, aistidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding

compound of the invention by reacting, for example, the appropriate acid or base with the compound of the current invention. When a basic group and an acid group are present in the same molecule, a compound of the current invention may also form internal salts.

GENERAL SYNTHETIC PROCEDURES

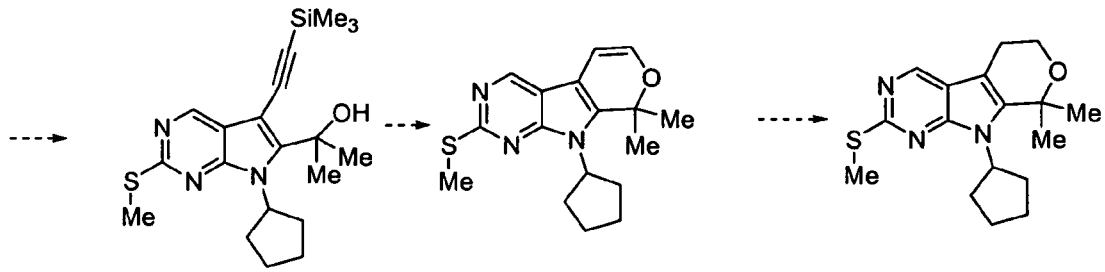
The compounds of the invention can be synthesized according to the procedures illustrated in the following working examples, as well as by alternative methods known to those of ordinary skill in the art..

Additional analogs can be prepared by the following general schemes.



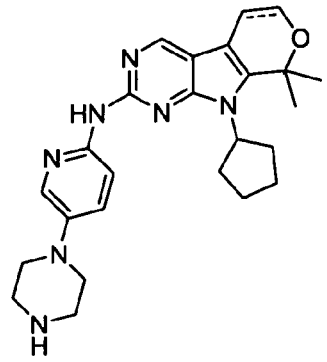
227 **A** **B**

Bromination of compound **227** with NBS in analogy to the preparation of compound **230** of example 168 provides bromo ester **A**. Sonagshira coupling provides the alkyne **B**. Grignard addition provides the tertiary alcohol **C**. Mild acidic workup provides the fused pyran **D.**

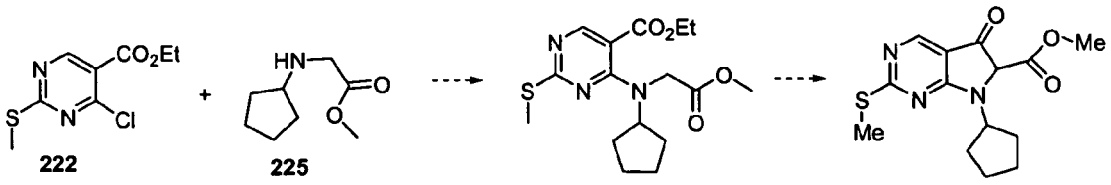


C D E

The thiomethyl group of compounds D and E can be converted to typical substituted heteroaryl and aryl amines in analogy to example 168 providing inhibitors such as F and G.

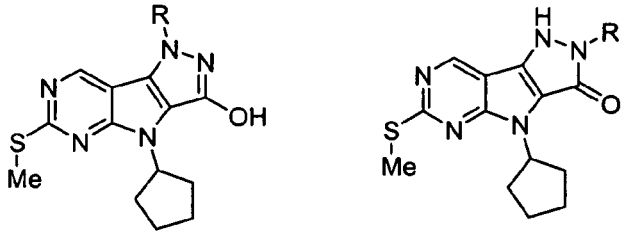


F/G

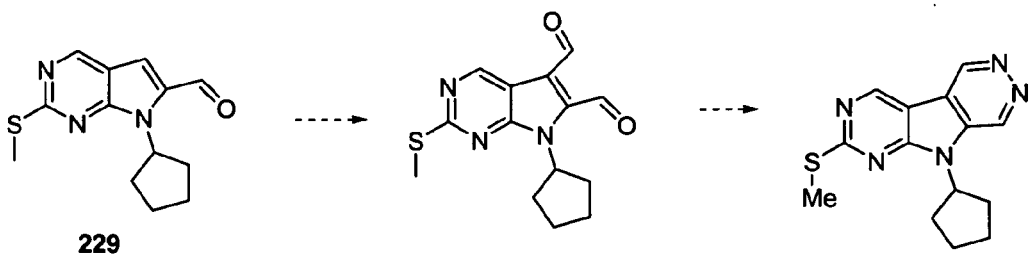


222 225 A2 B2

Condensation of amine **225** with pyrimidine **222** provides diester **A2** which can undergo claisen condensation to the keto ester **B2**, which is a versatile intermediate for a number of transformations. Condensation with hydrazines can lead to fused pyrazoles such a **C2** and **D2**, which can be further modified to examples of this invention.



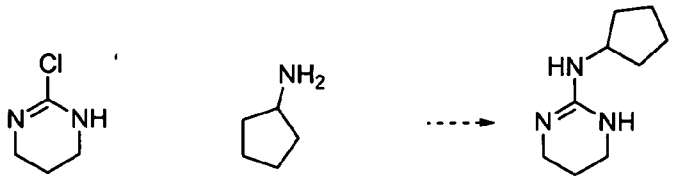
C2 **D2**



229

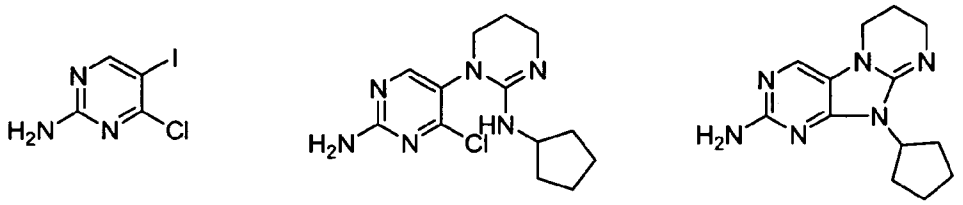
229 **A3** **B3**

Aldehdye **229** can be formylated to an equivalent of the dialdehyde **A3** which can be used to form the fused pyridazine **B3**, which can be further modified to examples of this invention.



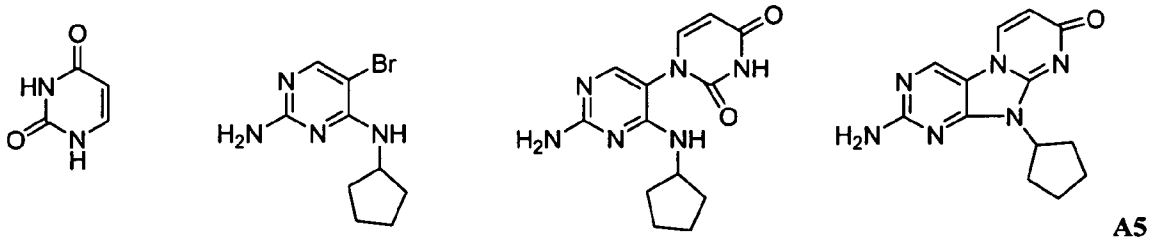
A4 **B4**

According to Kan, Wai Ming; Lin, Shih-Hsun; Chern, Ching-Yuh SynComm V35 p2633 y2005, amines such as cyclopentyl amine can be added to chloroformamidines such as **A4** to form guanidines such as **B4**. Buchwald coupling with halopyrimidines such as **C4** followed by intramolecular cyclization can provide substrates for elaboration to examples of this invention. The 5 and 7-member ring analogs of **A4** are also useable.



C4 **D4** **E4**

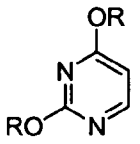
The use of uracil **A5** or dialkoxypyrimidine heterocycles can lead to more elaborate analogs.



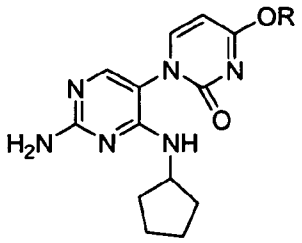
A5

B5 **C5** **D5**

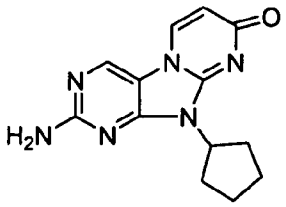
or



A6



C6

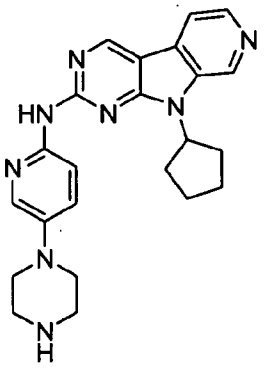


D5

EXAMPLES

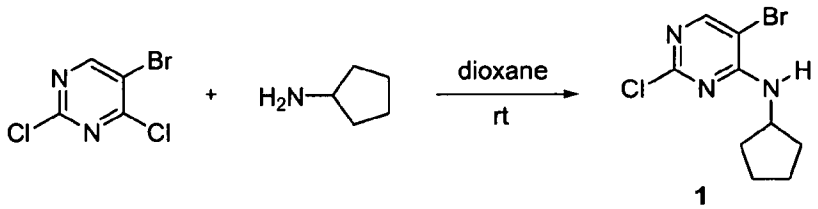
The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results.

EXAMPLE 1



7

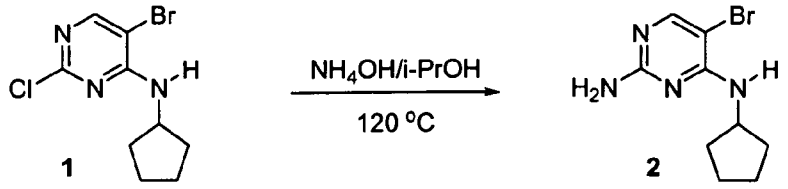
9-cyclopentyl-*N*-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



1

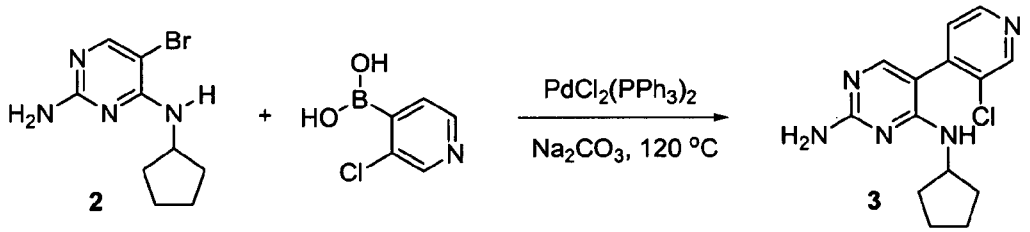
5-Bromo-2-chloro-*N*-cyclopentylpyrimidin-4-amine (1): To a solution of 5-bromo-2,4-dichloropyrimidine (45.6 g, 200 mmol) in dioxane (400 mL) was added *N*-cyclopentylamine (20.4 g, 240 mmol) at room temperature. The mixture thus obtained was stirred at room temperature for 6 h. The reaction mixture was then diluted with ethyl acetate and washed with brine and dried over $MgSO_4$. The solvent was evaporated to give the title compound as a light yellow solid (56 g, 100%) which was used in next step without further purification. ^1H NMR (500 MHz, *DMSO-d6*) δ 8.23 (1H, s), 7.37 (1H,

d, J=7.3 Hz), 4.31 (1H, m), 1.92 (2H, m), 1.71 (2H, m), 1.53-1.59 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 276.0, Calculated 275.9.



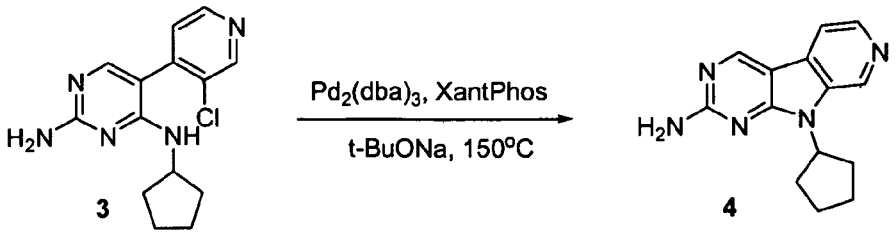
1 2

5-Bromo-N^4-cyclopentylpyrimidine-2,4-diamine (2): A solution of **1** (45 g, 200 mmol) in 28% NH_4OH/iso-propanol (1/1, 400 mL) was heated at 120 °C in a sealed tube for 22 h. The product was extracted with dichloromethane and the organic layers were washed with brine and dried. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with 25% ethyl acetate in hexanes to give the titled compound (**2**) as a white solid (34 g, 66%). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 7.77 (1H, s), 6.19 (2H, br. s), 6.12 (1H, d, 1H, J = 7.3 Hz), 4.33(1H, m)1.90 (2H, m), 1.69 (2H, m), 1.49-1.55 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 257.0, Calculated 257.0.

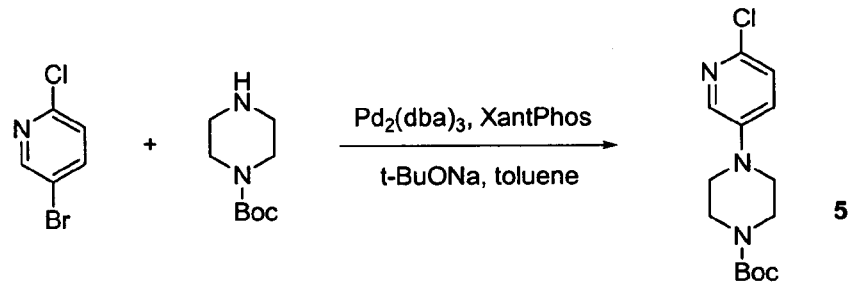


2 3

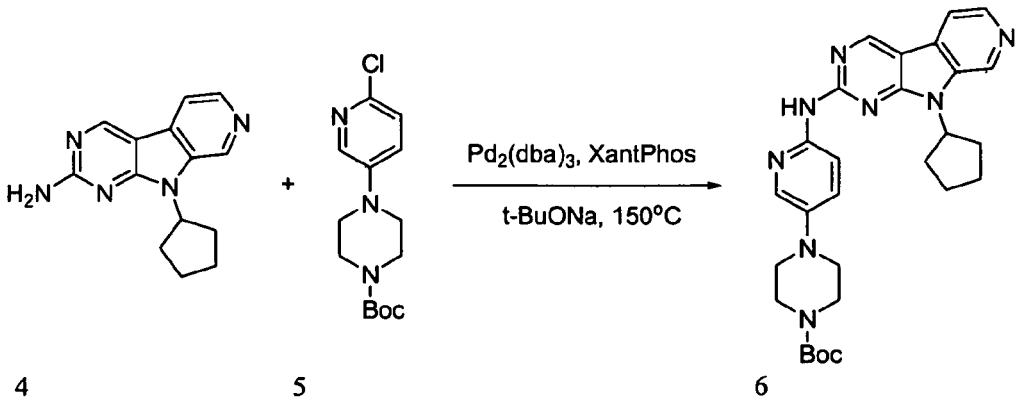
5-(3-Chloropyridin-4-yl)-N^4-cyclopentylpyrimidine-2,4-diamine (3): To a solution of **2** (2.57 g, 10.0 mmol) in dioxane (75 mL) were added 3-chloropyridine-4-boronic acid (4.72 g, 10.0 mmol), trans-dichlorobis(triphenylphosphine)-palladium(II)(702 mg, 1.0 mmol), and sodium carbonate (3.82 g, 36 mmol, in 36 mL of water). The mixture thus obtained was purged with N_2 for 10 min and heated at 120°C in a sealed tube for 22 h. The reaction mixture was diluted with water and the product was extracted with chloroform. The organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 2.5% methanol in dichloromethane to give the title compound (**3**) as a white solid (2.31g, 80%). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 8.64 (1H, s), 8.50 (1H, d, J = 4.9 Hz), 7.51 (1H, s), 7.34 (1H, d, 1H, J = 4.9 Hz), 6.21 (2H, d, 1H, br s), 5.97 (1H, d, J = 7.6 Hz), 4.43 (1 H, p, J = 7.4Hz), 1.84 (2H, m), 1.62 (2H, m), 1.40-1.49 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 290.0, Calculated 290.1.



9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (4): To a solution of **3** (2.3 g, 7.9 mmol) in dioxane (60 mL) were added tris(dibenzylideneacetone)dipalladium (0) (368 mg, 0.4 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (696 mg, 1.2 mmol), and sodium *t*-butoxide (1.15 g, 12 mmol). The mixture thus obtained was heated at 150 °C under microwave irradiation for 3 h. The reaction mixture was passed through a short pack silica gel column and concentrated. The residue was purified by flash chromatography on silica gel eluting with 2% methanol in dichloromethane to give the title compound (**4**) as a white solid (1.71 g, 85%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.05 (1H, s), 8.87 (1H, br. s), 8.37 (1H, d, J = 4.9 Hz), 7.93 (1H, d, J = 5.1 Hz), 6.97 (2H, br. s), 5.33 (1H, p, J = 8.6Hz), 2.27 (2H, m), 2.04 (4H, m), 1.76 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 254.1, Calculated 254.1.

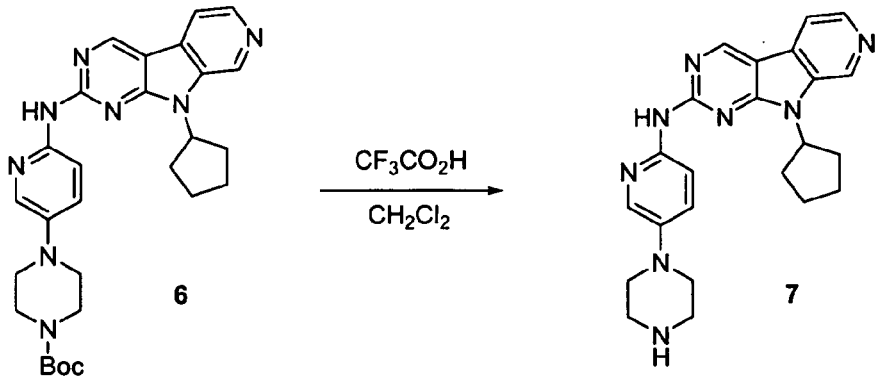


4-(4-Chloro-pyrid-2-yl)-piperidine-1-carboxylic acid t-butyl ester (5): As reported in Ji, J.; Li, T.; Bunnelle, W. H., *Org. Lett.* **2003,** 5, (24), 4611-4614, *t*-butyl 1-piperazinecarboxylate (11.18 g, 60 mmol), sodium t-butoxide (8.64 g, 90 mmol), $Pd_2(dba)_3$ (1.10 g, 1.20 mmol), and XantPhos (2.08 g, 3.6 mmol) were added to a solution of 5-bromo-2-chloropyridine (11.54 g, 60 mmol) in toluene (300 mL). The mixture was evacuated and purged with argon (3 cycles), then heated at 100 °C for 5 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (1200 mL) and washed with water (300 mL). The organic solution was concentrated under pressure, and the residue was purified by flash chromatography on silica gel eluting with 17% ethyl acetate in hexane to give compound **5** as a light yellow solid (14.56 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.19 – 7.18 (2H, m), 3.59 (4H, dd, J = 12 Hz, J = 4 Hz), 3.14 (4H, dd, J = 12 Hz, J = 4 Hz), 1.49 (9H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 298.1, Calculated 298.1.



4 5 6

t-Butyl 4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (6): To a solution of compound **4** (1.6 g, 6.3 mmol) in dioxane (60 mL) were added compound **5** (2.3 g, 7.6 mmol), tris(dibenzylideneacetone) dipalladium (0) (293 mg, 0.32 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (370 mg, 0.64 mmol), and sodium *t*-butoxide (908 mg, 9.45 mmol). The mixture thus obtained was heated at 150 °C under microwave irradiation for 1 h. The reaction mixture was passed through a short pack silica gel column and concentrated to give the title compound **6** as a yellow solid (3.28 g) which was used in next step without further purification. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.11 (1H, s), 8.93 (1H, br. s), 8.53 (1H, d, J = 5.1 Hz), 8.44 (1H, d, J = 9.3 Hz), 8.28 (1H, br. s), 8.09 (1 H, d, J = 2.9Hz), 7.87 (1H, dd, J = 5.1Hz, 0.9Hz), 7.41 (1H, dd, J = 9.3Hz, 2.9Hz), 5.40 (1H, p, J = 8.8Hz), 3.65 (4H, t, J = 5.2Hz), 3.15 (4H, t, J = 4.9Hz), 2.46 (2H, m), 2.15-24 (4H, m), 1.91 (2H, m), 1.52 (9H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 515.2, Calculated 515.3.

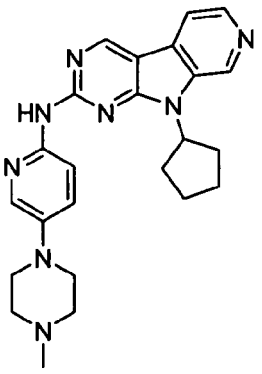


6 7

9-Cyclopentyl-*N*-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (7): A solution of compound **6** (3.28 g, 6.37 mmol) in TFA/DCM (60, 1:1) was stirred at room temperature for 30 min. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting with CH_2Cl_2/methanol/NH_4OH (200:10:1) to give the title compound (**7**) as an off-white solid (2.60 g, 98%). ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ 9.86 (1H, s), 9.28 (1H, s), 9.01 (1H, s), 8.68 (1H, br s), 8.45 (1H, d, J = 4 Hz), 8.23 (1 H, d, J = 8 Hz), 8.10 (1H, d, J = 4

Hz), 8.04 (1H, d, J = 8 Hz), 7.54 (1H, dd, J = 8 Hz, J = 4 Hz), 5.43 (1H, p, J = 8 Hz), 3.35 (4H, m), 3.26 (4H, m), 2.40 (2H, m), 2.03-2.10 (4H, m), 1.78 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 415.1, Calculated 415.2.

EXAMPLE 2

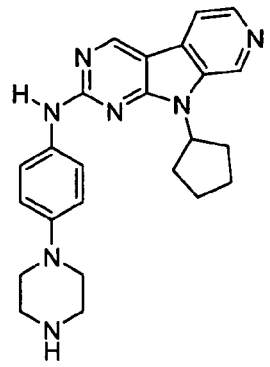


8

9-Cyclopentyl-*N*-(5-(1-(*N*^{4}-methylpiperazinyl))-2-pyridinyl)-9H-pyrido- [4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **8** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (1H, s), 8.90 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.39 (1H, d, J = 8 Hz), 8.06 (1H, s), 8.05 (1 H, s), 7.84 (1H, d, J = 5 Hz), 7.39 (1H, dd, J = 8 Hz, J = 2 Hz), 5.39 (1H, p, J = 8 Hz), 3.22 (4H, t, J = 5 Hz), 2.63 (4H, t, J = 5 Hz), 2.44 (2H, m), 2.39 (3H, s), 2.14-2.21 (4H, m), 1.88 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2, Calculated 429.2.

EXAMPLE 3

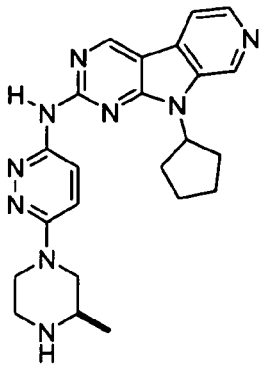


9

(9-Cyclopentyl-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(4-piperazin-1-yl-phenyl)-amine

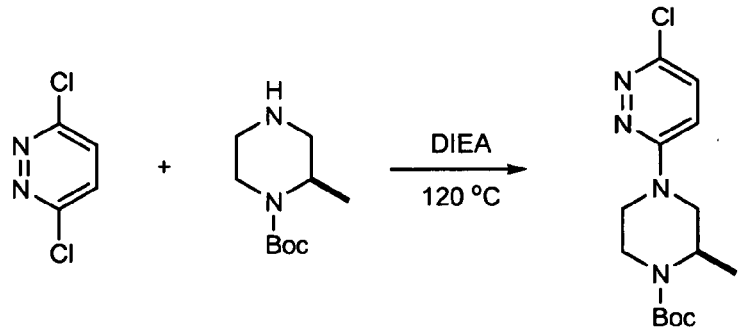
Compound **9** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.39 (1 H, s), 9.15 (1 H, s), 8.49 (2 H, s), 7.72 (2 H, d, *J*=5.0 Hz), 7.11 (2 H, d, *J*=5.0 Hz), 5.33 (1 H, m), 3.43 (8 H, m), 2.54 (2 H, m), 2.22 (2 H, m), 2.21 (2 H, m), 1.86 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 414.2, Calculated 414.2.

EXAMPLE 4



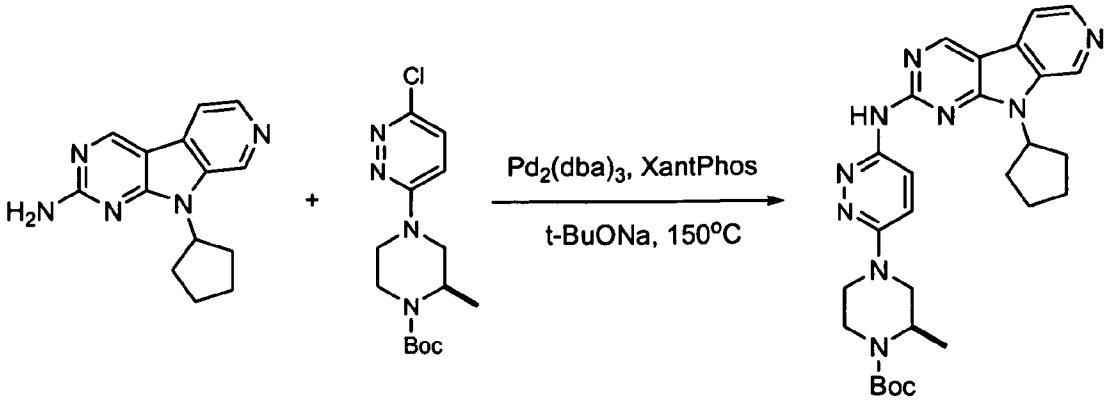
10

(*R*)-9-cyclopentyl-*N*-(6-(1-(3-methylpiperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine



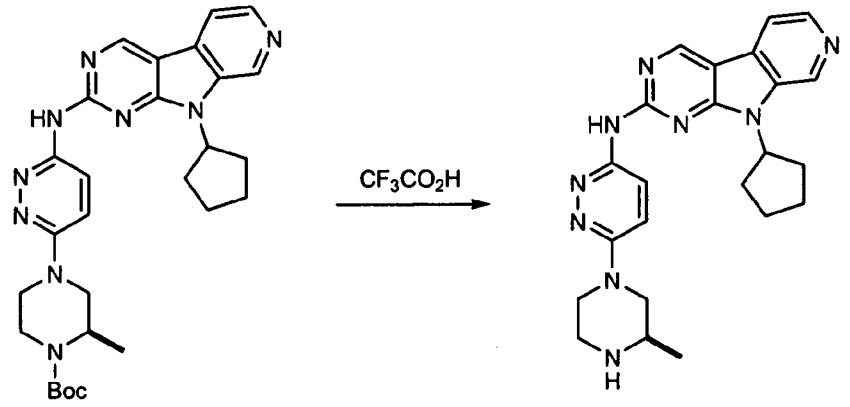
11

(*R*)-tert-butyl 4-(6-chloropyridazin-3-yl)-2-methylpiperazine-1-carboxylate (11): A mixture of 3,6-dichloropyridazine (298 mg, 2 mmol) and (*R*)-1-*N*-Boc-2-methyl piperazine (401 mg, 2.0 mmol) in N,N-diisopropylethylamine (0.7 mL, 4 mmol) was sitrred at 120 °C for 5 h. The reaction mixture was diluted with ethyl acetate and washed with brine (2x), then dried over $MgSO_4$. The salts were removed by filtration and the filtrate was concentrated and the residue was purified by chromatography on silica gel eluting with 20% to 80% ethyl acetate in hexane to give compound **11**as a light yellow solid (511 mg, 82%). . ^{1}H NMR (500 MHz, CD_3OD) δ 7.24 (1H, d, J = 10 Hz), 6.88 (1H, d, J = 10 Hz), 4.38 (1H, br s), 4.17 (1H, d, J = 10 Hz), 4.05 – 3.97 (2H, m), 3.39 (1H, dd, J = 15 Hz, J = 5 Hz), 3.29 (1H, ddd, J = 15 Hz, J = 10 Hz, J = 5 Hz), 1.51 (9H, s), 1.21 (3H, d, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 313.1, Calculated 313.1.



4 11 12

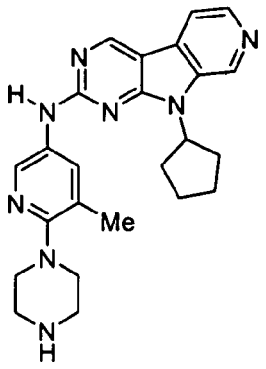
t-Butyl 4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinecarboxylate (12): To a solution of compound **4** (112 mg, 0.40 mmol) in dioxane (4 mL) were added compound **11** (150 mg, 0.48 mmol), tris(dibenzylideneacetone)dipalladium (0) (18.4 mg, 0.02 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (35 mg, 0.06 mmol), and sodium *t*-butoxide (58 mg, 0.60 mmol). The mixture thus obtained was heated at 150 °C under microwave irradiation for 1 h. The reaction mixture was passed through short pack silica gel column and concentrated to give a crude **12** (purity = 85%) as a yellow solid (240 mg) which was used in next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 530.3, Calculated 530.3.



12 10

(*R*)-9-cyclopentyl-*N*-(6-(1-(3-methylpiperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine (10): A solution of compound **12** (240 mg, purity = 85%, 0.385 mmol) in TFA/DCM (4 mL, 1:1) was stirred at room temperature for 30 min. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting with CH_2Cl_2/methanol/NH_4OH (200:10:1) to give compound **10** as an off-white solid (120 mg, 73%). ^1H NMR (500 MHz, *DMSO-d*$_6$) δ 10.19 (1H, s), 9.27 (1H, s), 9.01 (1H, s), 8.46 (1H, d, J = 5 Hz), 8.18 (1H, d, J = 10 Hz), 8.05 (1H, d, J = 5 Hz), 7.40 (1H, d, J = 10 Hz), 5.34 (1H, p, J = 10 Hz), 4.11 (2H, m), 2.97 (1H, m), 2.79 – 2.72 (3H, m), 2.44 – 2.34 (3H, m), 2.09 – 2.04 (4H, m), 1.74 (2H, m), 1.04 (3H, d, J = 5 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 430.2, Calculated 430.2.

EXAMPLE 5

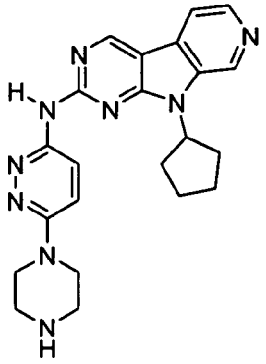


13

9-cyclopentyl-N-(5-methyl-6-(1-piperazinyl)-3-pyridinyl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **13** was prepared using chemistry similar to that described in example 4. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ 10.42 (1H, br s), 9.57 (1H, s), 9.38 (1H, s), 8.86 (2H, br s), 8.67 (1H, d,), 8.57 (1H, d, J = 6.1Hz), 8.52 (1H, d, J = 2.7Hz), 8.03 (1H, s), 5.33 (1H, p, J = 8.8 Hz), 3.26 (8H, m), 2.43 (2H, m), 2.32 (3H, s), 2.13 (2H, m), 2.00 (2H, m), 1.74 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2, Calculated 429.2.

EXAMPLE 6

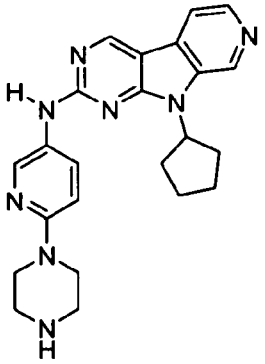


14

9-cyclopentyl-N-(6-(1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine

Compound **14** was prepared using chemistry similar to that described in example 4. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ 11.16 (1H, br s), 9.63 (1H, s), 9.41 (1H, s), 9.01 (2H, br s), 8.71 (1H, d, J = 6.1Hz), 8.64 (1H, d, J = 6.1Hz), 8.23 (1H, d, J = 9.8Hz), 7.69 (1H, d, J = 9.8Hz), 5.37 (1H, p, J = 8.8 Hz), 3.82 (4H, t, J = 5.4 Hz), 3.29 (4H, m), 2.39 (2H, m), 2.13 (2H, m), 2.04 (2H, m), 1.74 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 416.2, Calculated 416.2.

EXAMPLE 7

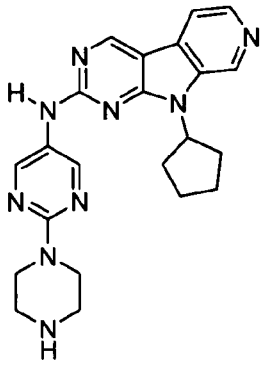


15

9-cyclopentyl-N-(6-(1-piperazinyl)-3-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **15** was prepared using chemistry similar to that described in example 4. ^{1}H NMR (500 MHz, CD_3OD) δ 9.43 (1H, s), 9.18 (1H, s), 8.65 (1H, d, J = 2.6 Hz), 8.53 (2H, s), 8.10 (1H, dd, J = 9.0 Hz, 2.4 Hz), 7.11 (1H, d, J = 9.3 Hz), 5.37 (1H, p, J = 8.6 Hz), 3.85 (4H, t, J = 5.3 Hz), 3.40 (4H, t, J = 5.1 Hz), 2.49 (2H, m), 2.23 (2H, m), 2.21 (2H, m), 1.86 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 415.1, Calculated 415.2.

EXAMPLE 8

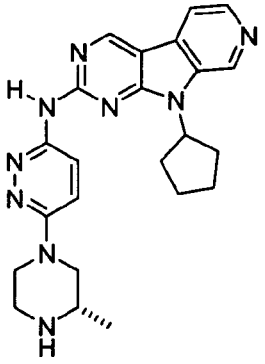


16

9-cyclopentyl-N-(2-(1-piperazinyl)-5-pyrimidinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **16** was prepared using chemistry similar to that described in example 4. ^{1}H NMR (500 MHz, *CD_3OD*) δ 9.40 (1H, s), 9.16 (1H, s), 8.82 (2H, s), 8.51 (1H, d, J = 6.1 Hz), 8.49 (1H, d, J = 6.1 Hz), 5.35 (1H, p, J = 8.5 Hz), 4.12 (4H, t, J = 5.4 Hz), 3.35 (4H, t, J = 5.4 Hz), 2.47 (2H, m), 2.23 (2H, m), 2.10 (2H, m), 1.85 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 416.2, Calculated 416.2.

EXAMPLE 9

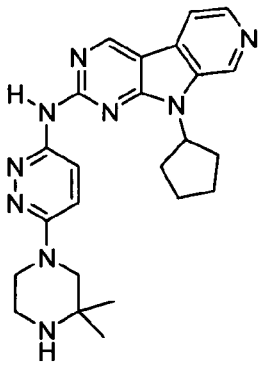


17

(*S*)-9-cyclopentyl-*N*-(6-(1-(3-methylpiperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine

Compound **17** was prepared using chemistry similar to that described in example 4. ^{1}H NMR (500 MHz, *DMSO-d_6-d6*) δ 10.19 (1H, s), 9.27 (1H, s), 9.01 (1H, s), 8.46 (1H, d, J = 5 Hz), 8.18 (1H, d, J = 10 Hz), 8.05 (1H, d, J = 5 Hz), 7.40 (1H, d, J = 10 Hz), 5.34 (1H, p, J = 10 Hz), 4.11 (2H, m), 2.97 (1H, m), 2.79 – 2.72 (3H, m), 2.44 – 2.34 (3H, m), 2.09 – 2.04 (4H, m), 1.74 (2H, m), 1.04 (3H, d, J = 5 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 430.2, Calculated 430.2.

EXAMPLE 10

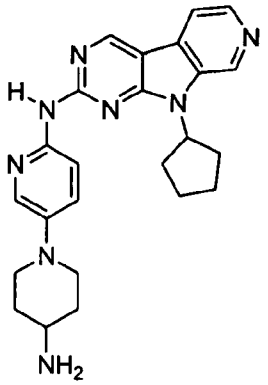


18

9-cyclopentyl-*N*-(6-(1-(3,3-dimethylpiperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine

Compound **18** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *$CDCl_3$*) δ 9.37 (1H, br s), 9.19 (1H, s), 8.87 (1H, s), 8.50 – 8.46 (2H, m), 7.84 (1H, d, J = 5 Hz), 7.04 (1H, d, J = 5 Hz), 5.34 (1H, p, J = 10 Hz), 3.54 (2H, t, J = 5 Hz), 3.36 (2H, br s), 3.07 (2H, t, J = 5 Hz), 2.36 (2H, m), 2.17 (2H, m), 2.09 (2H, m), 1.84 (2H, m), 1.21 (6H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 444.2, Calculated 444.3.

EXAMPLE 11

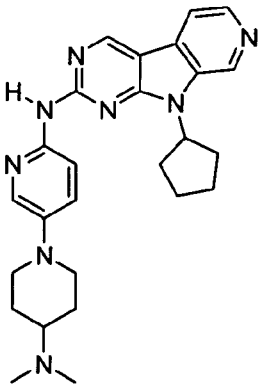


19

9-cyclopentyl-*N*-(5-(1-(4-aminopiperadinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine

Compound **19** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.72 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.15 (1H, d, J = 10 Hz), 8.03 (1H, d, J = 5 Hz), 8.02 (1H, d, J = 2Hz), 7.46 (1H, dd, J = 10 Hz, J = 2 Hz), 5.36 (1H, p, J = 5 Hz), 3.61 (2H, m), 2.77 – 2.71 (3H, m), 2.41 – 2.36 (3H, m), 2.09 – 2.05 (4H, m), 1.83 – 1.76 (4H, m), 1.39 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2, Calculated 429.2.

EXAMPLE 12

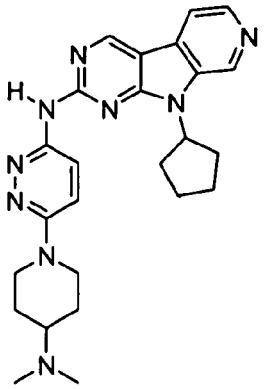


20

9-cyclopentyl-*N*-(5-(1-(*N*^{4},*N*^{4}-dimethylaminopiperadinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine

Compound **20** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (1H, s), 8.90 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.38 (1H, d, J = 10 Hz), 8.12 (1H, s), 8.07 (1H, d, J = 2Hz), 7.84 (1H, d, J = 5 Hz), 7.41 (1H, dd, J = 10Hz, J = 2 Hz), 5.38(1H, p, J = 10 Hz), 3.68 (2H, m), 2.77 (2H, td, J = 15 Hz, J = 5 Hz), 2.44 (2H, m), 2. 34 (6H, s), 2.29 (1H, m), 2.22 – 2.14 (4H, m), 1.97 (2H, m), 1.88 (2H, m), 1.72 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 457.2, Calculated 457.3.

EXAMPLE 13

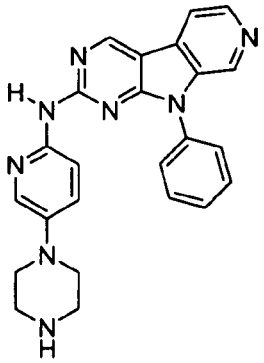


21

9-cyclopentyl-*N*-(6-(1-(N^4,N^4-dimethylaminopiperadinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine

Compound **21** was prepared using chemistry similar to that described in example 4. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 10.17 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.16 (1H, d, J = 10 Hz), 8.04 (1H, d, J = 5 Hz), 7.42 (1H, d, J = 10Hz), 5.33(1H, p, J = 10 Hz), 4.30 (2H, m), 2.88 (2H, td, J = 15 Hz, J = 5 Hz), 2.36 – 2.32 (3H, m), 2. 19 (6H, s), 2.10 – 2.02 (4H, m), 1.84 (2H, m), 1.74 (2H, m), 1.42 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 458.2, Calculated 458.3.

EXAMPLE 14

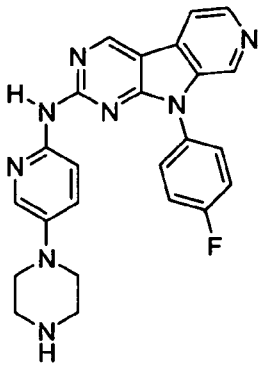


22

9-Phenyl-*N*-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **22** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 8.76 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.13 (1H, d, J = 5 Hz), 8.08 (1H, d, J = 10 Hz), 7.97 (1H, br s), 7.82 – 7.80 (2H, m), 7.32 – 7.30 (2H, m), 7.57(1H, dd, J = 10 Hz, J = 5 Hz), 7.31 (1H, dd, J = 10 Hz, J = 5 Hz), 3.03 (4H, m), 2.85 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 423.2, Calculated 423.2.

EXAMPLE 15

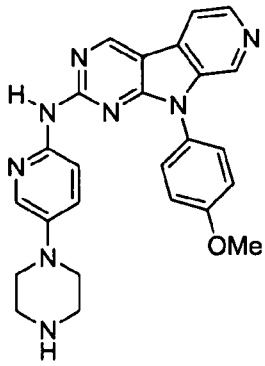


23

9-(4-fluorophenyl-*N*-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **23** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.86 (1H, s), 9.37 (1H, s), 8.73 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.13 (1H, d, J = 5 Hz), 8.06 (1H, d, J = 10 Hz), 7.97 (1H, s), 7.87(2H, d, J = 5 Hz), 7.55 (2H, dd, J = 10 Hz, J = 5 Hz), 7.34(1H, dd, J = 10 Hz, J = 5 Hz), 3.03 (4H, m), 2.85 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 441.1, Calculated 441.2.

EXAMPLE 16

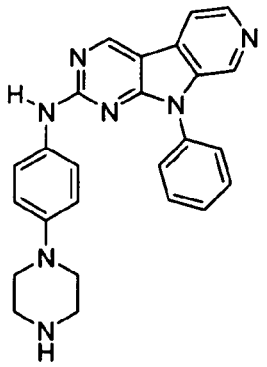


24

9-(4-methoxyphenyl-*N*-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **24** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.82 (1H, s), 9.36 (1H, s), 8.68 (1H, s), 8.50 (1H, d, J = 5 Hz), 8.11 (1H, d, J = 5 Hz), 8.08 (1H, s), 7.98 (1H, d, J = 5 Hz), 7.70(2H, d, J = 10 Hz), 7.34 (1H, d, J = 10 Hz), 7.25(1H, d, J = 10 Hz), 3.89 (3H, s), 3.05 (4H, m), 2.88 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 453.2, Calculated 453.2.

EXAMPLE 17

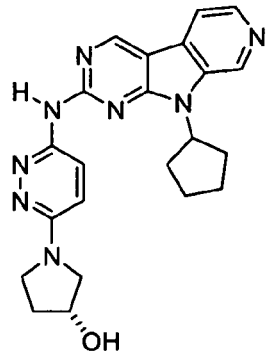


25

(9-Phenyl-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(4-piperazin-1-yl-phenyl)-amine

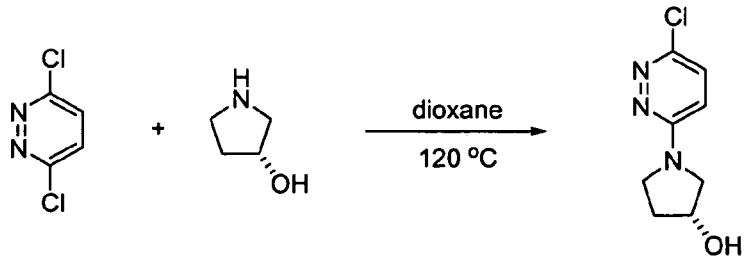
Compound **25** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (1H, s), 8.87 (1H, s), 8.58 (1H, d, J = 5 Hz), 7.87 (1H, s), 7.74 (2H, d, J = 5 Hz), 7.67 (2H, dd, J = 10 Hz, J = 5 Hz), 7.58 – 7.53 (3H, m), 6.92 (2H, d, J = 5 Hz), 3.13 (4H, m), 3.07 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 422.2, Calculated 422.2.

EXAMPLE 18



26

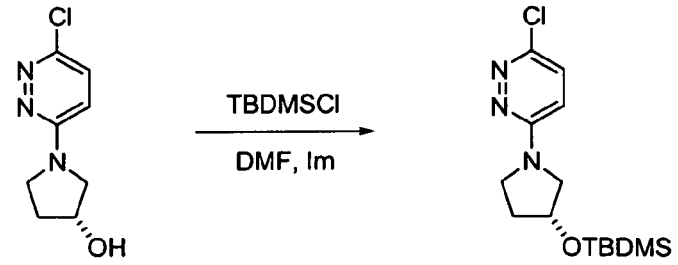
(*R*)-9-cyclopentyl-N-(6-(3-hydroxypyrrolidin-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine



27

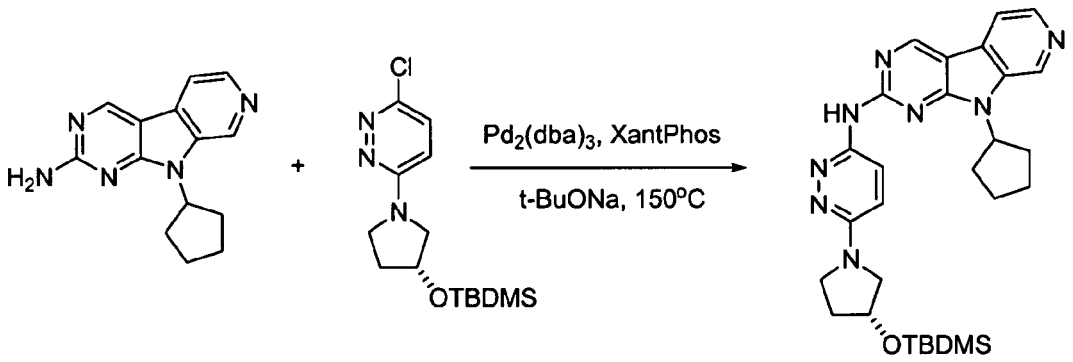
(*R*)-1-(6-Chloropyridazin-3-yl)pyrrolidin-3-ol (27): A solution of 3,6-dichloropydazine (1.49 g, 10 mmol) and (*R*)-3-hydroxypyrrolidine (871 mg, 10 mmol) in dioxane (20 mL) was heated at 120 °C for 10 h. The reaction mixture was diluted with ethyl acetate and washed with 5% $NaHCO_3$ and brine, dried. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting

with 2.5% methanol in dichloromethane to give the compound **27** as a yellow solid (815 mg, 41%). LCMS-ESI (POS), M/Z, M+1: Found 200.0, Calculated 200.0.



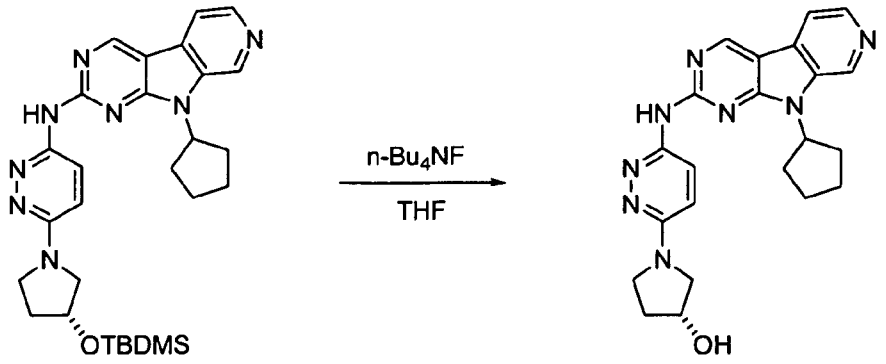
28

(*R*)-3-(3-(tert-butyldimethylsilyloxy)pyrrolidin-1-yl)-6-chloropyridazine (28): To a solution of compound **27** (815 mg, 4.08 mmol) in DMF (15 mL) were added *t*-butyldimethylsilyl chloride (738 mg, 4.9 mmol) amd imidazole (556 mg, 8.16 mmol). The thus obtained solution was stirred at room temperature for 6 h. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting with 15% to 50% to give the compound **28** as a white solid (1.087 g, 85%). LCMS-ESI (POS), M/Z, M+1: Found 314.1, Calculated 314.1.



4 **28** **29**

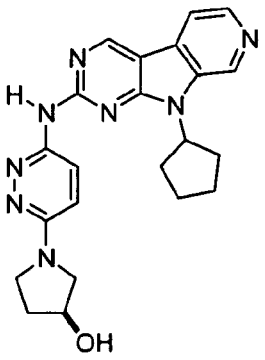
(*R*)-9-Cyclopentyl-*N*-(6-(3-(tert-butyldimethylsilyloxy)pyrrolidin -1-yl)-3-pyridazinyl)-9H-pyrido-[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine (29): To a solution of compound **4** (202 mg, 0.80 mmol) in dioxane (8 mL) were added compound **28** (313 mg, 1.0 mmol), tris(dibenzylideneacetone)dipalladium (0) (36.8 mg, 0.04 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (69.4 mg, 0.12 mmol), and sodium *t*-butoxide (115 mg, 1.2 mmol). The mixture thus obtained was heated at 150 °C under microwave irradiation for 1 h. The reaction mixture was passed through a short pack silica gel column and concentrated to give compound **29** as a yellow solid (316 mg, 82% purity) which was used in next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 531.1, Calculated 531.2.



29 26

(*R*)-9-cyclopentyl-N-(6-(3-hydroxypyrrolidin-1-yl)-3-pyridazinyl)-9H-pyrido-[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine (26): A solution of compound **29** (316 mg, purity 82%, 0.49 mmol) in THF (4 mL) was treated with 1M tetrabutylammonium fluoride in THF (1 mL) at room temperature for 0.5 h. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting with 2.5% methanol in dichloromethane to give a yellow solid. The yellow solid was washed with dichloromethane to give compound **26** as a light yellow solid (182 mg, 90%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 10.05 (1H, s), 9.24 (1H, s), 8.99 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.10 (1H, d, J = 10 Hz), 8.03 (1H, d, J = 5 Hz), 6.99 (1H, d, J = 10Hz), 5.32(1H, p, J = 10 Hz), 5.00 (1H, d, J = 5 Hz), 4.43 (1H, br s), 3.58 – 3.51 (3H, m), 3.40 (1H, m), 2.37 – 2.30 (2H, m), 2.09 – 2.02 (5H, m), 1.95 (1H, m), 1.74 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 417.3, Calculated 417.2.

EXAMPLE 19

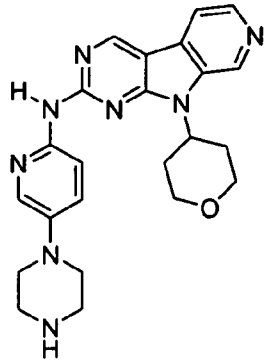


30

(*S*)-9-cyclopentyl-N-(6-(3-hydroxypyrrolidin-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine

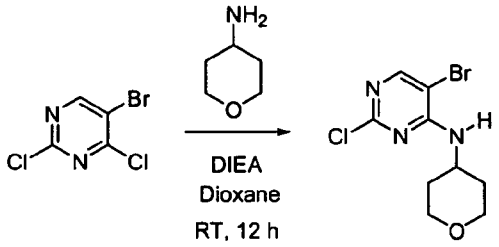
Compound **30** was prepared using chemistry similar to that described in example 18. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 10.05 (1H, s), 9.24 (1H, s), 8.99 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.10 (1H, d, J = 10 Hz), 8.03 (1H, d, J = 5 Hz), 6.99 (1H, d, J = 10Hz), 5.32(1H, p, J = 10 Hz), 5.00 (1H, d, J = 5 Hz), 4.43 (1H, br s), 3.58 – 3.51 (3H, m), 3.40 (1H, m), 2.37 – 2.30 (2H, m), 2.09 – 2.02 (5H, m), 1.95 (1H, m), 1.74 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 417.3, Calculated 417.2.

EXAMPLE 20



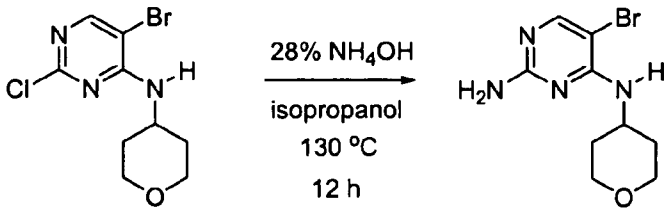
31

(5-Piperazin-1-yl-pyridine-2-yl)-[9-(tetrahydro-pyran-4-yl)-9*H*-pyrido-[4',3',4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl]-amine



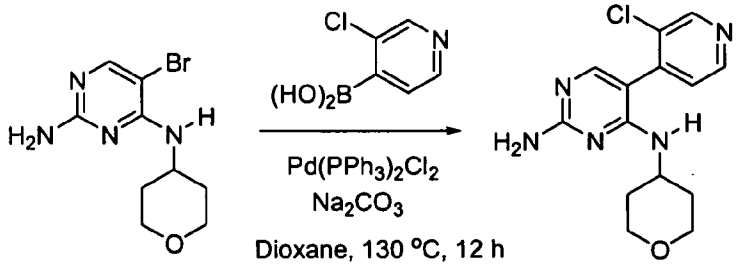
32

(5-bromo-2-chloro-pyrimidin-4-yl)-(tetrahydro-pyran-4-yl)-amine (32). 5-Bromo-2, 4-dichloropyrimidine (5.0 g, 21.9 mmol), tetrahydro-2H-pyran-4-amine (2.22 g, 21.9 mmol), and N-ethyl-N-isopropylpropan-2-amine (4.25 g, 32.9 mmol) were dissolved in dioxane (50 ml) and the reaction was stirred at room temperature for 12 hours. Ethyl acetate was added to the reaction mixture and the organic layer was washed with water and brine. The organic layer was dried with sodium sulfate. Removal of solvent gave (5-bromo-2-chloro-pyrimidin-4-yl)-(tetrahydro-pyran-4-yl)-amine (**32**) as a light yellow solid (6.75g, 99%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.04 (1 H, s), 4.14-4.21 (1 H, m), 3.89 (2 H, dd, J = 11.4, 4.3 Hz) 3.43 (2 H, td, J =11.9, 2.0 Hz), 1.80 (2 H, ddd, J = 12.6, 4.2, 1.8 Hz), 1.63 (2 H, qd, J =12.2, 4.5, Hz); LCMS-ESI (POS), M/Z, M+1: Found 292.0, Calculated 292.



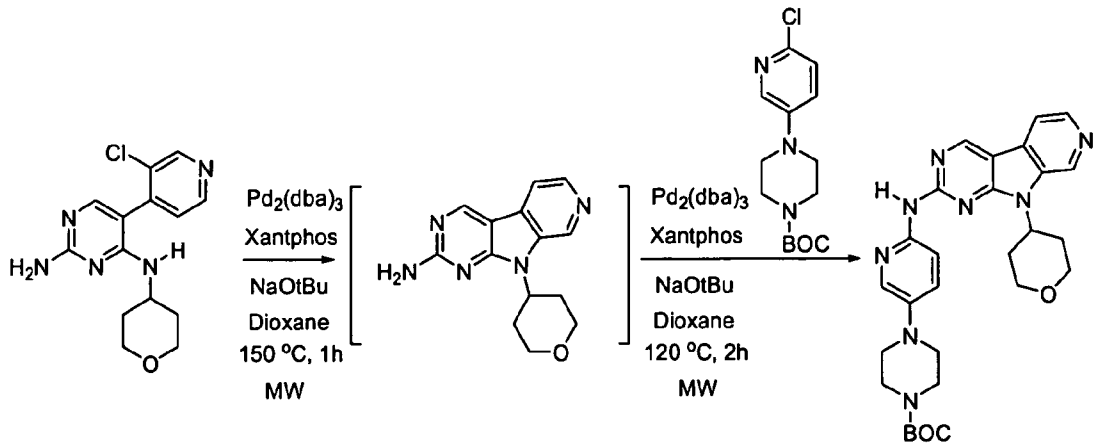
32 33

5-Bromo-N^4-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine (33): To a suspension of compound **32** (6.60 g, 23 mmol) in isopropyl alcohol (40 ml) was added ammonia (aq. 28%, 80 ml). This reaction mixture was heated to 130°C for 14 hours in a pressure vessel. The reaction mixture was cooled down to room temperature and to this mixture was added ethyl acetate. The reaction mixture was washed with water and brine. The ethyl acetate layer was dried with sodium sulfate and concentrated to give compound **33** (4.75 g, 77%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.79 (1 H, s), 4.24 (1 H, m), 3.99-4.02 (2 H, dd, *J*=11.0, 2.2 Hz), 3.52 (2 H, td, *J*=11.9, 2.0 Hz), 1.92-1.96 (2 H, m), 1.69 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 273, Calculated 273.0



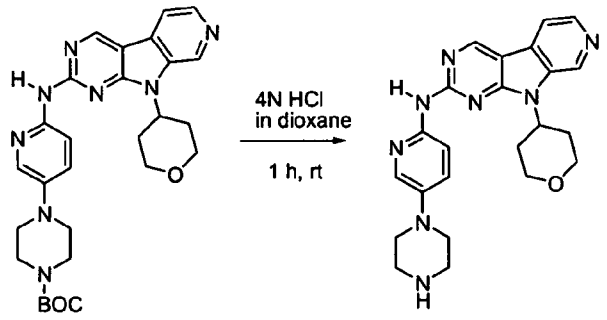
33 **34**

5-(3-Chloro-pyridin-4-yl)-N^4-(tetrahydro-pyran-4-yl)-pyrimidine-2, 4-diamine (34): A mixture of compound **33** (2.03g, 7.43 mmol), 3-chloropyridin-4-ylboronic acid (3.51 g, 22.3 mmol), and $Pd(PPh_3)_2Cl_2$ (0.522 g, 0.743 mmol) in dioxane (44 ml) in a pressure vessel was purged with N_2 for 20 minutes and to this mixture was added aq. Na_2CO_3 (1 M, 22 mL) by syringe. The reaction was further purged with N_2 for another 20 minutes and then heated to 130 °C for 12 hours. DCM was added to the reaction and the mixture was washed with water and brine. The organic layer was dried with sodium sulfate and concentrated to provide compound **34** (2.07 g, crude, 98%) which was used in the next reaction without further purification. LCMS-ESI (POS), M/Z, M+1: Found 306.1, Calculated 306.1.



34 **35**

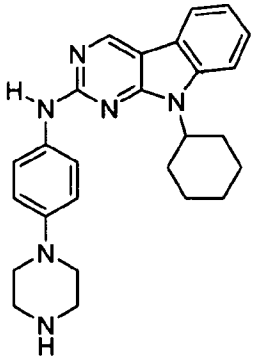
4-{6-[9-(Tetrahydro-pyran-4-yl)-9H-pyrido[4',3',4, 5]pyrrolo[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic acid *tert*-butyl ester (35): Compound **34** (150 mg, 491 μmol), $Pd_2(dba)_3$ (22.5 mg, 24.5 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (28.4 mg, 49.1 μmol), sodium 2-methylpropan-2-olate (118 mg, 1226 μmol) in dioxane (4 ml) was purged with N_2 for 20 minutes. The reaction was heated up to 150 °C in microwave for 1 hour. Then a solution of compound **5** (146 mg, 491 μmol) in dioxane (1 ml)) was added to the reaction mixture and the reaction was purged with N_2 for another 20 minutes. This reaction was heated to 120°C under microwave irradiation for 2 hours. DCM was added to the reaction and the mixture was washed with water and brine. The organic layer was dried with sodium sulfate and concentrated. Purification by flash chromatography (DCM/methanol) gave compound **35** (102 mg). LCMS-ESI (POS), M/Z, M+1: Found 531.2, Calculated 531.3



35 **31**

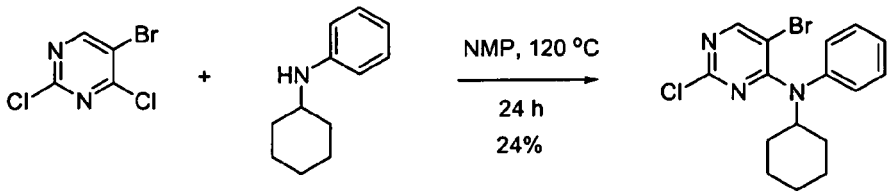
(5-Piperazin-1-yl-pyridine-2-yl)-[9-(tetrahydro-pyran-4-yl)-9*H*-pyrido[4',3',4,5]pyrrolo-[2,3-*d*]pyrimidin-2-yl]-amine (31): Compound **35** (100 mg) was treated with 5 mL of 4 N HCl in dioxane for 1 hour. The product, which was not soluble in dioxane, was collected and then washed with ethyl acetate and a small amount of methanol to obtain compound **31** as its HCl salt (20 mg, 25%). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 9.65 (1 H, s), 9.59 (1 H, s), 9.37 (1 H, s), 8.27 (2 H, s), 8.14 (1 H, s), 8.05 (1 H, s), 7.80(1 H, s), 5.20 (2 H, m), 4.10 (2 H, d, *J*=3.2 Hz), 3.71 (br s), 3.6 (2 H, m), 3.46 (4 H, s), 3.27 (4 H, s), 2.83 (2 H, dd, *J*=11.9, 3.8 Hz), 1.90 (2 H, d, *J*=10.5 Hz); LCMS-ESI (POS), M/Z, M+1: Found 431.2, Calculated 431.2

EXAMPLE 21



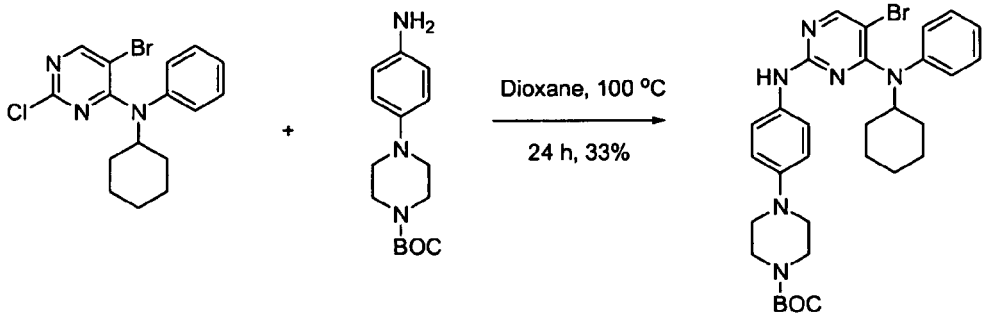
36

(9-Cyclohexyl-9*H*-pyrimido[4,5-*b*]indol-2-yl)-(4-piperazin-1-yl-phenyl)-amine



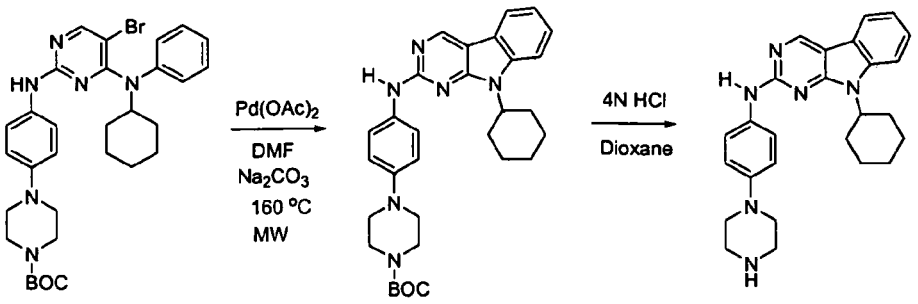
37

(5-Bromo-2-chloro-pyrimidin-4-yl)-cyclohexyl-phenyl-amine (37): 5-Bromo-2,4-dichloro-pyrimidine (2.17 ml, 17.14 mmol) and cyclohexyl-phenyl-amine (2.0 g, 11.43 mmol) were dissolved in N-methylpyrrolidone (NMP) (25 ml), and this reaction was heated to 120 °C for 24 hours. The reaction was cooled to room temperature and diluted with ethyl acetate, washed with water and brine. The organic phase was dried using sodium sulfate and concentrated. Purification by flash chromatography (ethyl acetate/hexane) gave compound **37** as a yellow solid (855 mg, 24%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 8.27 (1 H, s), 7.41 (3 H, m), 7.21 (2 H, m), 4.62 (1 H, m), 1.93 (2 H, d, *J*=10 Hz), 1.75 (2 H, d, *J*=10 Hz), 1.58 (1 H, d, *J*=10 Hz), 1.34 (2 H, m), 1.15 (2 H, m), 0.91 (1 H, m).



37 38

4-{4-[5-Bromo-4-(cyclohexyl-phenyl-amino)-pyrimidin-2-ylamino]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (38): Compound **37** (0.42 g, 1.15 mmol) and 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.64 g, 2.30 mmol) were dissolved in dioxane (2 mL), and this mixture was heated at 100 °C for 24 hours. The reaction was cooled to room temperature and diluted with ethyl acetate. This mixture was washed with water and brine. The organic layer was dried with sodium sulfate and purified by flash chromatography (ethyl acetate/hexane) to give compound **38** as a yellow solid (0.23 g, 33%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 9.18 (1 H, s), 7.97 (1 H, s), 7.55 (2 H, d, *J*=10 Hz), 7.37 (2 H, m), 7.31 (1 H, m), 7.12 (2 H, m), 6.89 (2 H, d, *J*=10 Hz), 4.68 (1 H, m), 3.44 (4 H, m), 3.00 (4 H, m), 1.91 (2 H, d, *J*=10 Hz), 1.72 (2 H, d, *J*=10 Hz), 1.57 (1 H, d, *J*=10 Hz), 1.41 (9 H, s), 1.35 (2 H, m), 1.14 (2 H, m), 0.92 (1 H, m); LCMS-ESI (POS), M/Z, M+1: Found 609.2, Calculated 607.2/609.2.

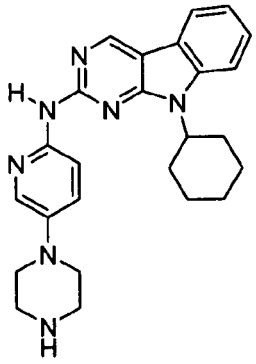


38 39 36

(9-Cyclohexyl-9*H*-pyrimido[4,5-*b*]indol-2-yl)-(4-piperazin-1-yl-phenyl)-amine (36).

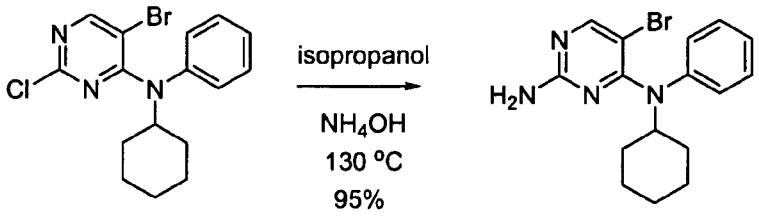
A mixture of compound **38** (0.12 g, 0.20 mmol), $Pd(OAc)_2$ (27 mg, 0.041 mmol), Na_2CO_3 (43mg, 0.41 mmol) in DMF (2 mL) was purged with N_2 for 20 minutes and the reaction was heated at 160 °C in a sealed tube for 4 hours. The reaction was cooled to room temperature, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated. Purification by reverse phase Prep-HPLC gave compound **39**: LCMS-ESI (POS), M/Z, M+1: Found 527.3, Calculated 527.3. Compound **39** was treated with 2 N HCl in dioxane (2 mL) for 2 hours at room temperature. Compound **36** (7 mg)was obtained as the HCl salt after removal of dioxane. ^1H NMR (500 MHz, CD_3OD) δ ppm 8.81 (1 H, s), 8.00 (1 H, d, *J*=7.4 Hz), 7.66 (1 H, d, *J*=7.4 Hz), 7.51 (1 H, t, *J*=6.5 Hz), 7.43 (2 H, d, *J*=7.4 Hz), 7.32 (1 H, t, *J*=7.5 Hz), 7.09 (2 H, d, *J*=10 Hz), 4.60 (1 H, m), 3.40 (4 H, m), 3.33 (4 H, m), 2.39-2.48 (2 H, m), 1.80-1.89 (4 H, m), 1.70-1.73 (1 H, m), 1.41-1.51 (2 H, m), 1.19-1.27 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 427.3, Calculated 427.3.

EXAMPLE 22



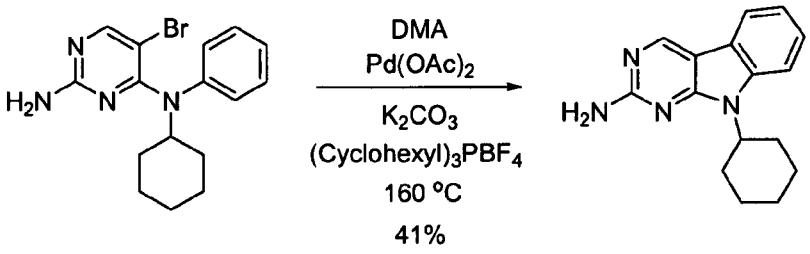
40

(9-Cyclohexyl-9*H*-pyrimido[4,5-*b*]indol-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine



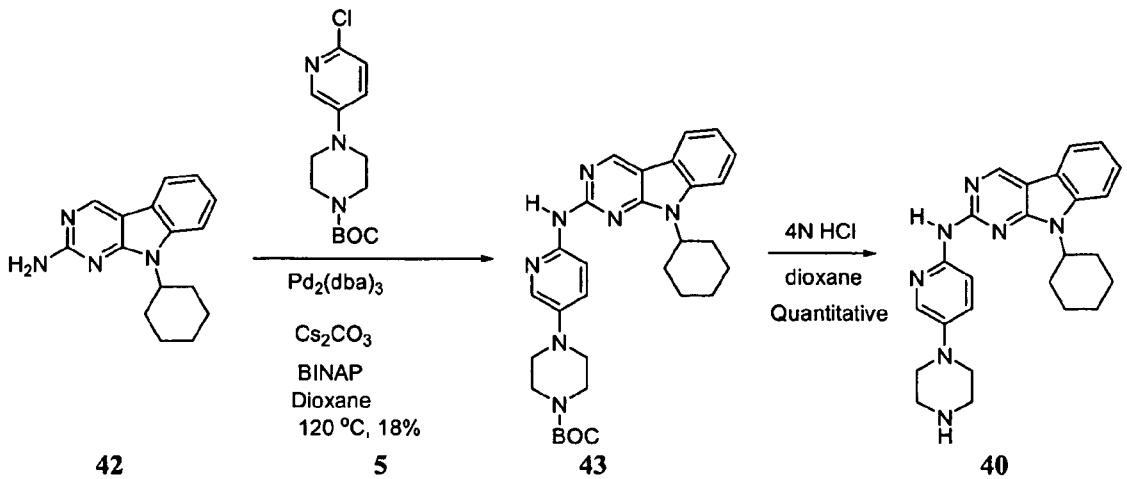
37 41

5-Bromo-*N*4-cyclohexyl-*N*4-phenyl-pyrimidine-2,4-diamine (41): Compound **41** was prepared using chemistry similar to that described in example 1. LCMS-ESI (POS), M/Z, M+1: Found 348.3, Calculated 348.3.



41 42

9-Cyclohexyl-9*H*-pyrimido[4,5-*b*]indol-2-ylamine (42). A mixture of compound **41** (0.35 g, 0.99 mmol), $Pd(OAc)_2$ (33 mg, 0.15 mmol), $(cyclohexyl)_3PBF_4$ (110 mg, 0.30 mmol), and K_2CO_3 (138 mg, 0.10 mmol) in DMA (3 mL) was purged with N_2 for 20 minutes and then heated at 160 °C for 3 hours. The reaction was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. Purification by flash chromatography (ethyl acetate/hexane) gave compound **42** as a yellow solid (110 mg, 41%). LCMS-ESI (POS), M/Z, M+1: Found 267.1, Calculated 267.2.



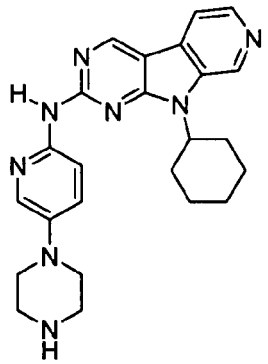
42 5 43 40

(9-Cyclohexyl-9*H*-pyrimido[4,5-*b*]indol-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine (40).

A mixture of compound **42** (98 mg, 0.37 mmol), compound **5** (121 mg, 0.41 mmol), $Pd_2(dba)_3$ (17 mg, 0.018 mmol), BINAP (23 mg, 0.037 mmol), and Cs_2CO_3 (168 mg, 0.52 mmol) in dioxane (3 mL) was purged with N_2 for 20 minutes. The reaction was heated at 120 °C for 14 hours. The reaction was then cooled down to room temperature and diluted with ethyl acetate. The reaction mixture was washed with water and brine. The organic layer was dried with sodium sulfate and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexane) to give compound **43** (34 mg, 18%). LCMS-ESI (POS), M/Z, M+1: Found 528.3, Calculated 528.3.

Compound **43** was then treated with 4N HCl in dioxane (5 mL) for 3 hours. The reaction mixture was concentrated and the residue was purified by Prep-HPLC to give compound **40** as a yellow solid TFA salt(32 mg). ^{1}H NMR (500 MHz, CD_3OD) δ 9.19 (1 H, s), 8.12 - 8.22 (2 H, m), 7.90 (1 H, d, *J*=7.3 Hz), 7.82 (1 H, d, *J*=7.9 Hz), 7.63 (1 H, t, *J*=7.6 Hz), 7.43 (1 H, t, *J*=7.0 Hz), 7.34 (1 H, d, *J*=7.9 Hz), 4.87 (1 H, s), 3.54 (4 H, s), 3.46 (4 H, s), 2.57 - 2.67 (2 H, m), 2.04 (2 H, d, *J*=14.0 Hz), 1.96 (2 H, d, *J*=11.0 Hz), 1.86 (1 H, d, *J*=12.2 Hz), 1.54 - 1.66 (2 H, m), 1.50 (1 H, d, *J*=12.2 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 428.2, Calculated 428.3.

Example 23

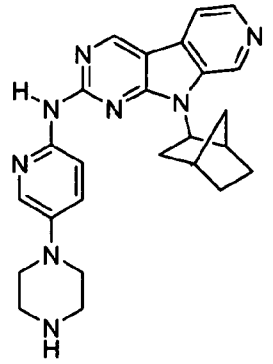


44

(9-Cyclohexyl-9*H*-pyrido[4',3',4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **44** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.84 (1 H, s), 9.59 (1 H, s), 8.88 (1 H, d, *J*=6.1 Hz), 8.74 (1 H, d, *J*=6.1 Hz), 8.32 (1 H, d, *J*=10.0 Hz), 8.12 (1 H, d, *J*=2.9 Hz), 7.67 (1 H, d, *J*=9.5 Hz), 5.03 (1 H, m), 3.76-3.78 (2 H, m), 3.64 (4 H, m), 3.48 (4 H, m), 2.63-2.70 (2 H, m), 2.06-2.09 (4 H, d, *J*=10.8 Hz), 2.03 (2 H, m), 1.64 (1 H, m); LCMS-ESI (POS), M/Z, M+1: Found 429.2, Calculated 429.2

EXAMPLE 24

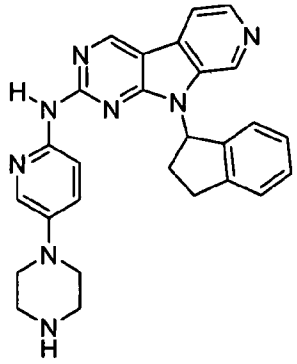


45

(9-Bicyclo[2.2.1]hept-2-yl-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **45** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 10.41 (1 H, s), 9.53 (1 H, s), 9.28 (1 H, s), 8.96 (2 H, s), 8.63 (1 H, d, *J*=10 Hz), 8.14 (2 H, d, *J*=2.4 Hz), 7.65 (1 H, d, *J*=10 Hz), 4.78 (1 H, m), 3.42 (4 H, m), 3.28 (4 H, m), 2.90 (1 H, m), 2.83 (1 H, s), 2.58 (1 H, s), 2.25 (1 H, d, *J*=10 Hz), 2.02 (1 H, t, *J*=10 Hz), 1.60-1.65 (3 H, m), 1.35 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 441.2, Calculated 441.2.

EXAMPLE 25

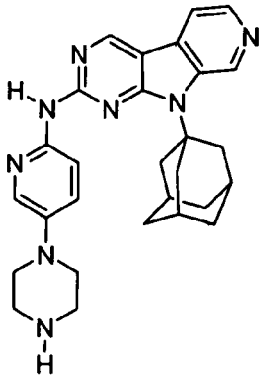


46

(9-Indan-1-yl-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **46** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.63 (1 H, s), 8.58-8.63 (2 H, dd, *J*=5.8, 21.1 Hz), 8.07 (1 H, d, *J*=2.7 Hz), 7.91 (1 H, s), 7.72 (1 H, s), 7.57 (1 H, d, *J*=5.0 Hz), 7.43 (1 H, t, *J*=5.0 Hz), 7.22 (1 H, t, *J*=5.0 Hz), 7.02 (1 H, d, *J*=5.0 Hz), 6.90 (1 H, t, *J*=5.0 Hz), 4.85 (1 H, m), 3.52 (4 H, m), 3.47 (4 H, m), 3.40 (1 H, m), 3.26 (1 H, m), 2.89 (1 H, m), 2.64 (1 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 463.1, Calculated 463.2.

EXAMPLE 26

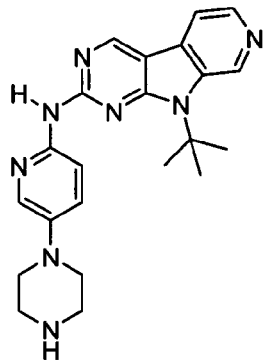


47

(9-Adamantan-1-yl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **47** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.60 (1 H, s), 9.53 (1 H, s), 8.62 (1 H, d, *J*=5.0 Hz), 8.56 (1 H, d, *J*=5.0 Hz), 8.12 (1 H, t, *J*=2.5 Hz), 7.95 (1 H, m), 3.52 (4 H, m), 3.47 (4 H, m), 2.95 (6 H, d, *J*=2.5 Hz), 2.38 (3 H, s), 2.04 (1 H, s), 2.01 (2 H, s), 1.94 (2 H, s), 1.91 (1 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 481.3, Calculated 481.3.

EXAMPLE 27

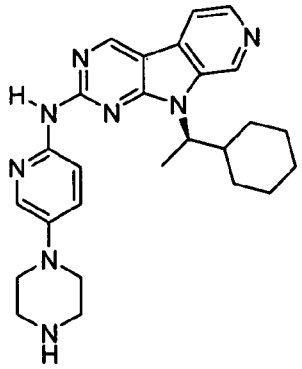


48

(9-tert-Butyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **48** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.85 (1 H, s), 9.60 (1 H, s), 8.88 (1 H, d, *J*=6.1 Hz), 8.71 (1 H, d, *J*=6.1 Hz), 8.33 (1 H, m), 8.11 (1 H, d, *J*=2.9 Hz), 7.69 (1 H, d, *J*=9.5 Hz), 3.61 (4 H, m), 3.48 (4 H, m), 2.17 (9 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 403.3, Calculated 403.2.

EXAMPLE 28

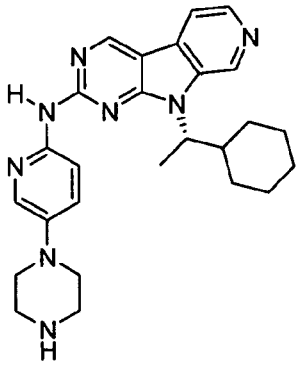


49

(*R*)-[9-(1-Cyclohexyl-ethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **49** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.68 (1 H, s), 9.43 (1 H, s), 8.69 (2 H, dd, J = 7.3, 10.5 Hz), 8.12 (1 H, s), 8.10 (1 H, s), 7.80 (1 H, d, J = 8.5 Hz), 4.93 (1 H, m), 3.57 (4 H, m), 3.47 (4 H, m), 2.18 (1 H, d, J = 10.1 Hz), 1.92 (1 H, d, J = 10.1 Hz), 1.82 (3 H, d, J = 7.1 Hz), 1.69 (1 H, d, J = 10.0 Hz), 1.59 (1 H, d, J = 10.0 Hz), 1.40 (1 H, m), 1.23 (2 H, m), 1.10 (2 H, m), 0.96 (1 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 457.3, Calculated 457.3.

EXAMPLE 29

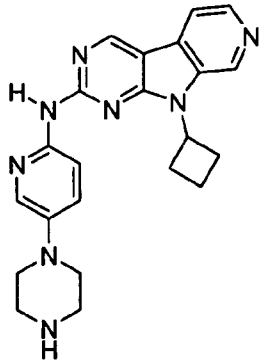


50

(*S*)-[[9-(1-Cyclohexyl-ethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **50** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.68 (1 H, s), 9.43 (1 H, s), 8.69 (2 H, dd, *J*=7.3, 10.5 Hz), 8.12 (1 H, s), 8.10 (1 H, s), 7.80 (1 H, d, *J*=8.5 Hz), 4.93 (1 H, m), 3.57 (4 H, m), 3.47 (4 H, m), 2.18 (1 H, d, *J*=10.1 Hz), 1.92 (1 H, d, *J*=10.1 Hz), 1.82 (3 H, d, *J*=7.1 Hz), 1.69 (1 H, d, *J*=10.0 Hz), 1.59 (1 H, d, *J*=10.0 Hz), 1.40 (1 H, m), 1.23 (2 H, m), 1.10 (2 H, m), 0.96 (1 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 457.3, Calculated 457.3.

EXAMPLE 30

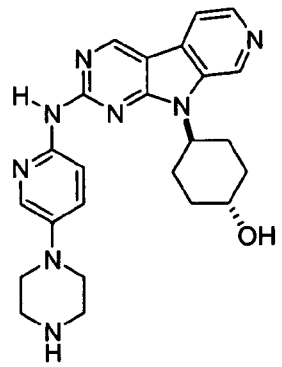


51

(9-Cyclobutyl-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **51** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.68 (1 H, s), 9.40 (1 H, s), 8.67 - 8.72 (2 H, dd, J = 5.0, 15 Hz), 8.13 (1 H, dd, J = 2.3, 10 Hz), 8.10 (1 H, d, J = 2.7 Hz), 7.83 (1 H, d, J = 10.0 Hz), 5.52 (1 H, m), 3.58 (4 H, m), 3.48 (4 H, m), 3.29 (2 H, m), 2.69 (2 H, m), 2.13 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 401.2, Calculated 401.2.

EXAMPLE 31

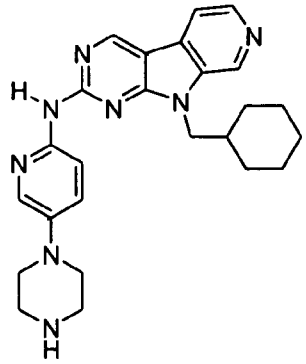


52

4-[2-(5-Piperazin-1-yl-pyridin-2-ylamino)-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-9-yl]-trans-cyclohexanol

Compound **52** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.62 (1 H, s), 9.42 (1 H, s), 8.64 (2 H, s), 8.11 (1 H, d, J = 2.5 Hz), 8.02 (1 H, d, J = 10.0 Hz), 7.87 (1 H, d, *J*=10.0 Hz), 4.98 (1 H, m), 3.89 (1 H, m), 3.55 (4 H, m), 3.47 (4 H, m), 2.77 (2 H, m), 2.21 (1 H, d, J = 15 Hz), 2.05 (2 H, m), 1.86 (1 H, m), 1.65 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 445.1, Calculated 445.2.

EXAMPLE 32

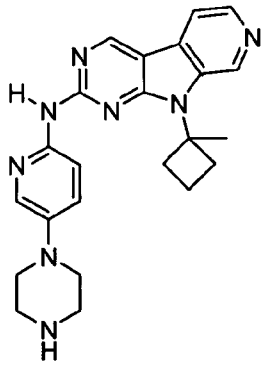


53

(9-Cyclohexylmethyl-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **53** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.73 (1 H, s), 9.60 (1 H, s), 9.56 (2 H, s), 8.75 (2 H, s), 8.14 (1 H, s), 8.08 (1 H, s), 7.96 (1 H, s), 4.41 (2 H, d, J = 5.0 Hz), 3.48 (4 H, s), 3.26 (4 H, s), 2.08 (1 H, s), 1.57-1.67 (5 H, m), 1.13 (5 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 443.2, Calculated 443.3.

EXAMPLE 33

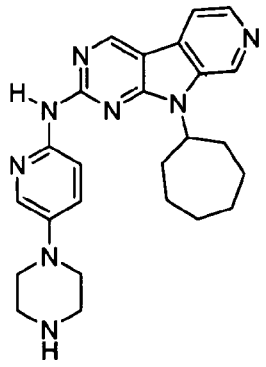


54

[9-(1-Methyl-cyclobutyl)-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **54** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.66 (1 H, s), 9.07 (1 H, s), 8.71 (1 H, d, *J*=5.0 Hz), 8.67 (1 H, d, *J*=5.0 Hz), 8.14 (1 H, dd, *J*=2.5, 10 Hz), 8.10 (1 H, d, *J*=2.5 Hz), 7.80 (1 H, d, *J*=10 Hz), 3.56 (4 H, m), 3.47 (4 H, m), 3.09 (2 H, q, *J*=5.0 Hz), 2.86 (2 H, t, *J*=2.5 Hz), 2.25 (1 H, m), 2.11 (1 H, m), 1.91 (3 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 415.1, Calculated 415.2.

EXAMPLE 34

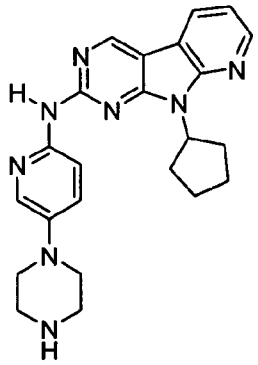


55

(9-Cycloheptyl-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **55** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.80 (1 H, s), 9.59 (1 H, s), 9.42 (2 H, s), 8.72 (2 H, s), 8.14 (1 H, s), 8.08 (1 H, s), 7.85 (1 H, s), 5.05 (1 H, m), 3.47 (4 H, s), 3.27 (4 H, s), 2.58 (1 H, m), 1.88 (1 H, m), 1.67-1.77 (10 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 443.2, Calculated 443.3.

EXAMPLE 35

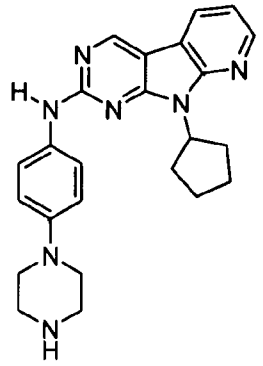


56

(9-Cyclopentyl-9*H*-pyrido[3',2':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **56** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.27 (1 H, s), 8.60 (1 H, dd, J = 2.5 5.0 Hz), 8.55 (1 H, dd, J = 2.5, 5.0 Hz), 8.10 (1 H, d, J = 5.0 Hz), 8.00 (1 H, dd, J = 5.0, 10.0 Hz), 7.45 (2 H, m), 5.63 (1 H, q, J = 10 Hz), 3.53 (4 H, m), 3.47 (4 H, m), 2.62 (2 H, m), 2.23 (2 H, m), 2.15 (2 H, m), 1.87 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 415.1, Calculated 415.2.

EXAMPLE 36

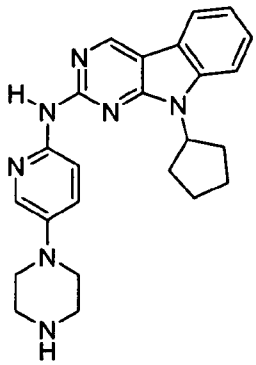


57

(9-Cyclopentyl-9*H*-pyrido[3',2':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(4-piperazin-1-yl-phenyl)-amine

Compound **57** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 8.99 (1 H, s), 8.49 (1 H, dd, J = 2.5, 5.0 Hz), 8.40 (1 H, dd, J = 2.5, 5.0 Hz), 7.59 (2 H, d, J = 10 Hz), 7.38 (1 H, dd, J = 5.0, 7.5 Hz), 7.14 (2 H, d, J = 10.o Hz), 5.53 (1 H, m), 3.44 (8 H, m), 2.52 (2 H, m), 2.06 (4 H, m), 1.77 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 414.2, Calculated 414.2

EXAMPLE 37

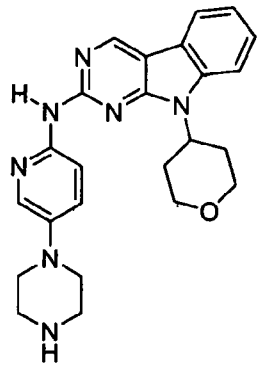


58

(9-Cyclopentyl-9*H*-pyrimido[4,5-*b*]indol-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **58** was prepared using chemistry similar to that described in example 22. ^{1}H NMR (500 MHz, CD_3OD) δ 7.82 (1 H, s), 6.80 (2 H, d, *J*=6.1 Hz), 6.56 (1H, d, *J*=8.5 Hz), 6.34 (1 H, d, *J*=8.5 Hz), 6.24 (1 H, t, *J*=7.3 Hz), 5.99 - 6.08 (2 H, m), 4.02 - 4.11 (1 H, m), 2.21 (4 H, m), 2.12 (4 H, m), 1.10 (2 H, s), 0.83 (4 H, s), 0.55 (2 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 414.2, Calculated 414.2

EXAMPLE 38

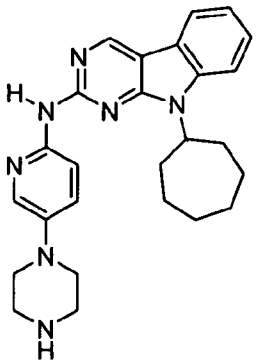


59

(5-Piperazin-1-yl-pyridin-2-yl)-[9-(tetrahydro-pyran-4-yl)-9*H*-pyrimido[4,5-*b*]indol-2-yl]-amine

Compound **59** was prepared using chemistry similar to that described in example 22. ^{1}H NMR (500 MHz, CD_3OD) δ 7.93 (1 H, s), 6.91 (1 H, d, J = 7.9 Hz), 6.86 (1 H, s), 6.65 (1 H, d, J = 8.5 Hz), 6.56 (1 H, d, J = 8.5 Hz), 6.36 (1 H, t, J = 7.9 Hz), 6.16 (1 H, t, J = 7.6 Hz), 6.07 (1 H, d, J = 9.2 Hz), 3.79 (1H, m), 2.91 (2 H, dd, J = 4.3, 11.6 Hz), 2.45 (2 H, m), 2.25 (4 H, m), 2.17 (4 H, s), 1.71 (2 H, dd, J = 12.5, 4.6 Hz), 0.60 (2 H, d, J = 9.8 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 430.1, Calculated 430.2.

EXAMPLE 39

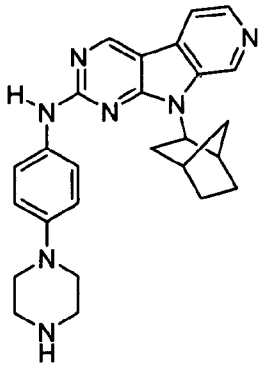


60

(9-Cycloheptyl-9*H*-pyrimido[4,5-*b*]indol-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

Compound **60** was prepared using chemistry similar to that described in example 22. ^{1}H NMR (500 MHz, CD_3OD) δ 7.40 (1 H, s), 6.43 (1 H, d, J = 7.3 Hz), 6.38 (1 H, d, J = 3.1 Hz), 6.12 (1 H, dd, J = 9.5, 2.7 Hz), 6.04 (1 H, d, J = 7.9 Hz), 5.89 (1 H, t, J = 10 Hz), 5.69 (1 H, t, J = 10 Hz), 5.50 (1 H, d, J = 10 Hz), 3.36 (1 H, m), 1.76 (4 H, m), 1.70 (4 H, m), 0.86 (2 H, m), 0.23-0.31 (4 H, m), 0.02-0.10 (6 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 442.3, Calculated 442.3.

EXAMPLE 40

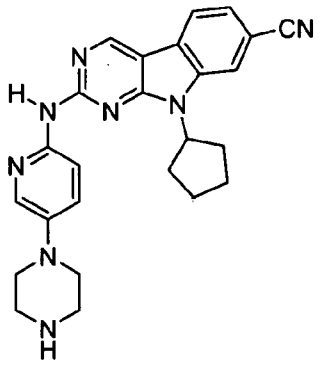


61

(9-Bicyclo[2.2.1]hept-2-yl-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(4-piperazin-1-yl-phenyl)-amine

Compound **61** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.37 (1 H, s), 9.10 (1 H, s), 8.50 (2 H, dd, J = 5, 15 Hz), 7.72 (2 H, d, J = 10 Hz), 7.11 (2 H, d, J = 10 Hz), 4.72 (1 H, m), 3.44 (8 H, m), 2.96 (1 H, d, J = 10 Hz), 2.92 (1 H, d, J = 2.5 Hz), 2.58 (1 H, s), 2.33 (1 H, d, J = 10 Hz), 2.08 (1 H, dd, J = 5, 15 Hz), 1.75 (2 H, m), 1.59 (1 H, t, J = 10 Hz), 1.44 (12 H, t, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 440.2, Calculated 440.3.

EXAMPLE 41

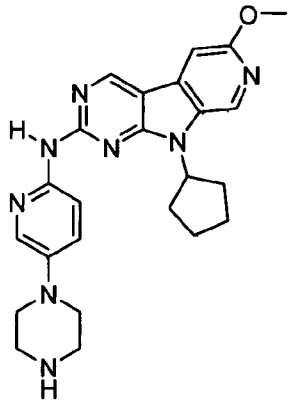


62

9-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-9*H*-pyrimido[4,5-*b*]indole-7-carbonitrile

Compound **62** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.33 (1 H, s), 8.34 (1 H, d, J = 8.1 Hz), 8.13 (1 H, s), 8.07 (1 H, d, J = 2.9 Hz), 8.01 (1 H, dd, J = 9.4, 2.8 Hz), 7.71 - 7.73 (1 H, d, J = 10 Hz), 7.63 (1 H, d, J = 9.3 Hz), 5.39 (1 H, m), 3.54 (4 H, m), 3.47 (4 H, m), 2.52 (2 H, m), 2.20 (4 H, m), 1.91 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 439.1, Calculated 439.2.

EXAMPLE 42

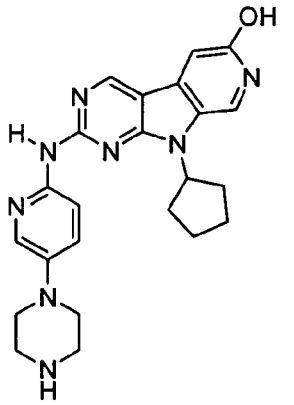


63

(9-Cyclopentyl-6-methoxy-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine

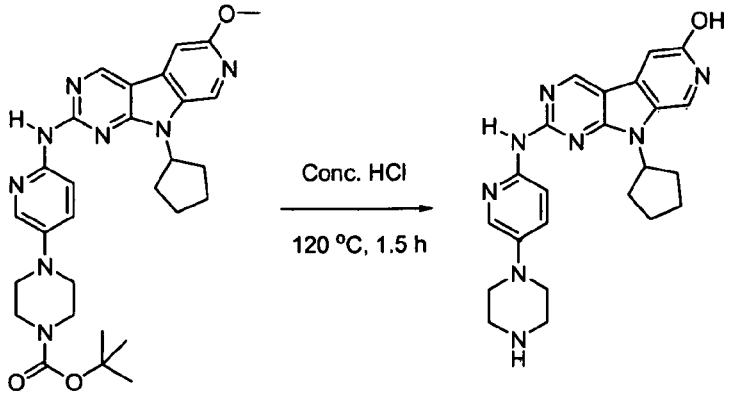
Compound **63** was prepared via compound **65** using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.36 (1 H, s), 8.66 (1 H, s), 8.18 (1 H, d, J = 2.7 Hz), 8.07 (1 H, dd, J = 9.3, 2.7 Hz), 7.67 (1 H, s), 7.54 (1 H, d, J = 9.3 Hz), 5.50 (1 H, m), 4.11 (3 H, s), 3.62 (4 H, m), 3.54 (4 H, m), 2.49-2.53 (2 H, m), 2.22 - 2.32 (4 H, m), 1.93 - 2.02 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 445.2, Calculated 445.2.

EXAMPLE 43



64

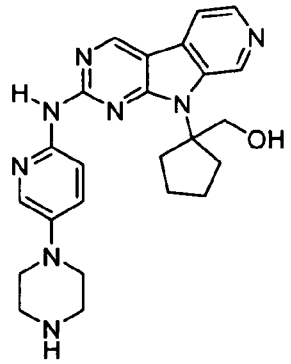
9-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-6-ol



65 64

9-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-6-ol (64) A mixture of compound **65** (366 mg) and conc. HCl (8 mL) was heated at 120 °C in a microwave reactor for 1.5 h. The reaction mixture was concentrated and and purified by prep-HPLC to give compound **64** as a yellow solid (21%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.15 (1 H, s), 8.10 (1 H, d, *J*=2.7 Hz), 7.99 (1 H, dd, *J*=9.3, 2.9 Hz), 7.91 (1 H, s), 7.48 (1 H, d, *J*=9.3 Hz), 7.26 (1 H, s), 5.18 (1 H, s), 3.54 (4 H, m), 3.47 (4 H, m), 2.35-2.37 (2 H, m), 2.11-2.16 (4 H, m), 1.86 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 431.2, Calculated 431.2.

EXAMPLE 44

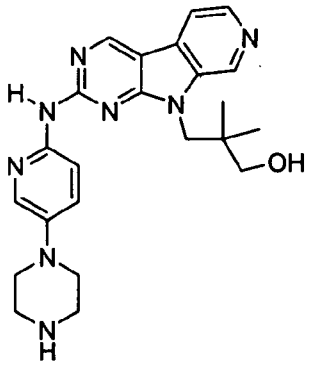


66

{1-[2-(5-Piperazin-1-yl-pyridin-2-ylamino)-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-9-yl]-cyclopentyl}-methanol

Compound **66** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.67 (1 H, s), 9.36 (1 H, s), 8.70 (1 H, d, J = 6.1 Hz), 8.62 (1 H, d, J = 6.1 Hz), 8.10 (1 H, d, J = 10 Hz), 8.08 (1 H, d, J = 2.7 Hz), 7.80 (1 H, d, J = 10 Hz), 3.99 (2 H, s), 3.55-3.57 (4 H, m), 3.46-3.48 (4 H, m), 3.07-3.11 (2 H, m), 2.60-2.66 (2 H, m), 1.97-2.01 (2 H, m), 1.89-1.92 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 445.1, Calculated 445.2.

EXAMPLE 45

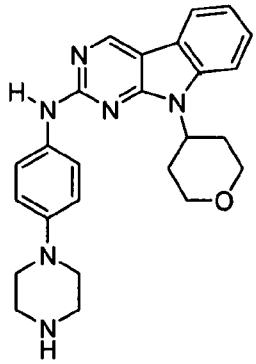


67

2,2-Dimethyl-3-[2-(5-piperazin-1-yl-pyridin-2-ylamino)-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-9-yl]-propan-1-ol

Compound **67** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.66 (1 H, s), 9.52 (1 H, s), 8.68 (2 H, s), 8.14-8.17 (1 H, dd, J = 9.5, 2.9 Hz), 8.04 (1 H, d, J = 2.9 Hz), 7.76 (1 H, d, J = 9.5 Hz), 4.58 (2 H, s), 3.58 (4 H, m), 3.48 (4 H, m), 3.36 (2 H, s), 1.11 (6 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 433.1, Calculated 433.2.

EXAMPLE 46

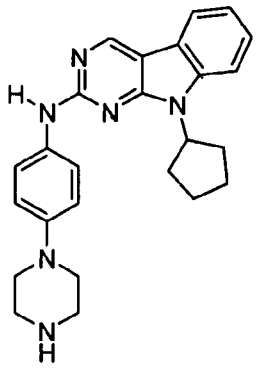


68

(4-Piperazin-1-yl-phenyl)-[9-(tetrahydro-pyran-4-yl)-9*H*-pyrimido[4,5-*b*]indol-2-yl]-amine

Compound **68** was prepared using chemistry similar to that described in example 22. ^{1}H NMR (500 MHz, CD_3OD) δ 7.40 (1 H, s), 6.55 (1 H, d, J = 9.2 Hz), 6.25 (1 H, d, J = 9.2 Hz), 6.09 (3 H, m), 5.89 (1 H, t, J = 9.2 Hz), 5.64 (2 H, d, J = 9.2 Hz), 3.44 (1 H, m), 2.63 (2 H, dd, J = 5, 10 Hz), 2.16 (2 H, t, J = 10 Hz), 1.94 (4 H, m), 1.89 (4 H, m), 1.42 (2 H, td, J = 5, 15 Hz), 0.35 (2 H, dd, J = 10, 2.5 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2, Calculated 429.2.

EXAMPLE 47

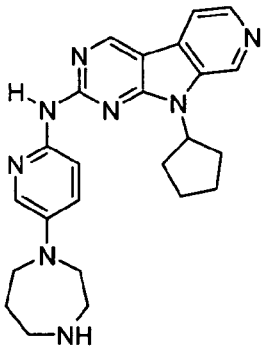


69

(9-Cyclopentyl-9*H*-pyrimido[4,5-*b*]indol-2-yl)-(4-piperazin-1-yl-phenyl)-amine

Compound **69** was prepared using chemistry similar to that described in example 22. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 10.05 (1 H, s), 9.30 (1 H, s), 9.22 (1 H, s), 8.16 (1 H, d, J = 7.8 Hz), 7.76 (1 H, d, J = 8.3 Hz), 7.54 - 7.57 (3 H, m), 7.39 (1 H, t, J = 7.5 Hz), 7.09 (2 H, d, J = 9.0 Hz), 5.24 (1 H, m), 3.72 (4 H, m), 3.50 (4 H, m), 2.32 (2 H, m), 2.05 (2 H, m), 1.95 (2 H, m), 1.71 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 413.2, Calculated 413.2.

EXAMPLE 48

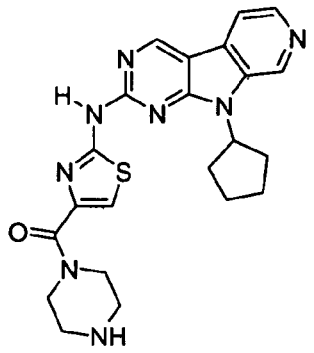


70

9-cyclopentyl-N-(5-(1,4-diazepan-1-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

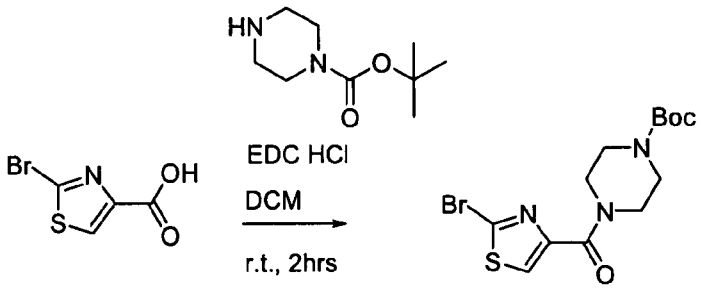
Compound **70** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 10.75 (1H, br s), 9.56 (1H, s), 9.34 (1H, s), 8.83 (2H, br s), 8.67 (1H, d, J = 6.3Hz), 8.57 (1H, d, J = 5.9Hz), 7.96 (1H, d, J = 2.7Hz), 7.92 (1H, d, J = 9.4Hz), 7.55 (1H, br s), 5.36 (1H, p, J = 8.7Hz), 3.76 (2H, t, J = 5.0 Hz), 3.56 (2H, t, J = 6.3 Hz), 3.30 (2H, br s), 3.19 (2H, br s), 2.41 (2H, m), 2.09 (6H, m), 1.75 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2

EXAMPLE 49



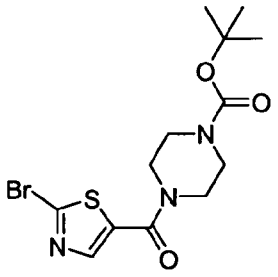
71

9-cyclopentyl-N-(4-(1-piperazinylcarbonyl)-1,3-thiazol-2-yl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



72

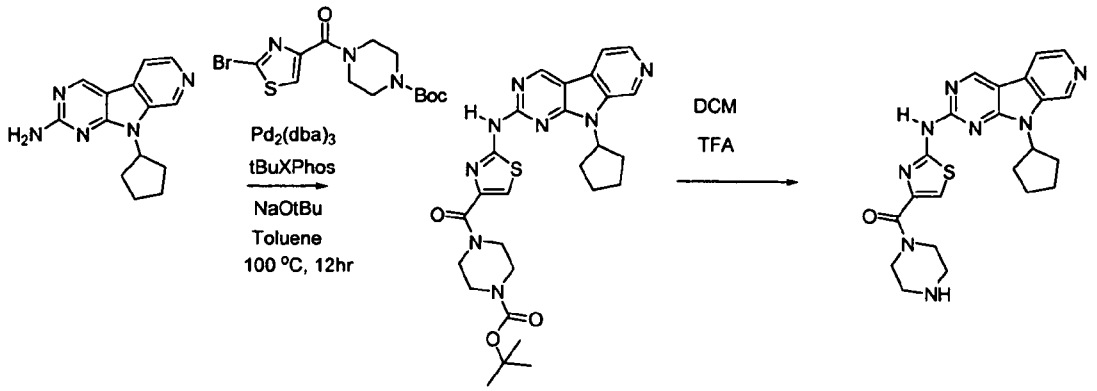
1,1-dimethylethyl 4-((2-bromo-1,3-thiazol-4-yl)carbonyl)-1-piperazinecarboxylate (72): 2-bromothiazole-4-carboxylic acid (1.31 g, 6.3 mmol) was combined with *tert*-butyl piperazine-1-carboxylate (1.2 g, 6.3 mmol) in DCM (15 mL), and then stirred at 20°C. until it formed a clear solution. N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (1.2 g, 6.3 mmol) was then added, and the reaction was stirred at 20°C. for 2 hours. The reaction was concentrated in vacuum, before transferring it to a separation funnel with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, water, NH_4Cl, and then with brine. After drying the organic layer with $MgSO_4$, it was concentrated in vacuum to yield compound **72** (2.2g, 91%) as a light yellow solid. ^1H NMR (500 MHz, *DMSO-d_6*) δ 8.16 (1H, s), 3.61 (4H, m), 3.38 (4H, m), 1.42 (9H, s) ppm; LCMS-ESI (POS), M/Z, M+1-C3H9: Found 320.0.



73

1,1-dimethylethyl 4-((2-bromo-1,3-thiazol-5-yl)carbonyl)-1-piperazinecarboxylate

Compound **73** was prepared according to the methods described for compound **72** in example 49. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 8.02 (1H, s), 3.62 (4H, m), 3.42 (4H, m), 1.43 (9H, s) ppm.

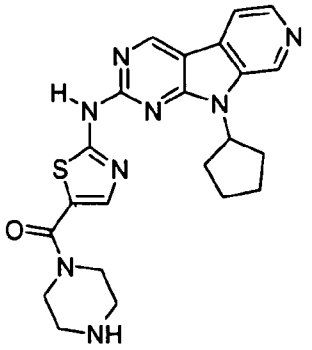


4 **72** **74** **71**

1,1-dimethylethyl 4-((2-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1,3-thiazol-4-yl)carbonyl)-1-piperazinecarboxylate (74): Compound **4** (0.075 g, 0.30 mmol) was combined with sodium 2-methylpropan-2-olate (0.085 g, 0.89 mmol) and compound **72** (0.14 g, 0.38 mmol) in toluene (2mL). This mixture was degassed by bubbling nitrogen through this solution for ~2 min followed by the addition of $Pd_2(dba)_3$ (0.014 g, 0.015 mmol) and *t*-Butyl-XPhos (0.025 g, 0.059 mmol). The reaction was heated overnight at 60°C. Additional compound **72**, 0.28 g, 0.76 mmol), $Pd_2(dba)_3$ (25 mg), t-Butyl-XPhos (54 mg), and the sodium 2-methylpropan-2-olate (0.085 g, 0.89 mmol) were added to the reaction which was heated overnight at 100°C. The reaction was cooled to 20°C and poured into a separation funnel, with ethyl acetate and water. The layers were partitioned and the aqueous layer was washed with ethyl acetate. The combined organic fractions were dried over $MgSO_4$ and concentrated. The product was purified by flash column chromatography, eluting with a gradient of DCM-6%methanol/0.3%NH4OH/DCM to yield compound **74** (95mg) as a brown film. LCMS-ESI (POS), M/Z, M+1: Found 549.3.

9-cyclopentyl-N-(4-(1-piperazinylcarbonyl)-1,3-thiazol-2-yl)-9H-pyrido[4',3':4,5]pyrrolo-[2,3-d]pyrimidin-2-amine (71): Compound **74** was dissolved in DCM (5 mL)and TFA (1.5 mL) and stirred at 20°C for 2.5 hrs. The reaction was concentrated in vacuum and purified by preparative HPLC eluting with a gradient 10%MeCN/water/0.1%TFA -50%MeCN/water/0.1%TFA to provide compound **71** (23 mg) as a yellow solid. ^{1}H NMR (500 MHz, *CD_3OD*) δ 9.63 (1H, s), 9.32 (1H, s), 8.68 (1H, d, J = 6.1Hz), 8.63 (1H, d, J = 6.4Hz), 7.84 (1H, s), 5.56 (1H, p, J = 8.1), 4.00-4.29 (4H, br s), 3.39 (4H, t, J = 5.3Hz), 2.63 (2H, m), 2.25 (4H, m), 1.98 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 449.2.

EXAMPLE 50

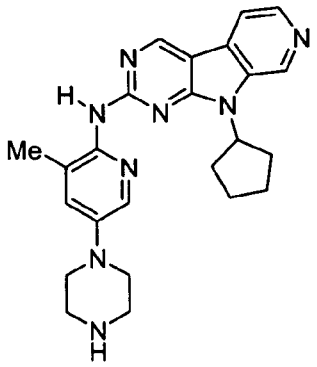


75

9-cyclopentyl-N-(5-(1-piperazinylcarbonyl)-1,3-thiazol-2-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

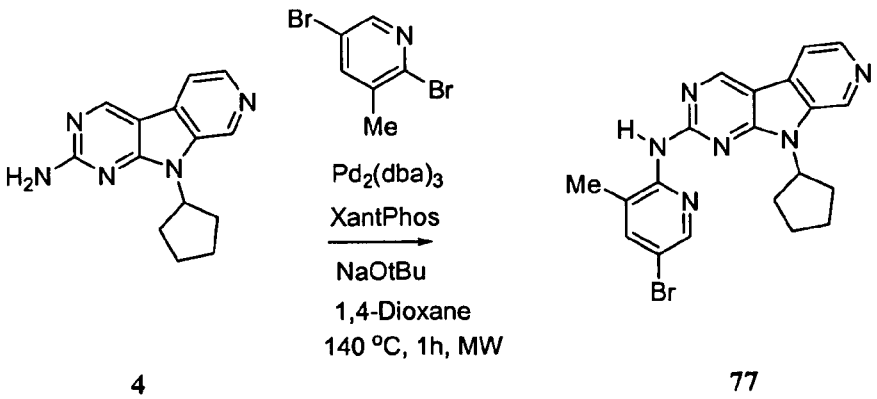
Compound **75** was prepared according to the methods described in example 49. ^{1}H NMR (500 MHz, CD_3OD) δ 9.63 (1H, s), 9.34 (1H, s), 8.65 (1H, d, J = 6.1Hz), 8.62 (1H, d, J = 6.1Hz), 7.93 (1H, s), 5.52 (1H, p, J = 9.3Hz), 4.10 (4H, t, J = 5.1Hz), 3.39 (4H, t, J = 5.1Hz), 2.70 (2H, m), 2.28 (4H, m), 1.95 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 449.2.

EXAMPLE 51



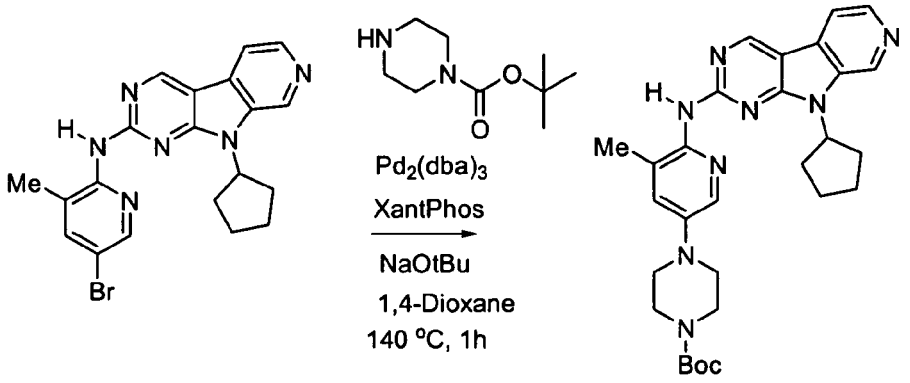
76

9-cyclopentyl-N-(3-methyl-5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



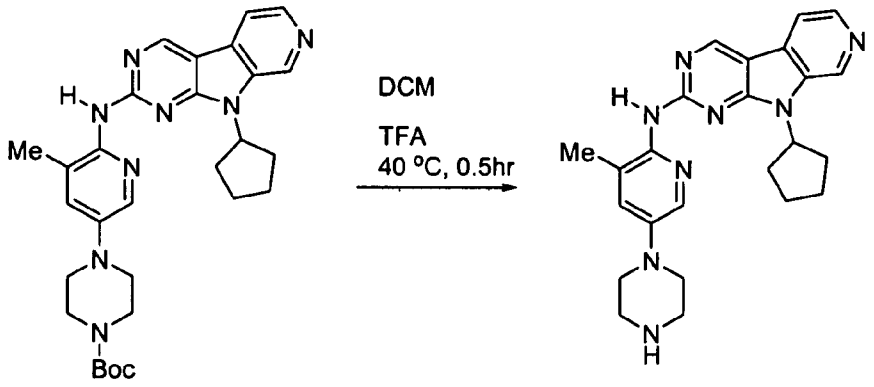
4 77

N-(5-bromo-3-methyl-2-pyridinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (77): Sodium 2-methylpropan-2-olate (0.142 g, 1.48 mmol) was combined with compound **4** (0.125 g, 0.493 mmol) and 2,5-dibromo-3-methylpyridine (0.149 g, 0.592 mmol) in 1,4-dioxane (3 ml). The reaction mixture was degassed by bubbling nitrogen through the solution for ~ 1min, followed by the addition of XANTPHOS (0.0428 g, 0.0740 mmol) and $Pd_2(dba)_3$ (0.0339 g, 0.0370 mmol). The reaction was heated to 140 °C using microwave irradiation for 1 hour. The reaction mixture was poured into sat. NH_4Cl and extracted with 10% isopropanol/DCM. The organic layer was dried with $MgSO_4$ and concentrated in vacuum. Purification by flash column chromatography, eluting with a gradient of DCM-5%methanol/DCM provided compound **77** as a yellow solid (150 mg, 71%). LCMS-ESI (POS), M/Z, M+1: Found 423.1



77 **78**

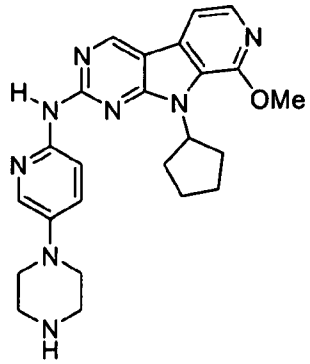
1,1-dimethylethyl 4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-5-methyl-3-pyridinyl)-1-piperazinecarboxylate (78): Sodium 2-methylpropan-2-olate (0.100 g, 1.06 mmol) was combined with compound **77** (0.150 g, 0.354 mmol) and *tert*-butyl 1-piperazinecarboxylate (0.099 g, 0.532 mmol) in 1,4-dioxane (3 ml). Nitrogen was bubbled through the solution for 1min before adding XANTPHOS (0.031 g, 0.053 mmol) and $Pd_2(dba)_3$ (0.024 g, 0.026 mmol). The reaction mixture was heated to 140°C using microwave irradiation for 1 hour. The reaction mixture was poured into sat. NH_4Cl, and extracted with 10% isopropanol/DCM. The organic layer was dried over $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash column chromatography, eluting with a gradient of DCM-7%methanol/DCM to provide compound **78** as a brown oil (100 mg). LCMS-ESI (POS), M/Z, M+1: Found 529.3.



78 76

9-cyclopentyl-N-(3-methyl-5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (76): Compound **78** (0.100 g, 0.189 mmol) was dissolved in DCM (3 mL) followed by TFA (1 mL) and stirred at 40°C in a water bath for 30 min. Concentration under vacuum provided a yellowish oil which was partially dissolved in water and then filtered. The filtrate was purified by preparative RP-HPLC eluting with a gradient of 5%MeCN/water/0.1%TFA-30%MeCN/water/0.1%TFA to yield compound **76** as a yellow solid (33 mg). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 10.18 (1H, s), 9.51 (1H, s), 9.31 (1H, s), 8.95 (2H, br s), 8.65 (1H, d, J = 6.2Hz), 8.55 (1H, d, J = 6.1Hz), 8.12 (1H, d, J = 3.0), 7.58 (1H, d, J = 2.4Hz), 5.25 (1H, p, J = 8.3Hz), 3.46 (4H, t, J = 5.4Hz), 3.30 (4H, m), 2.24 (3H, s), 2.18 (2H, m), 2.01 (2H, m), 1.70 (2H, m), 1.55 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2.

EXAMPLE 52

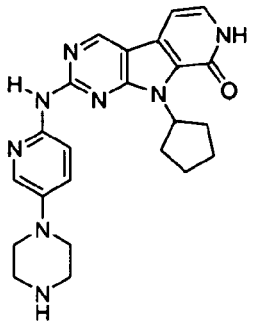


79

9-cyclopentyl-8-(methyloxy)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine

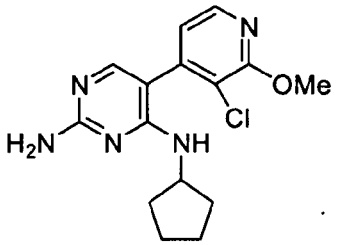
Compound **79** was prepared using compound **82** and chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.12 (1 H, s), 8.24(1 H, d), 8.02 (1 H, d), 7.98 (1 H, d), 7.63 (1 H, d), 7.56 (1 H, m), 5.90 (1 H, b), 4.15 (3 H, s), 3.20 (4 H, m), 3.06 (4 H, m), 2.50-2.60 (2 H, b), 2.09-2.11 (4 H, b), 1.80 (2 H, b) ppm; LCMS-ESI (POS), M/Z, M+1: Found 445.1, calculated 445.2.

EXAMPLE 53



80

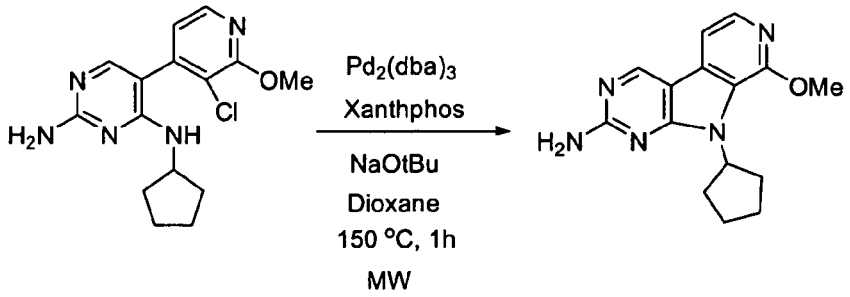
9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-7,9-dihydro-8H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-one



81

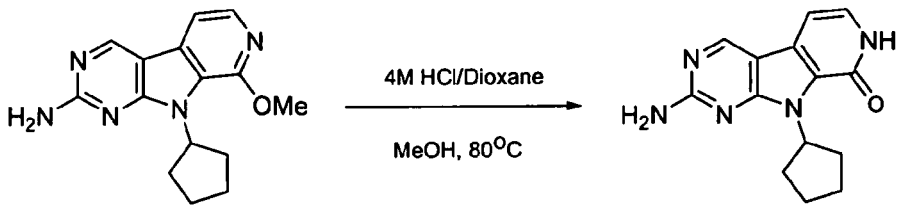
5-(3-chloro-2-(methyloxy)-4-pyridinyl)-N^4-cyclopentyl-2,4-pyrimidinediamine

Compound **81** was prepared using chemistry similar to that described in example 1. LCMS-ESI (POS), M/Z, M+1: Found 320.0, calculated 320.1.



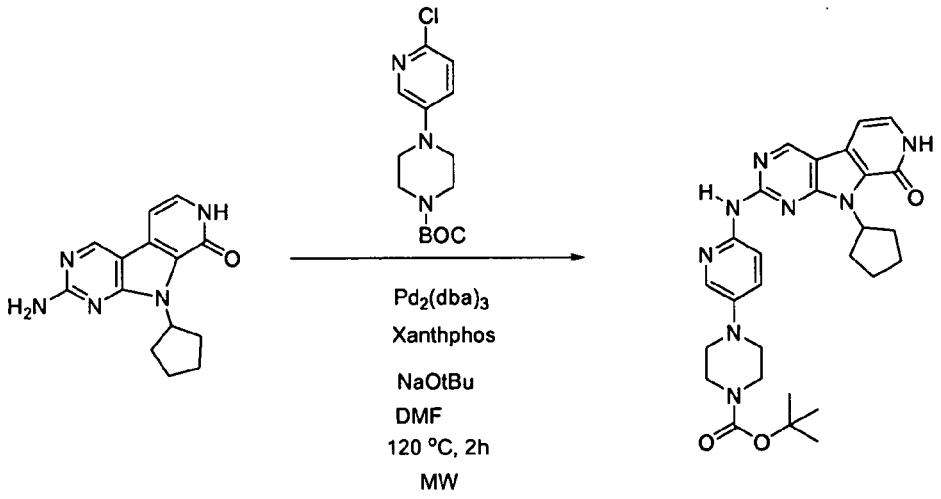
81 82

9-cyclopentyl-8-(methyloxy)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine(82): A solution of $Pd_2(dba)_3$(0.60 g, 0.65 mmol), sodium 2-methylpropan-2-olate (1.9g, 20 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.75 g, 1.3 mmol) and compound **81** (2.08 g, 6.5 mmol) in dioxane (20 mL) was purged with N_2 for 20 min. The reaction mixture was heated at 150°C for one hour under microwave irradiation. The reaction mixture was concentrated and residue was diluted with DCM. Resulting solution was washed with brine, dried and concentrated. Purification by flash chromatography (10%methanol/DCM/1%NH_4OH) gave compound **82** as a yellow solid (1.8 g, 98%). LCMS-ESI (POS), M/Z, M+1: Found 284.1, calculated 284.1.



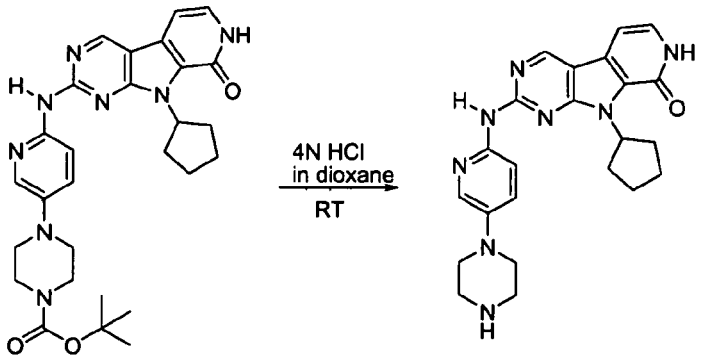
82 83

2-amino-9-cyclopentyl-7,9-dihydro-8H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-one (83): A solution of compound **82** (1.80g, 6.35 mmol) in 4M HCl in dioxane(60 mLl) and methanol(6 mL) was heated at 80°C for one hour. Solid was collected by filtration to give a pale yellow solid as HCl salt which was then dissolved in water and basified by addition of solid sodium bicarbonate to pH 5~6. The precipitate was collected by filtration to provide compound **83** as a white solid.(0.715g, 42%). LCMS-ESI (POS), M/Z, M+1: Found 270.1, calculated 270.1.



83 5 84

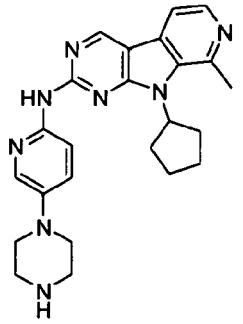
1,1-dimethylethyl 4-(6-((9-cyclopentyl-8-oxo-8,9-dihydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (84): Compound **84** was prepared by analogy to example 1. LCMS-ESI (POS), M/Z, M+1: Found 531.2, calculated 531.3.



84 80

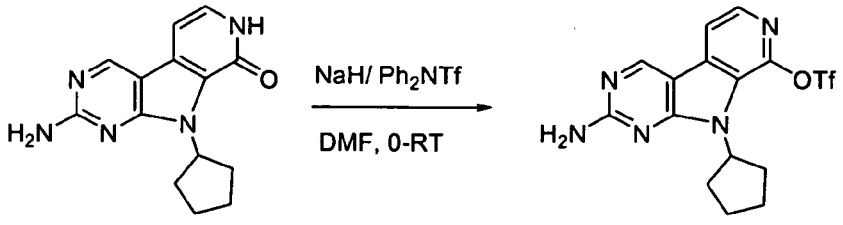
9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-7,9-dihydro-8H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-8-one (80): Compound **80** was prepared according to the methods described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.31 (1 H, s), 8.03(1 H, d), 8.01 (1 H, d), 7.75 (1 H, d), 7.35 (1 H, d), 7.16 (1 H, m), 6.25 (1 H, b), 3.52 (4 H, m), 3.47 (4 H, m), 2.50-2.60 (2 H, b), 2.09-2.25 (4 H, b), 1.75 (2 H, b) ppm; LCMS-ESI (POS), M/Z, M+1: Found 431.2, calculated 431.2

EXAMPLE 54



85

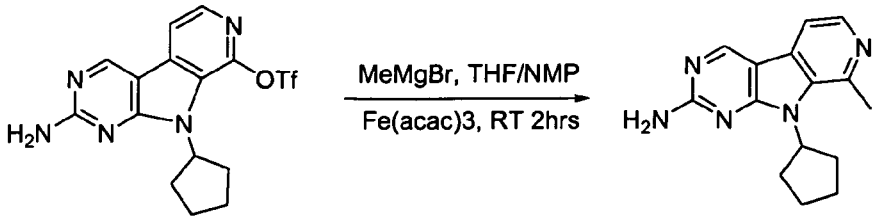
9-cyclopentyl-8-methyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



83 86

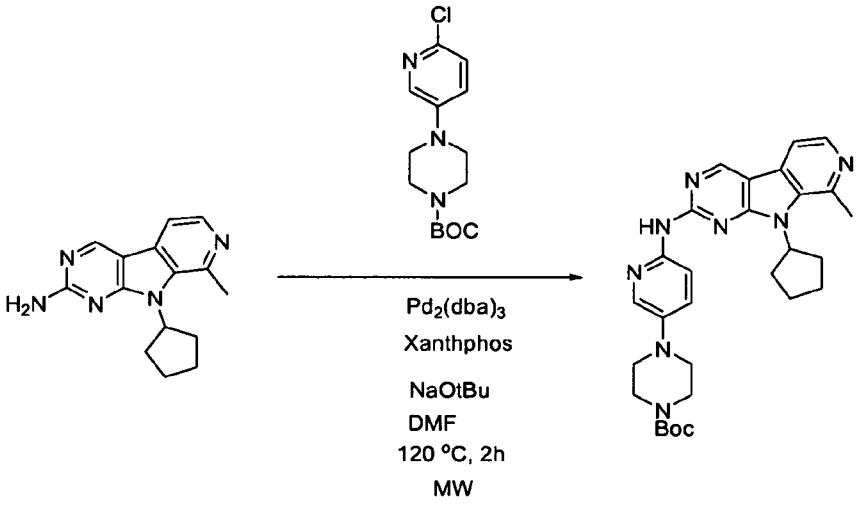
2-Amino-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-yl trifluoromethanesulfonate (86): Sodium hydride (60% in oil, 16 mg) was added to a solution of compound **83**(0.100g, 0.371 mmol) in DMF(2 mL) and stirred at 0°C for 30 min., then N-phenyl-bis(trifluoromethanesulfonimide)(0.146g, 0.408 mmol) in DMF (1 mL) was added dropwise at 0° C and

the resulting mixture was stirred at 0 °C for two hours. The reaction mixture was concentrated and dissolved in DCM. The resulting organic solution was washed with brine, dried and concentrated . Purification by flash chromatography(10%methanol/DCM/1%NH_4OH) gave compound **86** (0.102g, 67%) as a yellow solid. LCMS-ESI (POS), M/Z, M+1: Found 402.1, calculated 402.1.



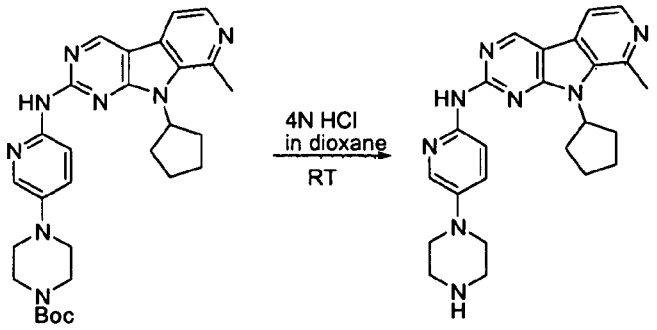
86 **87**

9-cyclopentyl-8-methyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (87):
A flame-dried two-necked flask was charged under argon with compound **86** (0.100g, 0.25 mmol), ferric acetylacetonate(0.0044, 0.012 mmol), THF(2 ml) and N-methylpyrrolidone (0.1 ml). Methylmagnesium bromide (0.27 g, 2.2 mmol, 3M in ether) was added via syringe to the resulting red solution. A yellow precipitate formed immediately. The reaction was stirred at room temperature for 30 min and quenched with 5% $NaHCO_3$, then extracted into DCM The resulting organic solution was washed with brine, dried and concentrated . Purification by flash chromatography (10%methanol/DCM/1%NH_4OH) gave compound **87** as a light yellow solid(0.036g, 54%). LCMS-ESI (POS), M/Z, M+1: Found 268.1, calculated 268.2.



87 **5** **88**

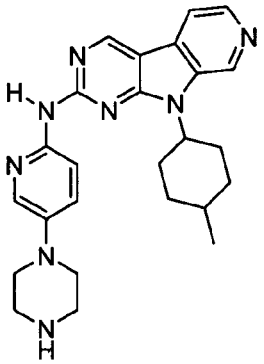
1,1-dimethylethyl 4-(6-((9-cyclopentyl-8-methyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (88): Compound **88** was prepared according to the methods described in example 1. LCMS-ESI (POS), M/Z, M+1: Found 529.3, calculated 529.3.



88 85

9-cyclopentyl-8-methyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (85): Compound **85** was prepared according to the methods described in example 1. ^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (1 H, s), 8.36(1H,s), 8.29(2 H, d), 8.01 (1 H, s), 7.62 (1 H, d), 7.28 (1 H, d), 5.36 (1 H, m), 3.09 (4 H, m), 3.02 (4 H, m), 2.95 (3 H, s), 2.73-2.70 (2 H, m), 2.09-1.98 (4 H, m), 1.80 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2, calculated 429.2.

EXAMPLE 55

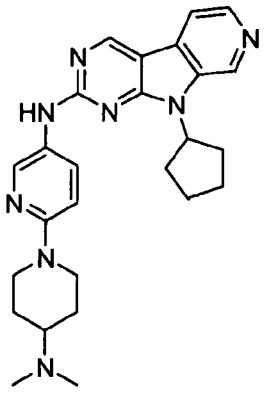


89

9-(4-methylcyclohexyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

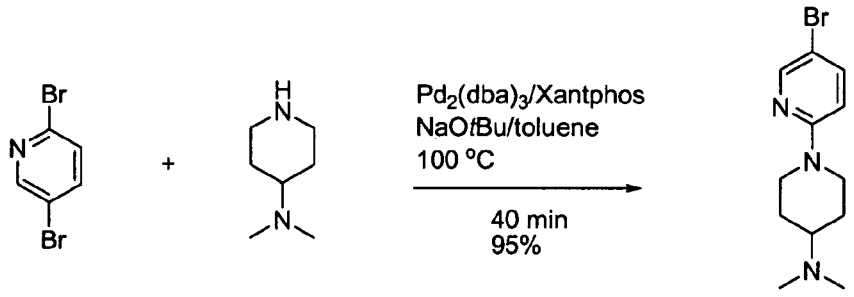
Compound **89** was prepared according to the methods described in example 1. 1H NMR (500 MHz, CD_3OD) δ 9.19 (1 H, s), 8.97(1H,s), 8.39(1 H, d), 8.29(0.5H,d), 8.24 (0.5H, d), 8.05 (1 H, m), 7.53 (1 H, m), 3.20 (4 H, m), 3.07 (4 H, m), 2.80 (1 H, m), 2.60(1H, m), 2.10(1H, b), 1.97 (3 H, b), 1.75 (3 H, m), 1.40 (1 H, m), 1.2 5(1.5H, d), 1.08 (1.5H, d) ppm; LCMS-ESI (POS), M/Z, M+1: Found 443.2, calculated 443.2.

EXAMPLE 56



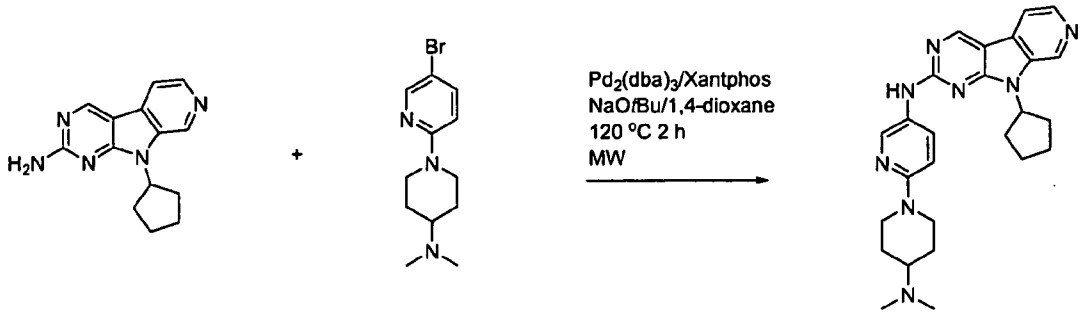
90

9-cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



91

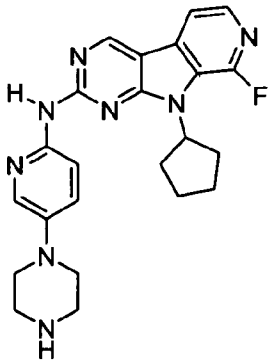
1-(5-bromopyridin-2-yl)-N,N-dimethylpiperidin-4-amine (91): To a 100 mL single-necked round-bottom flask were placed 2,5-dibromopyridine (2 g, 8 mmol), 4-(dimethylamino)piperidine (1 ml, 8 mmol), tris(dibenzylideneacetone)dipalladium (o) (0.07 g, 0.08 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.1 g, 0.2 mmol), and sodium *t*-butoxide (1 g, 12 mmol). The flask was subjected to 3 cycles of evacuation and back-filling with N_2 before toluene (40 mL) was introduced under N_2. The resulting mixture was stirred at a preheated oil bath at 100 °C for 40 min. The crude mixture was poured into ice and 4 N NaOH aqueous solution and extracted with ethyl acetate (2 X). The combine organics were dried over sodium sulfate and concentrated in vacuo to give 2.7 g crude product. Trituration with ethyl acetate/hexanes gave highly pure 1-(5-bromopyridin-2-yl)-N,N-dimethylpiperidin-4-amine (**91**) (1.9 g, 95%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (1 H, d, J = 2.3 Hz), 7.52 (1 H, dd, J = 9.0, 2.7 Hz), 6.58 (1 H, d, J = 9.0 Hz), 4.30 (2 H, d, J = 12.9 Hz), 2.79 - 2.91 (2 H, m), 2.49 (1 H, br. s.), 2.37 (6 H, s), 1.97 (2 H, d, J = 12.5 Hz), 1.45 - 1.60 (2 H, m) ppm.



4 91 90

9-cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (90): To a microwave reaction vessel were placed compound **4** (30 mg, 118 μmol), compound **91** (50 mg, 178 μmol), tris(dibenzylideneacetone)dipalladium (0) (5.4 mg, 5.9 μmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (8.6 mg, 15 μmol), and sodium *tert*-butoxide (34 mg, 355 μmol). 1,4-dioxane (4 mL) was added and the vessel was purged with N_2 for 3 min, then capped and subjected to microwave irradiation for 2 h at 120° C. After removal of the volatiles, the residue was dissolved in methanol and filtered. The filtrate was subjected to reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 5 to 40%) to give ~ 15 mg of compound **90** as a TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ 9.43 (1 H, s), 9.16 (1 H, s), 8.65 (1 H, d, *J*=2.3 Hz), 8.48 - 8.57 (2 H, m), 8.12 (1 H, dd, *J*=9.4, 2.3 Hz), 7.21 (1 H, d, *J*=9.4 Hz), 5.29 - 5.47 (1 H, m), 4.45 (2 H, d, *J*=13.7 Hz), 3.49 - 3.58 (1 H, m), 3.03 - 3.18 (2 H, m), 2.92 (6 H, s), 2.37 - 2.54 (2 H, m), 2.04 - 2.29 (6 H, m), 1.76 - 1.93 (4 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 457.3, Calculated 457.2.

EXAMPLE 57

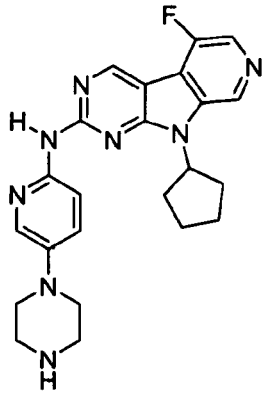


92

9-Cyclopentyl-8-fluoro-*N*-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **92** was prepared using chemistry similar to that described in example 22. ^{1}H NMR (500 MHz, CD_3OD) δ 9.46 (1 H, s), 8.10 - 8.15 (3 H, m), 8.05 (1 H, d, J = 2.9 Hz), 7.64 (1 H, d, J = 9.5 Hz), 5.20 (1 H, m), 3.51 - 3.57 (4 H, m), 3.42 - 3.51 (4 H, m), 2.40-2.50 (2 H, m), 2.10-2.25 (4 H, m), 1.80-1.90 (2H, m) ppm, LCMS-ESI (POS), M/Z, M+1: Found 433.1, Calculated 433.2.

EXAMPLE 58

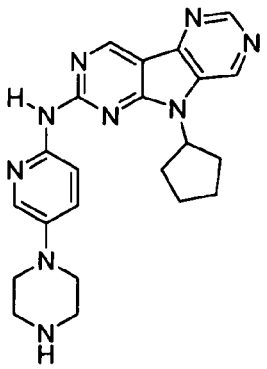


93

9-Cyclopentyl-5-fluoro-*N*-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **93** was prepared using chemistry similar to that described in example 22. ^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (1 H, s), 8.75 (1 H, s), 8.28 (1 H, s), 8.23 (1 H, d, J = 9.0 Hz), 8.02 (1 H, d, J = 2.9 Hz), 7.46-7.49 (1 H, dd, J = 9.0, 2.6 Hz), 5.41 (1 H, m), 3.33 (4 H, m), 3.19 (1 H, m), 2.44-2.49 (2 H, m), 2.11-2.24 (4 H, m), 1.87-1.90 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 433.1, Calculated 433.2.

EXAMPLE 59

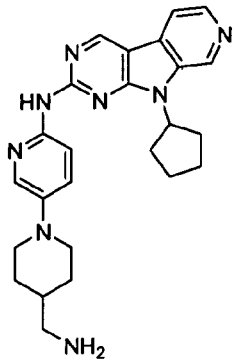


94

5-Cyclopentyl-*N*-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrimido[4',5':4,5]pyrrolo[2,3-d]pyrimidin-7-amine

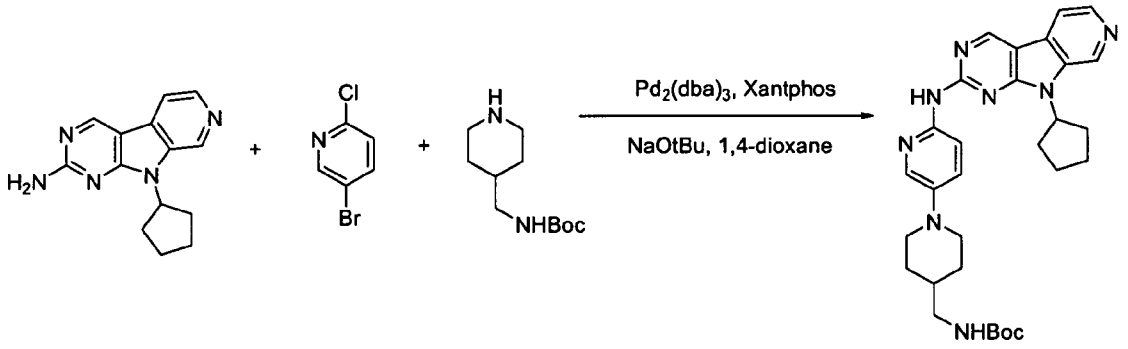
Compound **94** was prepared using chemistry similar to that described in example 22. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.21 (1 H, s), 8.96 (1 H, s), 8.83 (1 H, s), 8.32 (3 H, d, *J*=9.0 Hz), 7.98 (2 H, d, *J*=2.2 Hz), 7.31 (2 H, dd, *J*=9.0, 2.7 Hz), 5.23 - 5.31 (1 H, m), 3.05 (4 H, m), 2.95 (4 H, m), 2.47 (1 H, s), 2.28 (2 H, m), 2.10 - 2.20 (2 H, m), 1.98 - 2.08 (2 H, m), 1.70 - 1.84 (2 H, m) ppm, LCMS-ESI (POS), M/Z, M+1: Found 416.2, Calculated 416.2.

EXAMPLE 60



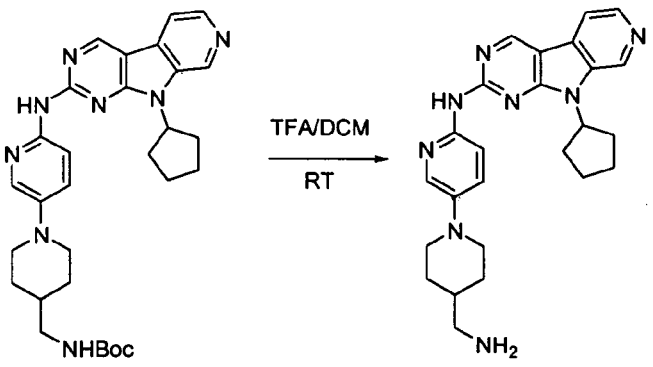
95

4-Aminomethyl-1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-piperidine



4 97 98

1,1-Dimethylethyl 1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinemethyl carboxylate (98): A mixture of 5-bromo-2-chloropyridine (0.019 g, 0.099 mmol), *tert*-butyl piperidin-4-ylmethylcarbamate (**97**) (0.024 g, 0.099 mmol), Xentphos (0.0086 g, 0.015 mmol), $Pd_2(dba)_3$ (0.0068 g, 0.0074 mmol), and sodium *tert*-butoxide (0.014 g, 0.15 mmol) in dioxane was purged with nitrogen gas for 1 min. The reaction was heated at 80°C for 2 hours and then cooled to room temperature. Compound (**4**)(0.0250 g, 0.099 mmol), Xantphos (0.0086 g, 0.015 mmol), $Pd_2(dba)_3$ (0.0068 g, 0.0074 mmol) and sodium tert-butoxide (0.014 g, 0.15 mmol) were added. The mixture was purged again with nitrogen again for 1 min. And heated at 100°C for 1.5~2 hours and then cooled to room temperature. The solvent was removed using Gene Vac. The residue was sonicated with 2mL methanol. The solid was removed by filtration, washed with 2x1mL methanol. The combined solution was purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide compound **98** as a TFA salt. LCMS-ESI (POS), M/Z, M+1: 543.2

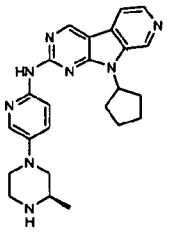
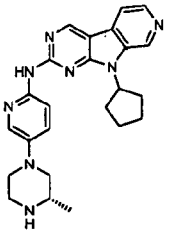


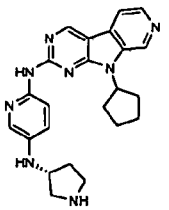
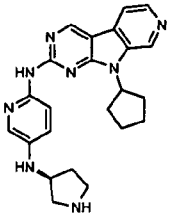
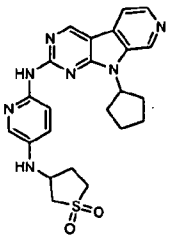
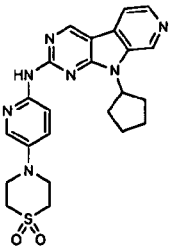
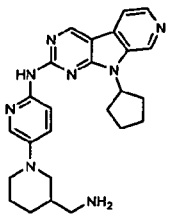
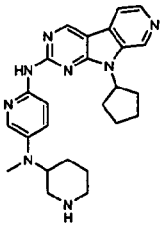
98 95

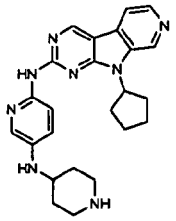
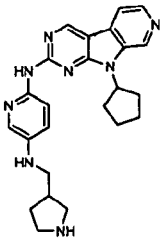
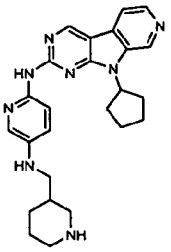
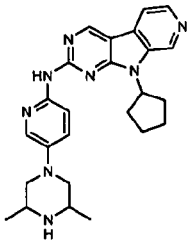
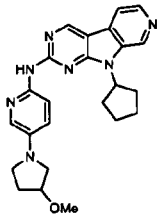
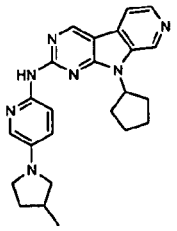
4-Aminomethyl-1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-piperidine (95): Compound **98** was treated with 1:1 TFA/DCM (2mL) at room temperature for an hour. The solvent was evaporated. The residue was re-dissolved in 4ml methanol and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide compound **95** as a TFA salt. LCMS retention time (minutes): 0.708. LCMS-ESI (POS), M/Z, M+1: 443.2

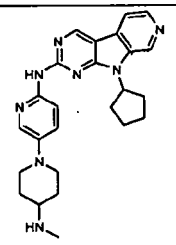
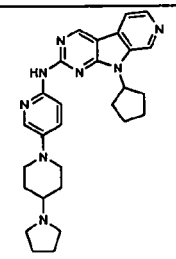
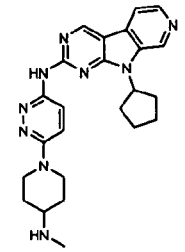
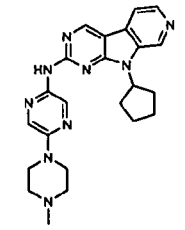
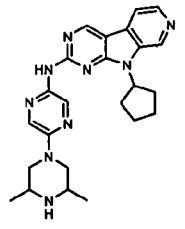
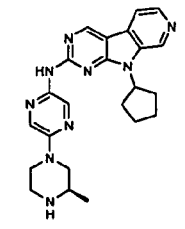
Examples 61-100 (listed in Table 1) were prepared using conditions as described for example 60 with deprotection when necessary, replacing 5-bromo-2-chloropyridine and **97** with proper chemical reagents. The reaction conditions such as temperature and reaction time were the same unless indicated in Table 1. All LCMS data was obtained using Agilent 1100 series LC/MSD, column: CAPCELL UG120 (3um, 4.6 mm I.D. x 50 mm), solvent system: water-acetonitile 95:5 with 0.1% formic acid.

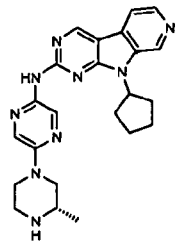
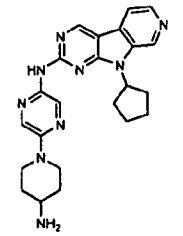
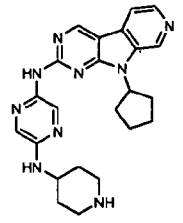
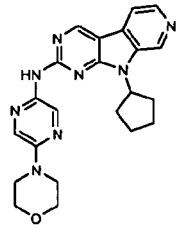
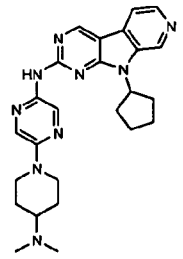
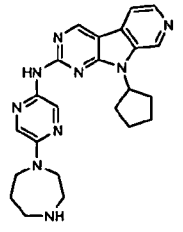
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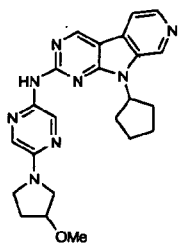
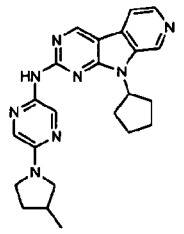
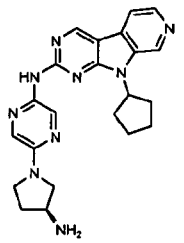
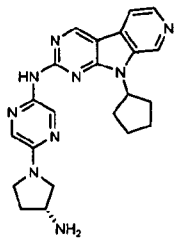
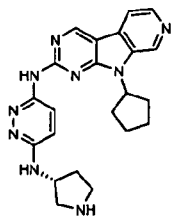
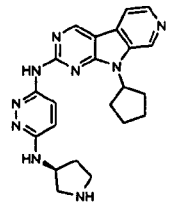
Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS -ESI (M+1)
61			0.701	429.2
62			0.704	429.2

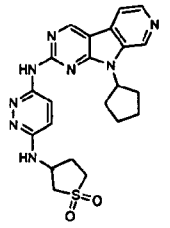
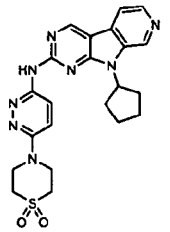
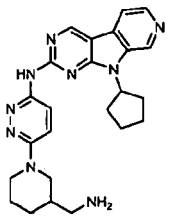
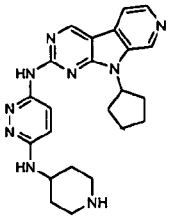
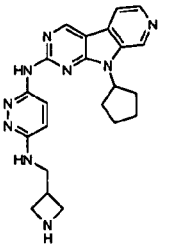
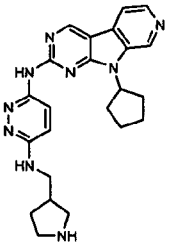
Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS -ESI (M+1)
63			0.660	415.1
64			0.660	415.1
65			0.842	464.2
66			0.878	464.2
67			0.753	443.2
68			0.742	443.2

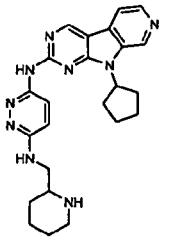
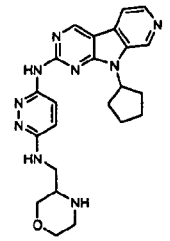
Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS -ESI (M+1)
69			0.672	429.2
70			0.718	429.2
71			0.735	443.2
72		Step1. 70°C, 2hour; Step2. 90°C, 2hour.	0.696	443.2
73			0.942	430.1
74			1.20	414.2

Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS -ESI (M+1)
75			0.742	443.2
76			0.765	483.3
77		Step1. 80°C, 2hour; 120°C, 2hour.	0.700	444.2
78		Step1. 60°C, 2hour; 80°C, 2hour.	0.736	430.2
79		Step1. 60°C, 2hour; 80°C, 2hour.	0.771	444.2
80		Step1. 60°C, 2hour; 80°C, 2hour.	0.755	430.1

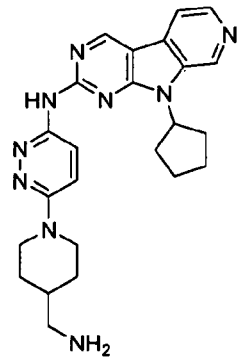
Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS -ESI (M+1)
81		Step1. 60°C, 2hour; 80°C, 2hour.	0.757	430.2
82		Step1. 60°C, 2hour; 80°C, 2hour.	0.771	430.2
83		Step1. 60°C, 2hour; 80°C, 2hour.	0.738	430.2
84		Step1. 60°C, 2hour; 80°C, 2hour.	1.07	417.3
85		Step1. 60°C, 2hour; 80°C, 2hour.	0.817	458.2
86		Step1. 60°C, 2hour; 80°C, 2hour.	0.823	430.1

Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS -ESI (M+1)
87		Step1. 60°C, 2hour; 80°C, 2hour.	1.09	431.2
88		Step1. 60°C, 2hour; 80°C, 2hour.	1.27	415.2
89		Step1. 60°C, 2hour; 80°C, 2hour.	0.761	416.2
90		Step1. 60°C, 2hour; 80°C, 2hour.	0.740	416.2
91		Step1. 70°C, 0.5hour; 100°C, 0.5hour.	0.642	416.2
92		Step1. 70°C, 0.5hour; 100°C, 0.5hour.	0.649	416.2

Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS -ESI (M+1)
93		Step1. 70°C, 0.5hour; 100°C, 0.5hour.	0.792	465.1
94		Step1. 70°C, 0.5hour; 100°C, 0.5hour.	0.848	465.1
95		Step1. 70°C, 0.5hour; 100°C, 0.5hour.	0.658	444.2
96		Step1. 60°C, 0.5hour; 100°C, 0.5hour.	0.641	430.1
97		Step1. 70°C, 0.5hour; 100°C, 0.5hour.	0.624	416.2
98		Step1. 80°C, 0.5hour; 120°C, 0.5hour.	0.635	430.2

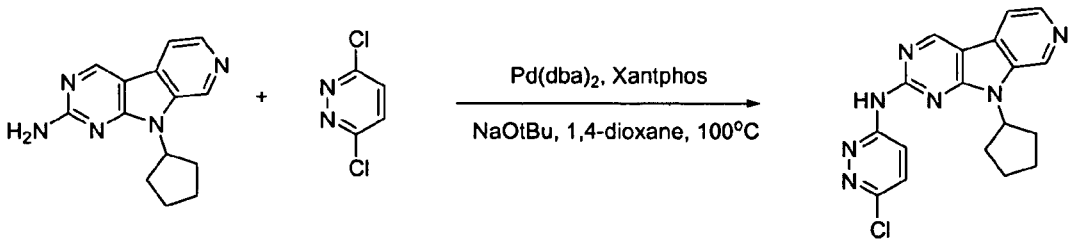
Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS -ESI (M+1)
99		Step1. 60°C, 0.5hour; 100°C, 0.5hour.	0.675	444.2
100		Step1. 70°C, 0.5hour; 100°C, 0.7hour.	0.663	446.2

EXAMPLE 101



138

4-Aminomethyl-1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-piperidine

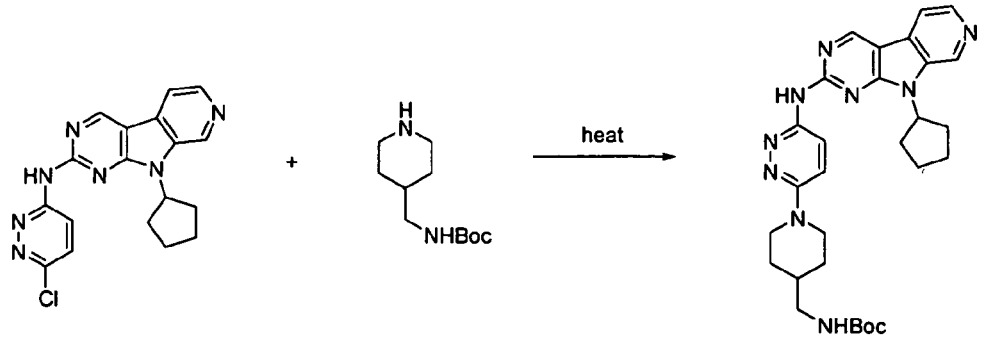


4

140

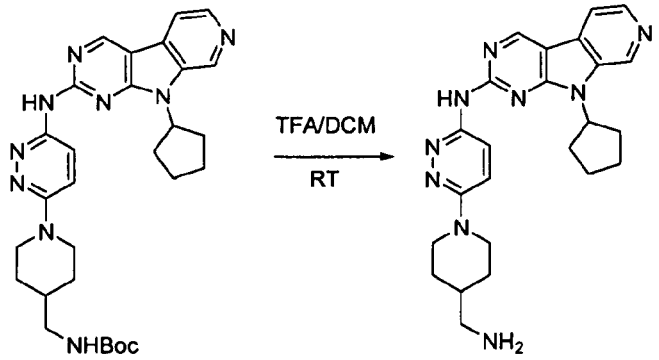
6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-chloro-pyridazine (140): A mixture of compound 4 (1.50g, 5.92 mmol), 3,6-dichloropyridazine (0.882g, 5.92 mmol), bis(dibenzylideneacetone)palladium(0.170g, 0.296 mmol), Xantphos(0.514g, 0.888 mmol) and sodium tert-butoxide(0.854, 8.88mmol) in toluene (80mL) was purged with nitrogen. The reaction was then

heated at 100°C for one hour in a sealed vessel. After cooling to room temperature, the mixture was loaded onto a silica gel column and eluted with 2-10% methanol/DCM. Evaporation of combined fractions provided compound **140** (2.1g) as a yellowish solid. LCMS-ESI, M+1: 366.1



140 **97** **142**

1,1-Dimethylethyl 1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-4-piperidinemethyl carboxylate (142): The neat mixture of compound **140** (0.0300g, 0.0820 mmol) and compound **97** (0.176 g, 0.820 mmol) was heated at 150 °C for 1.5 hours using microwave. The crude material was dissolved in 4mL methanol, filtered and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide the title compound **142** as a TFA salt. LCMS-ESI (POS), M/Z, M+1: 544.3

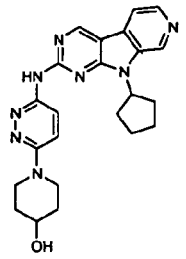
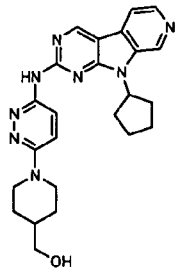
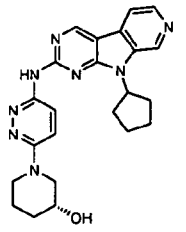
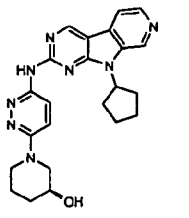
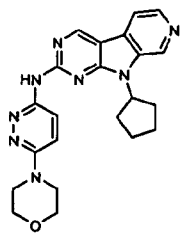


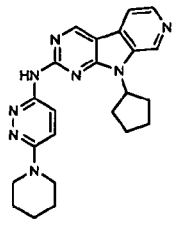
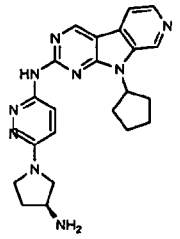
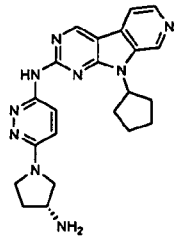
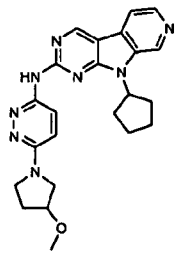
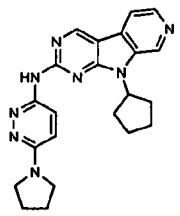
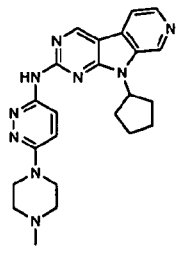
142 **138**

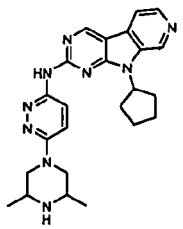
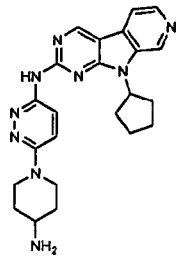
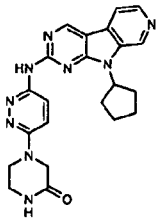
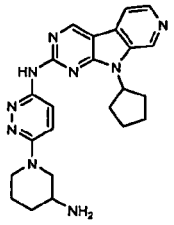
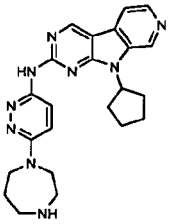
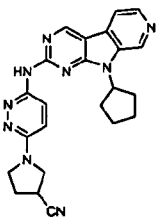
4-Aminomethyl-1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-piperidine (138): Compound 142 was treated with 15% TFA/DCM (2mL) at room temperature for one hour. The solvent was evaporated. The residue was re-dissolved in 4mL methanol and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide the desired product as TFA salt. LCMS retention time (minutes): 0.666. LCMS-ESI (POS), M/Z,M+1: 444.3

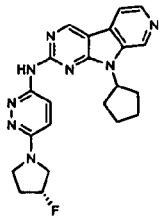
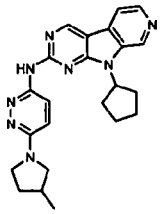
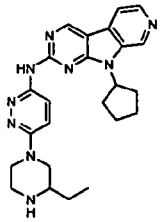
Examples 102-121 (table 2) were prepared using conditions as described for example 101 with deprotection when necessary, replacing compound **97** with proper amine. The reaction conditions such as solvent, temperature, and reaction time for Step 2 were the same unless indicated in Table 2.

Table 2

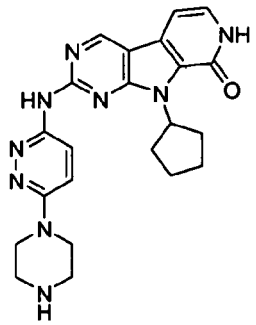
Example #	Structure	Reaction Conditions	LSMS retention time (min)	LCMS-ESI (M+1)
102		DMSO/155°C/1.5 hours	0.835	431.2
103		DMSO/155°C/1.5 hours	0.854	445.1
104		NMP/180°C/2 hours	0.790	431.2
105		NMP/180°C/2 hours	0.800	431.2
106		DMSO/155°C/1.5 hours	0.909	417.3

Example #	Structure	Reaction Conditions	LSMS retention time (min)	LCMS-ESI (M+1)
107		DMSO/150°C/1.5 hours	0.997	415.1
108		DMSO/155°C/1.5 hours	0.659	416.2
109		DMSO/145°C/0.5 hour	0.620	416.1
110		NMP/165°C/0.7 hour	0.808	431.2
111		DMSO/140°C/1 hour	0.850	401.2
112		NMP/180°C/2 hours	0.652	430.1

Example #	Structure	Reaction Conditions	LSMS retention time (min)	LCMS-ESI (M+1)
113		NMP/180°C/1 hour	0.747	444.2
114		NMP/150°C/2 hours	0.661	430.1
115		NMP/185°C/2 hours	0.769	430.1
116		NMP/180°C/1 hour	0.680	430.1
117		DMSO/155°C/1.5 hours	0.730	430.1
118		NMP/175°C/1 hour	0.836	426.2

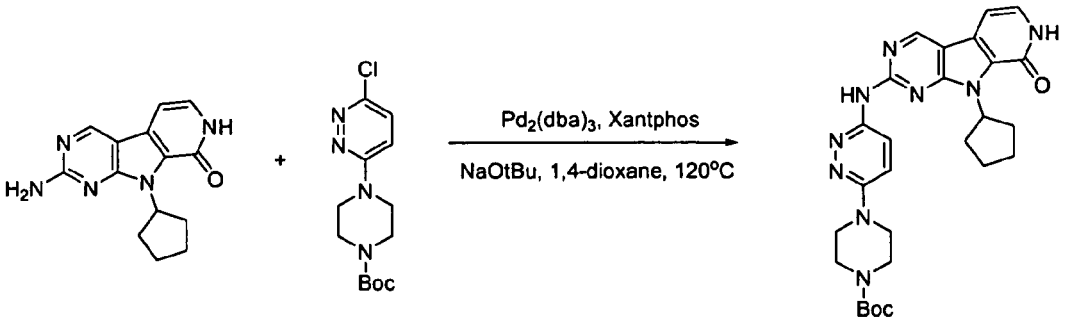
Example #	Structure	Reaction Conditions	LSMS retention time (min)	LCMS-ESI (M+1)
119		NMP/175°C/1 hour	0.828	419.2
120		NMP/175°C/1 hour	0.885	415.1
121		NMP/175°C/1 hour	0.743	444.2

EXAMPLE 122



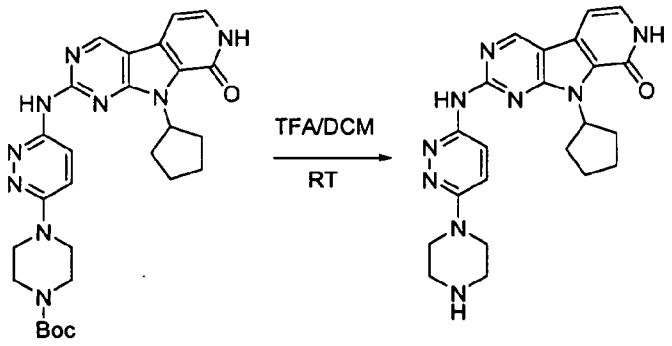
161

9-Cyclopentyl-2-((6-(1-piperazinyl)-3-pyridazinyl)amino)-7,9-dihydro-8H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-one



83 **162**

1,1-Dimethylethyl 4-(6-((9-cyclopentyl-8-oxo-8,9-dihydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinecarboxylate (162): A mixture of *tert*-butyl 4-(6-chloropyridazin-3-yl)piperazine-1-carboxylate (0.060 g, 0.20 mmol), compound **83** (0.054 g, 0.20 mmol), Xantphos (0.017 g, 0.030 mmol), $Pd_2(dba)_3$ (0.014 g, 0.015 mmol), and sodium *tert*-butoxide (0.029 g, 0.30 mmol) in dioxane was purged with nitrogen gas for 1 minute. The reaction was heated at 120°C for 6 hours and then cooled to room temperature. The solvent was removed by filtration. The residue was washed with 2 x 1ml dioxane. The product was then dissolved in 10mL methanol/DCM (1:1) and concentrated. The crude material was re-dissolved in 4mL methanol and purified on a C-18 reversephase column (150 x 30 mm, 4 micro) using Mass directed preperative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to give the title compound **162**. LCMS-ESI (POS), M/Z, M+1: 532.3

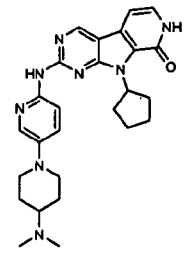
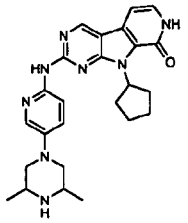
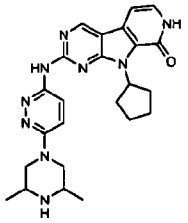
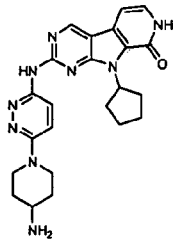
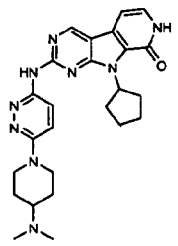
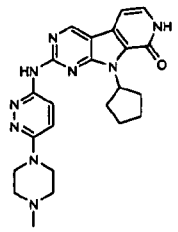


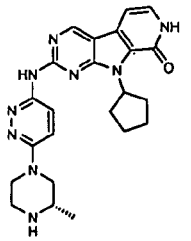
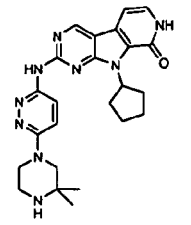
162 **161**

9-Cyclopentyl-2-((6-(1-piperazinyl)-3-pyridazinyl)amino)-7,9-dihydro-8H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-8-one (161): Compound **162** was treated with 1:1 TFA/DCM (2mL) at room temperature for an hour. The solvent was evaporated. The residue was re-dissolved in 4mLl methanol and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide the title compound **161** as a TFA salt. LCMS retention time (minutes): 0.793. LCMS-ESI (POS), M/Z, M+1: 432.2

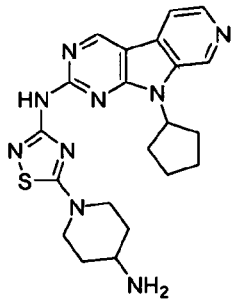
Examples 123-130 (table 3) were prepared using conditions as described for example 122 with deprotection when necessary, replacing *tert*-butyl 4-(6-chloropyridazin-3-yl)piperazine-1-carboxylate with proper reagent.

Table 3

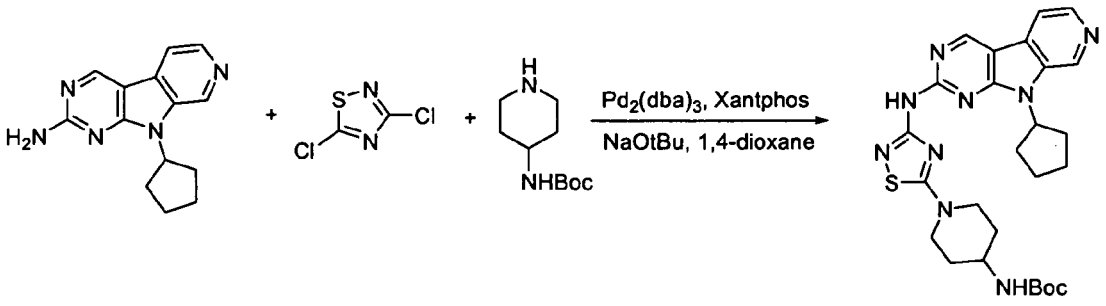
Example #	Structure	LCMS retention time (min)	LCMS -ESI (M+1)
123		0.884	473.4
124		0.873	459.2
125		0.830	460.2
126		0.821	446.2
127		0.832	474.2
128		0.809	446.2

Example #	Structure	LCMS retention time (min)	LCMS -ESI (M+1)
129		0.819	446.2
130		0.838	460.3

EXAMPLE 131



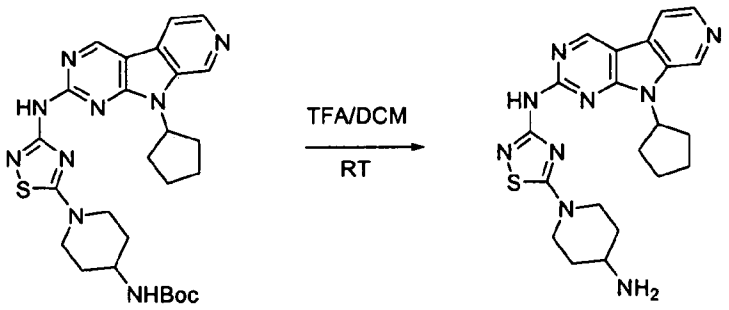
170



4 171

1,1-Dimethylethyl 1-(3-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-5-1,2,4-thiadiazolyl)-4-piperidine carboxylate (171): A mixture of 3,5-dichloro-1,2,4-thiadiazole (0.015g, 0.099mmol) and *tert*-butyl piperidin-4-ylcarbamate (0.020g, 0.099mol) in 1mL dioxane was purged with nitrogen gas for 1 minute. The reaction was stirred at room temperature for 30 minutes. To it was added compound 4 (0.0250 g, 0.099 mmol), Xantphos (0.0086 g, 0.015 mmol), $Pd_2(dba)_3$ (0.0068 g, 0.0074 mmol) and sodium *tert*-butoxide (0.024 g, 0.25 mmol). The mixture was purged

again with nitrogen for 1 min and heated at 115°C for 3 h. After cooling to room temperature, the solvent was removed using Gene Vac. The residue was sonicated with 2mL methanol. The solid was removed by filtration, washed with 2x1mL methanol. The combined solution was purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of CH_3CN in water containing 0.1%TFA to provide compound **171** as a TFA salt. LCMS-ESI (POS), M/Z, M+1: 536.2

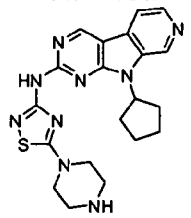
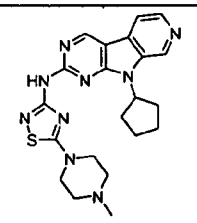


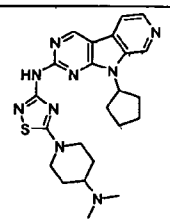
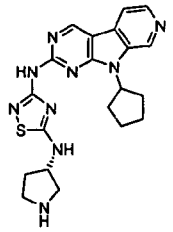
171 **170**

4-Amino-1-(3-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-5-1,2,4-thiadiazolyl)-piperidine (170): Compound **171** was treated with 15% TFA/DCM (2mL) at room temperature for an hour. The solvent was evaporated. The residue was re-dissolved in 4mL methanol and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of CH_3CN in water containing 0.1%TFA to provide compound **170** as a TFA salt. LCMS retention time (time): 0.752. LCMS-ESI (POS), M/Z, M+1: 436.1

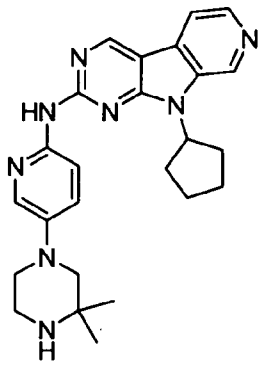
Examples 132-135 (table 4) were prepared using conditions as described for example 131 with deprotection when necessary, replacing *tert*-butyl piperidin-4-ylcarbamate with proper amine.

Table 4

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
132		0.729	422.2
133		0.746	436.1

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
134		0.738	464.2
135		0.747	422.2

EXAMPLE 136

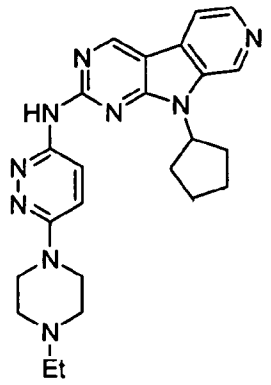


172

9-Cyclopentyl-*N*-(5-(3,3-dimethyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **172** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 9.76 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.16 (1H, d, J = 10 Hz), 8.02 (1 H, d, J = 5 Hz), 8.00 (1H, d, J = 2 Hz), 7.43 (1H, dd, J = 10 Hz, J = 2 Hz), 5.36 (1H, p, J = 10 Hz), 2.99 (2H, t, m), 2.89 (2H, m), 2.83 (2H, s), 2.39 (2H, m), 2.20-2.05 (4H, m), 1.77 (2H, m), 1.13 (6H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 442.2, Calculated 442.3.

EXAMPLE 137

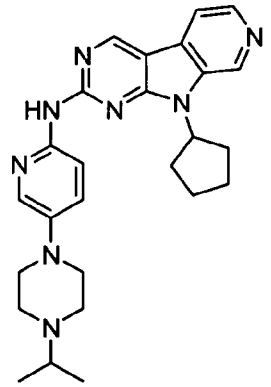


173

9-Cyclopentyl-*N*-(6-(4-ethyl-1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **173** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 9.08 (1H, s), 8.91 (1H, s), 8.55 (1H, d, J = 10 Hz), 8.52 (1H, d, J = 5 Hz), 8.33 (1 H, s), 7.86 (1H, d, J = 5 Hz), 7.09 (1H, d, J = 10 Hz), 5.36 (1H, p, J = 10 Hz), 3.66 (4H, t, J = 5 Hz), 2.63 (4H, t, J = 5 Hz), 2.51 (2H, q, J = 5 Hz), 2.39 (2H, m), 2.20 (2H, m), 2.13 (2H, m), 1.89 (2H, m), 1.16 (3H, t, J = 5 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 443.2, Calculated 443.3.

EXAMPLE 138



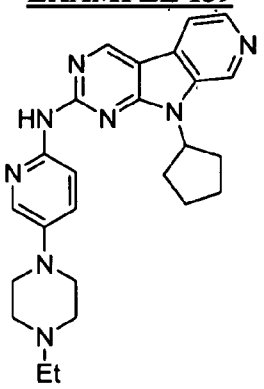
174

9-Cyclopentyl-N-(5-(4-(1-methylethyl)-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **174** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 9.09 (1H, s), 8.90 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.39 (1H, d, J = 10 Hz), 8.33 (1 H, bs), 8.09 (1H, d, J = 5 Hz), 7.83 (1H, dd, J = 5 Hz, J = 2 Hz), 7.39 (1H, dd, J = 5 Hz,

J = 2 Hz), 5.36 (1H, p, J = 10 Hz), 3.22 (4H, t, J = 5 Hz), 2.76 (1H, m, J = 10 Hz), 2.74 (4H, t, J = 5 Hz), 2.44 (2H, m), 2.20 (2H, m), 2.14 (2H, m), 1.88 (2H, m), 1.12 (6H, d, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 456.1, Calculated 456.3.

EXAMPLE 139

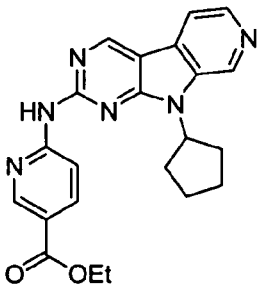


175

9-Cyclopentyl-*N*-(5-(4-ethyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **175** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 9.08 (1H, s), 8.91 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.41 (1H, d, J = 10 Hz), 8.22 (1 H, bs), 8.08 (1H, d, J = 2 Hz), 7.83 (1H, d, J = 5 Hz), 7.40 (1H, dd, J = 10 Hz, J = 2 Hz), 5.36 (1H, p, J = 10 Hz), 3.27 (4H, m), 2.71 (2H, m), 2.56 (2H, m), 2.44 (2H, m), 2.20 (2H, m), 2.14 (2H, m), 1.89 (2H, m), 1.19 (3H, t, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 442.2, Calculated 442.3.

EXAMPLE 140



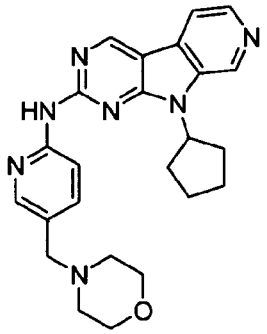
176

Ethyl 6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinecarboxylate

Compound **176** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 10.80 (1H, s), 9.48 (1H, s), 9.17 (1H, s), 8.87 (1H, d, J = 2 Hz), 8.56 (1H, d, J = 5 Hz), 8.53 (1H, d, J = 10 Hz), 8.31 (1 H, dd, J = 10 Hz, J = 2 Hz), 8.25 (1H, d, J =

5 Hz), 5.36 (1H, p, J = 10 Hz), 4.34 (2H, q, J = 10 Hz), 2.42 (2H, m), 2.16 – 2.08 (4H, m), 1.81 (2H, m), 1.35 (3H, t, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 402.1, Calculated 402.2.

EXAMPLE 141

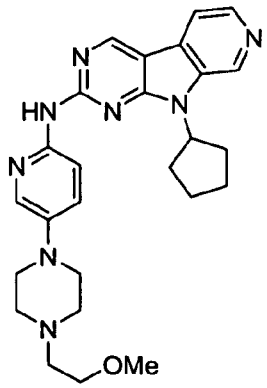


177

9-Cyclopentyl-*N*-(5-(4-morpholinylmethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **177** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 10.04 (1H, s), 9.33 (1H, s), 9.04 (1H, s), 8.45 (1H, d, J = 5 Hz), 8.35 (1H, d, J = 10 Hz), 8.23 (1H, d, J = 2 Hz), 8.07 (1 H, d, J = 10 Hz), 7.75 (1H, dd, J = 10 Hz, J = 2 Hz), 5.39 (1H, p, J = 10 Hz), 3.58 (4H, t, J = 5 Hz), 2.05 (2H, s), 2.45 – 2.40 (6H, m), 2.20 – 2.06 (4H, m), 1.79 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.1, Calculated 429.2.

EXAMPLE 142

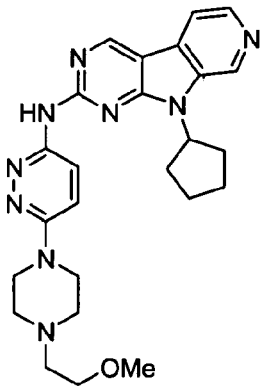


179

9-Cyclopentyl-*N*-(5-(4-(2-(methyloxy)ethyl)-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **179** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 9.74 (1H, s), 9.25 (1H, s), 8.99 (1H, s), 8.43 (1H, d, J = 5 Hz), 8.16 (1H, d, J = 10 Hz), 8.03-8.02 (2 H, m), 7.46 (1H, dd, J = 10 Hz, J = 2 Hz), 5.35 (1H, p, J = 10 Hz), 3.47 (2H, t, J = 5 Hz), 3.25 (3H, s), 3.13 (4H, t, J = 5 Hz), 2.58 (4H, t, J = 5 Hz), 2.53 (2H, t, J = 5 Hz), 2.38 (2H, m), 2.15 – 2.05 (4H, m), 1.76 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 472.2, Calculated 472.2.

EXAMPLE 143

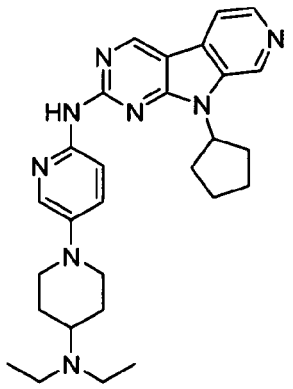


180

9-Cyclopentyl-N-(6-(4-(2-(methyloxy)ethyl)-1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **180** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 9.09 (1H, s), 8.92 (1H, s), 8.55 (1H, d, J = 10 Hz), 8.53 (1H, d, J = 5 Hz), 8.40 (1H, bs), 7.86 (1 H, d, J = 5 Hz), 7.09 (1H, d, J = 10 Hz), 5.39 (1H, p, J = 10 Hz), 3.69 (4H, m), 3.60 (2H, t, J = 5 Hz), 2.80 – 2.69 (6H, m), 2.37 (2H, m), 2.20 (2H, m), 2.13 (2H, m), 1.90 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 473.2, Calculated 473.3.

EXAMPLE 144

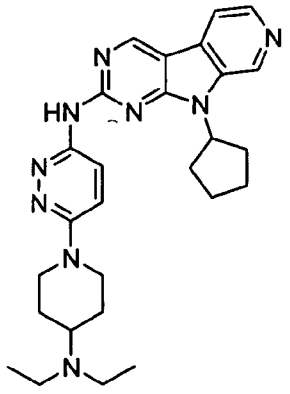


181

9-Cyclopentyl-*N*-(5-(4-(diethylamino)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **181** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 9.74 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.15 (1H, d, J = 10 Hz), 8.03 (1 H, s), 8.02 (1H, d, J = 2 Hz), 7.46 (1H, dd, J = 10 Hz, J = 5 Hz), 5.36 (1H, p, J = 10 Hz), 3.72 (2H, d, J = 15 Hz), 2.68 (2H, t, J = 10 Hz), 2.52 (4H, m), 2.39 (2H, m), 2.07 (4H, m), 1,77 (4H, m), 1.57 (2H, m), 0.98 (6H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 484.2, Calculated 484.3.

EXAMPLE 145

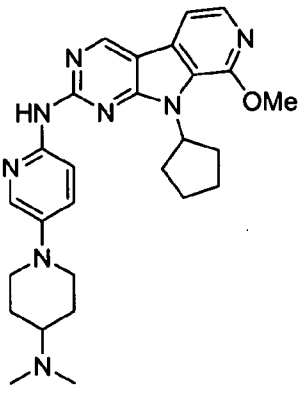


182

9-Cyclopentyl-*N*-(6-(4-(diethylamino)-1-piperidinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **182** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 10.16 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.15 (1H, d, J = 10 Hz), 8.03 (1 H, s), 7.41 (1H, dd, J = 10 Hz), 5.32 (1H, p, J = 10 Hz), 4.32 (2H, d, J = 15 Hz), 2.68 (2H, t, J = 10 Hz), 2.52 (4H, m), 2.39 (2H, m), 2.07 (4H, m), 1,77 (4H, m), 1.57 (2H, m), 0.98 (6H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 485.2, Calculated 485.3.

EXAMPLE 146

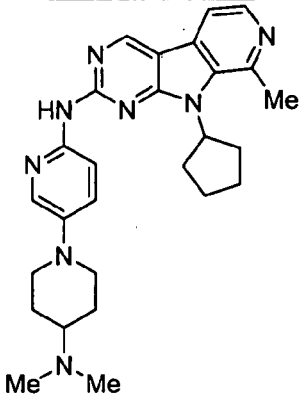


183

9-Cyclopentyl-*N*-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-8-(methyloxy)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **183** was prepared using chemistry similar to that described in example 53. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 9.09 (1H, s), 8.38 (1H, d, J = 10 Hz), 8.12 (1H, bs), 7.99 (1 H, d, J = 5 Hz), 7.44 (1H, d, J = 5 Hz), 7.37 (1H, dd, J = 10 Hz, J = 5 Hz), 5.81 (1H, p, J = 10 Hz), 4.14 (3H, s), 3.66 (2H, d, J = 15 Hz), 2.75 (2H, t, J = 10 Hz), 2.33 (6H, s), 2.31 (2H, m), 2.08 (4H, m), 1.80 (2H, m), 1,74 (2H, m), 1.69 (2H, m)ppm; LCMS-ESI (POS), M/Z, M+1: Found 486.2, Calculated 486.3.

EXAMPLE 147

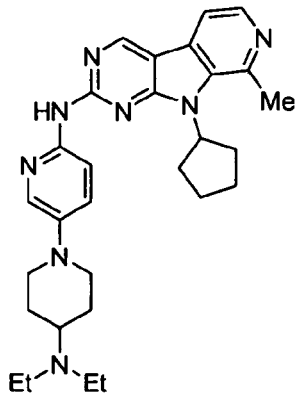


184

9-cyclopentyl-N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-8-methyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **184** was prepared using chemistry similar to that described in example 54. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 9.12 (1H, s), 8.82 (1H, s), 8.35 (1H, d, J = 5 Hz), 8.33 (1 H, d, J = 10 Hz), 8.12 (1H, d, J = 2 Hz), 7.68 (1H, d, J = 5 Hz), 7.35 (1H, dd, J = 10 Hz, J = 2 Hz), 5.42 (1H, p, J = 10 Hz), 3.67 (2H, d, J = 15 Hz), 3.02 (3H, s), 2.82 – 2.73 (4H, m), 2.33 (6H, s), 2.31 (1H, m), 2.14 (2H, m), 2.08 (2H, m), 1.99 (2H, m), 1,80 (2H, m), 1.69 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 470.3, Calculated 470.3.

EXAMPLE 148

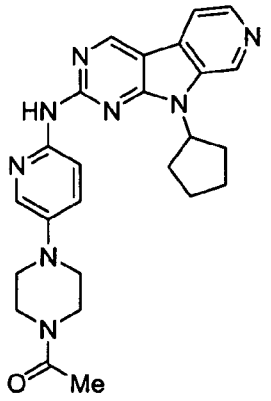


185

9-Cyclopentyl-*N*-(5-(4-(diethylamino)-1-piperidinyl)-2-pyridinyl)-8-methyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

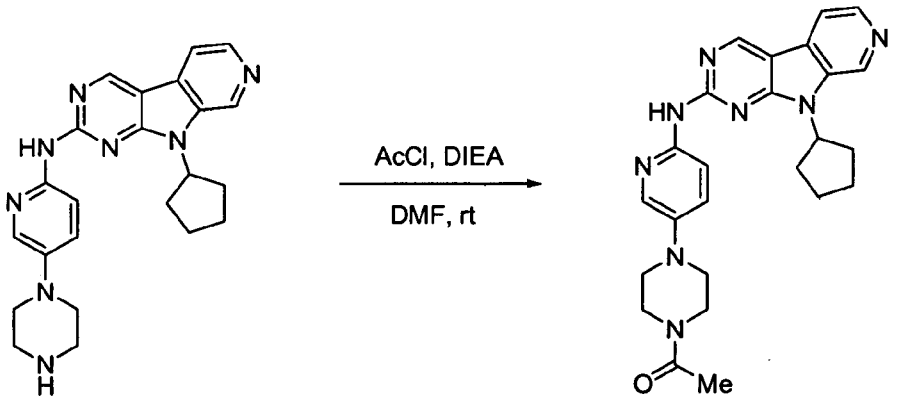
Compound **185** was prepared using chemistry similar to that described in example 54. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 9.05 (1H, s), 8.37 (1H, d, J = 5 Hz), 8.32 (1 H, d, J = 10 Hz), 8.05 (1H, d, J = 2 Hz), 7.99 (1H, s), 7.68 (1H, d, J = 5 Hz), 7.35 (1H, dd, J = 10 Hz, J = 2 Hz), 5.44 (1H, p, J = 10 Hz), 3.68 (2H, d, J = 15 Hz), 3.03 (3H, s), 2.80 – 2.73 (4H, m), 2.63-2.61 (5H, s), 2.16 (1H, m), 2.08 (2H, m), 1.93 (2H, m), 1,80 (2H, m), 1.75 (2H, m), 1.08 (6H, t, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 498.3, Calculated 498.3.

EXAMPLE 149



186

***N*-(5-(4-Acetyl-1-piperazinyl)-2-pyridinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

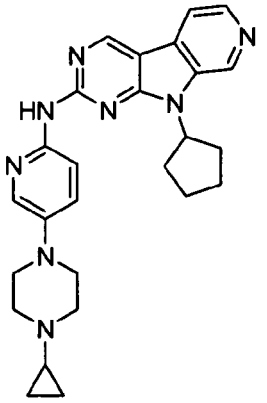


7 **186**

***N*-(5-(4-Acetyl-1-piperazinyl)-2-pyridinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (186):** To a solution of compound **7** (207 mg, 0.50 mmol) in DMF (5 mL) were added N,N-diisopropylethylamine (174 uL, 1.0 mmol) and acetyl chloride (43 uL, 0.60 mmol) in DMF (2 mL) at 0 °C and the resulted mixture was stirred at 0 °C for 1 hr. The reaction mixture was concentrated and the residue was washed with water (sonicated) and the

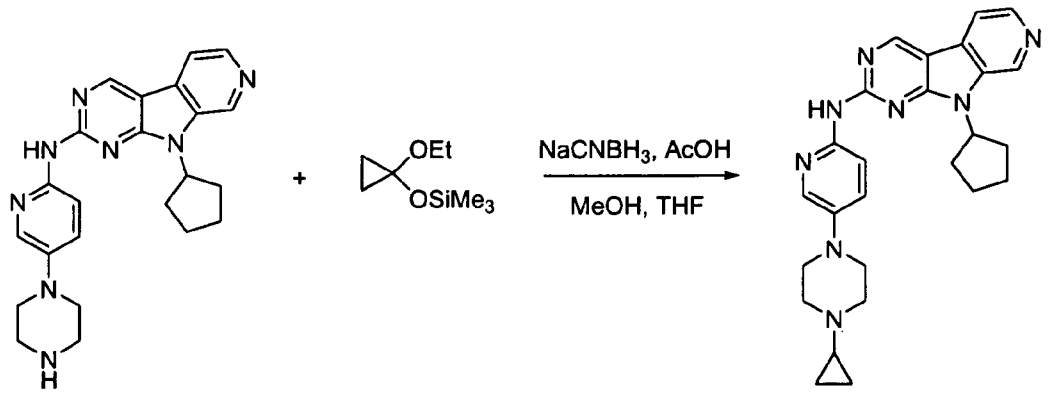
solid was collected by filtration, dried under high vacuumn to give compound **186** (170 mg, 74% yield) as a light yellow solid. . ^{1}H NMR (500 MHz, *DMSO-d6*) δ 9.82 (1H, s), 9.27 (1H, s), 9.01 (1H, s), 8.44 (1 H, d, J = 5 Hz), 8.21 (1H, d, J = 10 Hz), 8.07 (1H, d, J = 2 Hz), 8.04 (1H, d, J = 5 Hz), 7.52 (1H, dd, J = 10 Hz, J = 2 Hz), 5.37 (1H, p, J = 10 Hz), 3.61 (4H, q, J = 5 Hz), 3.17 (2H, t, J = 5 Hz), 3.10 (2H, t, J = 5 Hz), (3H, s), 2.40 (2H, m), 2.08 (4H, m), 2.06 (3H, s), 1.78 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 456.1, Calculated 456.2.

EXAMPLE 150



187

9-Cyclopentyl-*N*-(5-(4-cyclopropyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

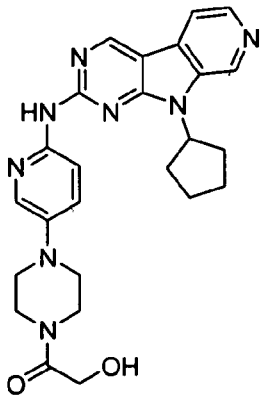


7 **187**

9-Cyclopentyl-*N*-(5-(4-cyclopropyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (187): To a solution of compound **7** (207 mg, 0.50 mmol) in THF (5 mL) were added water (0.05 mL), (1-ethoxy-1-cyclopropyloxy)-trimethylsilane (1174 mg, 1.0 mmol), acetic acid (0.55 mL) and sodium cyanoborohydride (1 mL, 1 M in THF, 1.0 mmol). The mixture was stirred at 60 °C overnight. The reaction mixture was concentrated and the residue was disolved in ethyl acetate and washed with saturated $NaHCO_3$

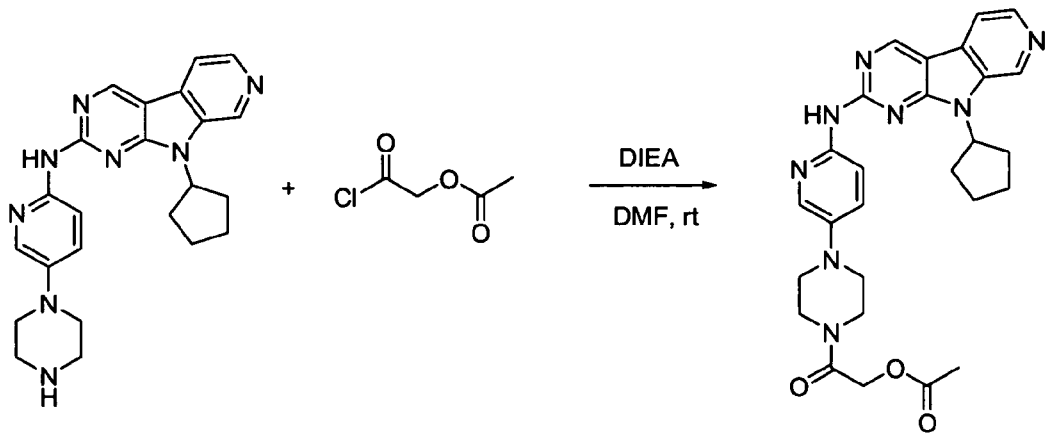
and brine then dried. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting with CH_2Cl_2:methanol:NH_4OH (400:10:1) to give compound **187** as a yellow solid (60 mg, 26% yield). ^1H NMR (500 MHz, *CDCl₃*) δ 9.08 (1H, s), 8.90 (1H, s), 8.51 (1 H, d, J = 5 Hz), 8.39 (1H, d, J = 10 Hz), 8.18 (1H, bs), 8.07 (1H, d, J = 2 Hz), 7.84 (1H, d, J = 5 Hz), 7.39 (1H, dd, J = 10 Hz, J = 2 Hz), 5.38 (1H, p, J = 10 Hz), 3.17 (4H, q, J = 5 Hz), 2.83 (2H, t, J = 5 Hz), 2.42 (2H, m), 2.21- 2.14 (4H, m), 1.88 (2H, m), 1.71 (1H, m), 0.53- 0.46 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 454.2, Calculated 454.3.

EXAMPLE 151



188

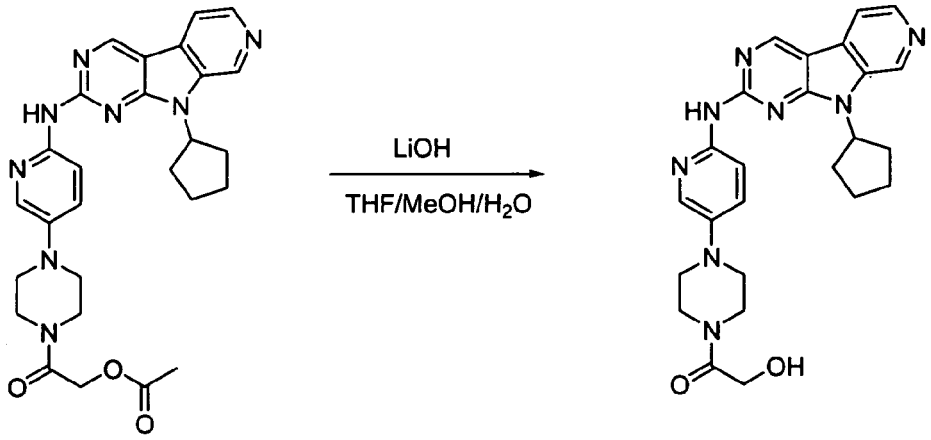
2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethanol



7 **189**

2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethyl acetate (189): To a solution of compound **7** (207 mg, 0.50 mmol) in DMF (5 mL) were added N,N-diisopropylethylamine (174 uL, 1.0 mmol) and acetoxyacetyl chloride (65 uL, 0.60 mmol) and the resulted mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated to give compound **189** as a yellow

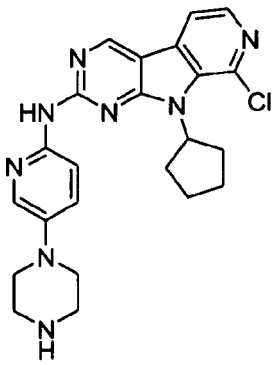
solid which was used in next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 514.2, Calculated 514.2.



189 188

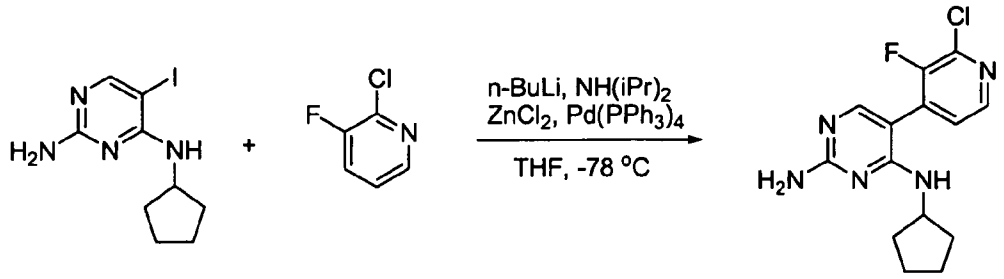
2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethanol (188): To a solution of compound **189** (~ 0.5 mmol) in THF/methanol/H2O (3:1:1, 10 mL) was added 12 mg of LiOH and the mixture was stirred at 60 °C overnight. The reaction mixture was concentrated and the residue was dissolved in dichloromethane then washed with water and brine then dried. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting with CH_2Cl_2:methanol:NH_4OH (400:10:1) to give compound **188** as a yellow solid (150 mg, 63% in two steps). ^1H NMR (500 MHz, *DMSO-d6*) δ 9.82 (1H, s), 9.27 (1H, s), 9.01 (1H, s), 8.44 (1 H, d, J = 5 Hz), 8.21 (1H, d, J = 10 Hz), 8.07 (1H, d, J = 2 Hz), 8.04 (1H, d, J = 5 Hz), 7.52 (1H, dd, J = 10 Hz, J = 2 Hz), 5.37 (1H, p, J = 10 Hz), 4.65 (1H, t, J = 5 Hz), 4.15 (2H, d, J = 5 Hz), 3.65 (2H, m), 3.53 (2H, m), 3.15 (4H, m), 2.40 (2H, m), 2.08 (4H, m), 1.78 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 472.2, Calculated 472.3.

EXAMPLE 152



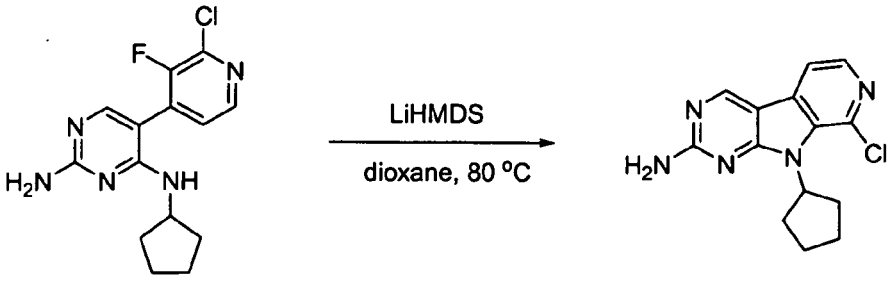
190

8-Chloro-9-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



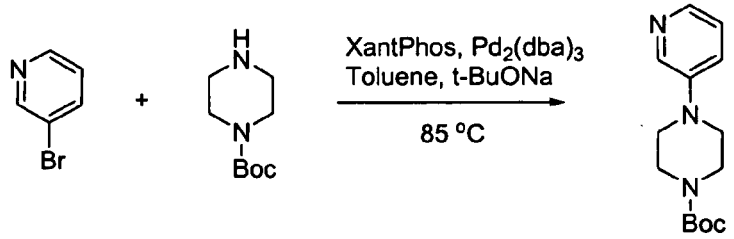
243 **193**

5-(2-Chloro-3-fluoropyridin-4-yl)-*N*4-cyclopentylpyrimidine-2,4-diamine (193): To a 500 mL three-necked round-bottomed flask equipped with a thermometer and a stir bar was added diisopropylamine (14.7 mL, 104 mmol). The flask was cooled in a Et_2O-dry ice bath and butyllithium 2.5M in hexane (43.0 mL, 107 mmol) was added cautiously. The solution was allowed to warm to room temperature. After stirring at room temperature for 5 minutes, a white solid formed and it was cooled in an Et_2O-dry ice bath then diluted with 170 mL of anhydrous THF. The solution was then cooled to -75 °C. 2-chloro-3-fluoropyridine (10.3 mL, 104 mmol) was dissolved in 100 mL of anhydrous THF. This solution was then slowly cannulated into the LDA solution over a period of 20 minutes while the temperature was held below -69 °C. The solution was stirred for 30 minutes before a solution of zinc (II) chloride 0.5M in THF (111 mL, 55.4 mmol) was slowly added with the temperature maintained below -68 °C. The yellow solution was then allowed to warm to room temperature. After 30 minutes of stirring at room temperature, compound **243** (see example 200) (10.538 g, 34.6 mmol) and $Pd(PPh_3)_4$ (2.00 g, 1.73 mmol) were added and the solution was heated at 60 °C overnight. The solution was concentrated under vacuum, and then cooled in an ice bath. Saturated NH_4Cl aqueous solution was added with ice and the solution was stirred for 10 minutes and then extracted with DCM. The aqueous layer was washed with 10 % i-PrOH/DCM. The combined organics were dried over $MgSO_4$ and concentrated under vacuum. The residue obtained was purified by flash chromatography (methanol/DCM/Aq NH4OH) to give compound **193** (4.13g, 38.7%) as a white solid. ^1H NMR (500 MHz, *DMSO-d_6*) δ 8.22 (1 H, d, J= 4.9 Hz), 7.63 (1 H, s), 7.40 (1 H, t, J= 5.1 Hz), 6.28 - 6.41 (3 H, m), 4.37 - 4.49 (1 H, m), 1.78 - 1.93 (2 H, m), 1.57 - 1.69 (2 H, m), 1.36 - 1.54 (4 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 308.0.



193 194

8-Chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (194): Compound **193** (3.10 g, 10.1 mmol) was combined with 30 mL of anhydrous 1,4-dioxane. To this was added LiHMDS 1M in THF (30.2 mL, 30.2 mmol) and the solution was heated to 85 °C for 5 hours. The solution was cooled to room temperature and then diluted with ice/sat. $NaHCO_3$. The product was extracted with 15%2-propanol/DCM and the organics were dried over $MgSO_4$ before being concentrated under vacuum. The residue obtained was purified on CombiFlash column (dry loaded), eluting with a gradient of 2% methanol/DCM to 6% methanol/DCM. Trituration with acetone and ethyl acetate left a light brown solid. Repurification of the supernatants provided additional material. The solids were combined to give compound **194** (1.60 g, 55.2%) as a light brown solid. ^1H NMR (500 MHz, *DMSO-d_6*) δ 9.11 (1 H, s), 8.14 (1 H, d, J= 4.9 Hz), 7.98 (1 H, d, J= 4.9 Hz), 7.07 (2 H, br. s.), 5.90 (1 H, quin, J= 8.7 Hz), 2.44 - 2.49 (2 H, m), 2.04 - 2.13 (2 H, m), 1.95 - 2.03 (2 H, m), 1.63 - 1.73 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 288.1.

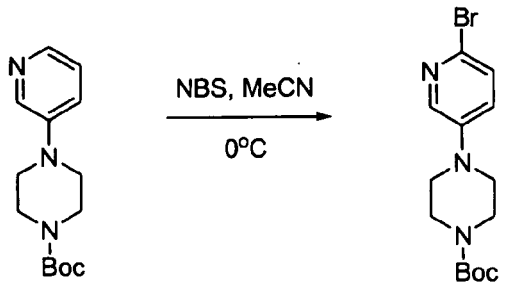


195

tert-Butyl 4-(pyridin-3-yl)piperazine-1-carboxylate (195): Sodium 2-methylpropan-2-olate (1.83 g, 19.1 mmol), 3-bromopyridine (2.010 g, 12.7 mmol), and *tert*-butyl piperazine-1-carboxylate (3.55 g, 19.1 mmol) were combined in 10 mL of anhydrous toluene. N_2 was bubbled through the solution briefly before adding 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.368 g, 0.636 mmol) and $Pd_2(dba)_3$ (0.183 g, 0.318 mmol). The solution was then heated to 85 °C overnight.

The solution was cooled to room temperature and diluted with sat's NH_4Cl and then extracted with DCM. The organics were dried over $MgSO_4$ and then concentrated under vacuum. The residue obtained was purified on CombiFlash column eluting with a gradient of DCM to 4%

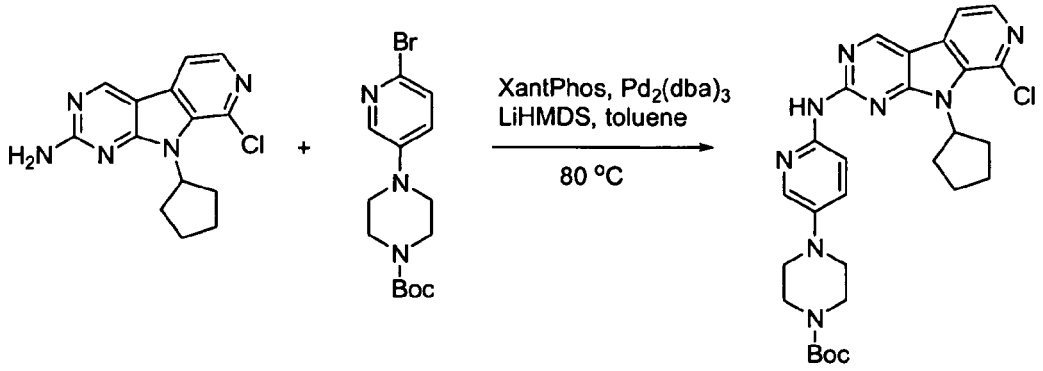
methanol/DCM. The fractions containing the product were combined and concentrated under vacuum to give compound **195** (2.06g, 61.5% yield) as a reddish yellow solid. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ 8.31 (1 H, d, J= 2.9 Hz), 8.02 (1 H, dd, J= 4.5, 1.3 Hz), 7.33 (1 H, ddd, J= 8.5, 3.0, 1.5 Hz), 7.20 - 7.24 (1 H, m), 3.43 - 3.49 (4 H, m), 3.11 - 3.20 (4 H, m), 1.42 (9 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 264.1.



195 **196**

***tert*-Butyl 4-(6-bromopyridin-3-yl)piperazine-1-carboxylate (196)**: By the method of Audouze et al. J. Med.Chem. **49** (2006) 3159 – 3171, compound **195** (2.06 g, 7.82 mmol) was dissolved in 40 mL of acetonitrile under an atmosphere of N_2.

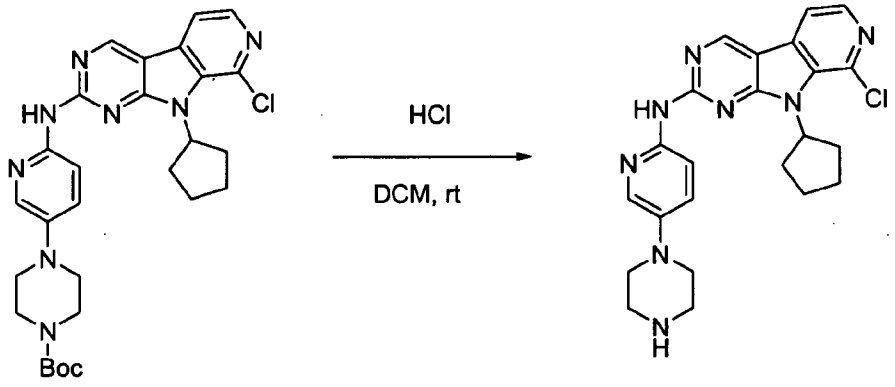
The solution was cooled in a ice bath before a solution of N-bromosuccinimide (1.46 g, 8.21 mmol) in 15 mL of acetonitrile was added over a period of 10 minutes. The solution was then stirred in the ice bath for 2 hours. Added silica gel and DCM, and the slurry was then concentrated under vacuum. Purified on CombiFlash column (dry loaded), eluting with a gradient of 5% ethyl acetate/hexane to 40% ethyl acetate/hexane. The fractions containing the product were combined and concentrated under vacuum to give compound **196** (1.9847 g, 74 % yield) as an off white solid. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.07 (1 H, d, J= 3.2 Hz), 7.42 (1 H, d, J= 8.8 Hz), 7.34 (1 H, dd, J= 8.9, 3.3 Hz), 3.42 - 3.48 (4 H, m), 3.12 - 3.21 (4 H, m), 1.42 (9 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 342.1.



194 **196** **197**

***tert*-Butyl 4-(6-((8-chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]-pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (197)**: Compound **196** (0.178 g, 0.521

mmol), compound **194** (0.125 g, 0.434 mmol), and LiHMDS 1M in THF (1.30 mL, 1.30 mmol) were combined in 5mL of anhydrous toluene. N_2 was bubbled through the solution briefly before adding $Pd_2(dba)_3$ (0.0298 g, 0.0326 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0377 g, 0.0652 mmol). The solution was then heated to 80 °C for 2 hours with microwave irradiation. The solution was diluted with DCM before it was poured into sat's NH_4Cl. Partitioned the layers and washed the aqueous layer with 10% i-PrOH/DCM. The combined organics were dried over MgSO4 and then concentrated under vacuum. The residue obtained was purified on CombiFlash column (dry loaded), eluting with a gradient of 60% ethyl acetate/hexane to 100% ethyl acetate. The fractions containing the product were combined and concentrated under vacuum. The residue obtained was repurified on CombiFlash column (dry loaded), eluting with a gradient of 2% methanol/0.1% NH_4OH (~28% in water)/DCM to 4% methanol/0.2% NH_4OH(~28% in water)/DCM. The fractions containing the product were combined and concentrated under vacuum. The residue obtained was sonicated in methanol. Filtration provided an off-white solid as compound **197** (0.173 g, 72 %). LCMS-ESI (POS), M/Z, M+1: Found 549.1.

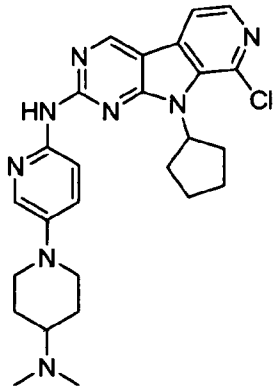


197 **190**

8-Chloro-9-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (190): Compound **197** (0.173 g, 0.315 mmol) was dissolved in 10 mL of DCM and to this was added 4N HCl in dioxane (1.97 mL, 7.88 mmol). The solution was stirred at room temperature overnight and then concentrated under vacuum to give a yellow solid. The solid obtained was sonicated in Et_2O and a yellowish solid was collected on filter paper to give compound **190** as an HCl salt (0.164 g, 100%). ^1H NMR (500 MHz, *DMSO-d_6*) δ 10.56 (1 H, br. s.), 9.42 (1 H, s), 8.87 (2 H, br. s.), 8.28 (1 H, d, J= 4.9 Hz), 8.19 (1 H, d, J= 5.1 Hz), 8.09 (1 H, d, J= 2.9 Hz), 7.97 (1 H, d, J= 9.0 Hz), 7.75 (1 H, dd, J= 9.3, 2.0 Hz), 5.96 - 6.07 (2 H, m, J= 9.2, 8.9, 8.8, 8.8 Hz), 3.37 - 3.43 (4 H, m), 3.26 - 3.33 (4

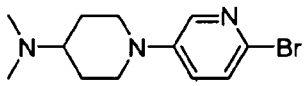
H, m), 2.54 - 2.65 (2 H, m), 2.01 - 2.12 (4 H, m), 1.66 - 1.77 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 449.2.

EXAMPLE 153



198

8-Chloro-9-cyclopentyl-N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

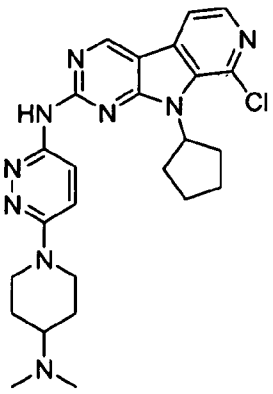


199

1-(6-Bromopyridin-3-yl)-*N,N*-dimethylpiperidin-4-amine (199): Compound **199** was prepared by analogy to compound **196**. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.05(1H, d, J = 2.7Hz), 7.35-7.38 (1H, m), 7.30-7.33 (1H, m), 3.69-3.79 (2H, m), 2.73 (2H, td, J =12.2, 2.7Hz), 2.19-2.27 (1H, m), 2.17 (6H, s), 1.75-1.86 (2H, m), 1.36-1.50 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 284.0.

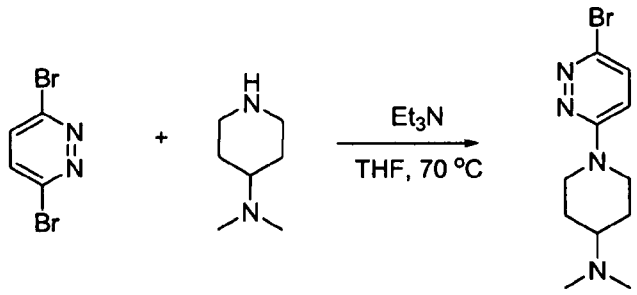
8-Chloro-9-cyclopentyl-N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (198) Compound **198** was prepared from compound **199** using methods described in example 152. ^{1}H NMR (500 MHz, D_2O) δ 8.79 (1 H, s), 7.97 (1 H, d, J = 4.9 Hz), 7.78 (1 H, br. s.), 7.53 (1 H, br. s.), 7.20 (1 H, br. s.), 6.94 (1 H, d, J = 9.0 Hz), 5.71 (1 H, br. s.), 3.65 (2 H, br. s.), 3.42 (1 H, br. s.), 2.92 (6 H, s), 2.68 - 2.82 (2 H, m), 2.16 - 2.33 (4 H, m), 2.04 (4 H, br. s.), 1.74 (4 H, br. s.) ppm; LCMS-ESI (POS), M/Z, M+1: Found 491.2.

EXAMPLE 154



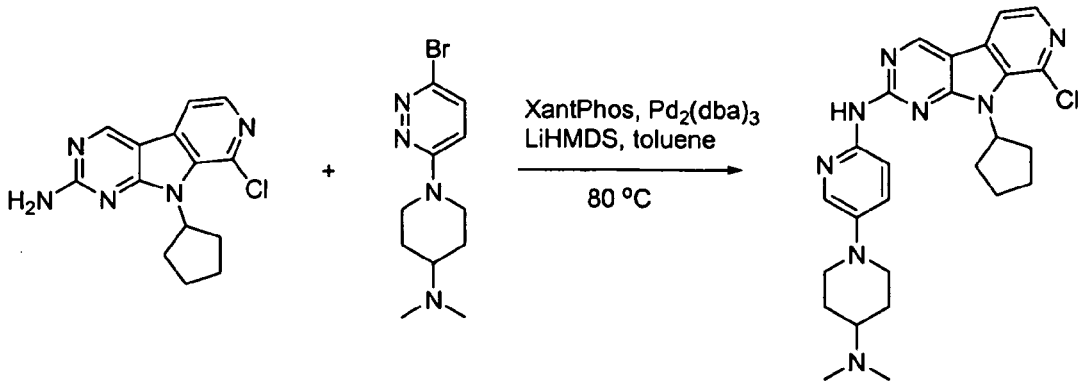
200

8-Chloro-9-cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



201

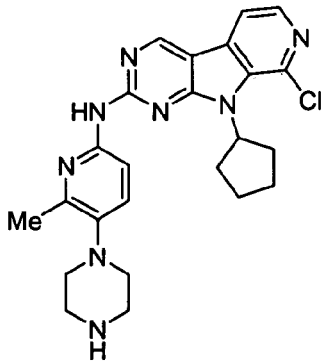
1-(6-Bromo-3-pyridazinyl)-*N,N*-dimethyl-4-piperidinamine (201): N,N-dimethylpiperidin-4-amine (0.505 g, 3.94 mmol), 3,6-dibromopyridazine (0.511 g, 2.15 mmol), and triethylamine (0.599 mL, 4.30 mmol) were combined in 5 mL of THF. The solution was heated at 70 °C for 17 hours. The solution was cooled to room temperature and then purified on CombiFlash column (dry loaded), eluting with 10% methanol/0.5%NH_4OH(~28% in water)/DCM isocratic. The fractions containing the product were combined and concentrated under vacuum to give compound **201** (0.550 g, 89.8% yield) as an off white solid. ^{1}H NMR (500 MHz, *MeOD-d3*) δ 7.51 (1 H, d, J= 9.8 Hz), 7.24 (1 H, d, J= 9.8 Hz), 4.45 (2 H, d, J= 13.7 Hz), 2.98 (2 H, td, J= 13.0, 2.2 Hz), 2.61 (1 H, tt, J= 11.5, 3.8 Hz), 2.38 (6 H, s), 1.99 - 2.07 (2 H, m), 1.45 - 1.58 (2 H, m, J= 12.5, 12.2, 12.2, 4.2 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 285.0.



194 201 200

8-chloro-9-cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (200): Compound **200** was prepared using methods described in Example 152 using **201**. ^{1}H NMR (500 MHz, *CD_3OD*) δ 9.48 (1 H, s), 8.31 (1 H, d, J= 5.1 Hz), 8.18 (1 H, d, J= 5.1 Hz), 8.08 (1 H, d, J= 10.3 Hz), 7.89 (1 H, d, J= 10.0 Hz), 6.19 (1 H, quin, J= 8.7 Hz), 4.54 (2 H, d, J= 13.9 Hz), 3.53 - 3.62 (1 H, m), 3.11 - 3.19 (2 H, m), 2.92 (6 H, s), 2.63 - 2.73 (2 H, m), 2.13 - 2.29 (6 H, m), 1.79 - 1.91 (4 H, m)) ppm; LCMS-ESI (POS), M/Z, M+1: Found 492.2.

EXAMPLE 155

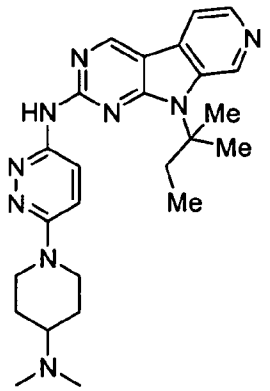


202

8-Chloro-9-cyclopentyl-N-(6-methyl-5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **202** was prepared using methods described in Example 152. ^{1}H NMR (500 MHz, *D_2O*) δ 8.86 (1 H, s), 7.97 (1 H, d, J= 4.9 Hz), 7.80 - 7.93 (2 H, m), 7.10 (1 H, d, J= 9.0 Hz), 5.69 - 5.81 (1 H, m), 3.46 - 3.51 (4 H, m), 3.22 (4 H, br. s.), 2.52 (3 H, br. s.), 2.23 - 2.36 (2 H, m), 1.98 - 2.16 (4 H, m), 1.70 - 1.81 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 463.1.

EXAMPLE 156

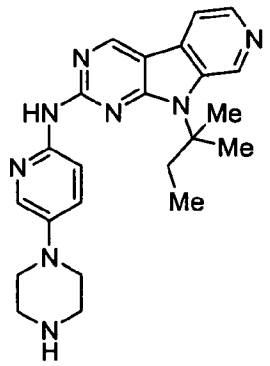


203

N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(1,1-dimethylpropyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **203** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ 11.69 (1 H, br. s.), 11.30 - 11.46 (1 H, m), 9.77 (1 H, s), 9.47 (1 H, s), 8.82 (1 H, d, J= 6.3 Hz), 8.72 (1 H, d, J= 6.3 Hz), 8.32 (1 H, d, J= 10.2 Hz), 8.15 (1 H, d, J= 10.2 Hz), 4.51 (2 H, d, J= 13.3 Hz), 3.44 - 3.55 (1 H, m), 3.16 (2 H, t, J= 12.3 Hz), 2.71 (6 H, d, J= 5.1 Hz), 2.36 (2 H, q, J= 7.4 Hz), 2.23 (2 H, d, J= 11.7 Hz), 2.03 (6 H, s), 1.71 - 1.88 (2 H, m), 0.65 (3 H, t, J=7 .2 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 460.3.

EXAMPLE 157



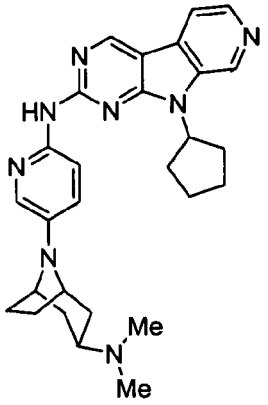
204

9-(1,1-dimethylpropyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **204** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ 11.27 (1 H, br. s.), 9.74 (1 H, s), 9.56 (2 H, br. s.), 9.43 (1 H, s), 8.79 (1 H, d, J= 5.9 Hz), 8.70 (1 H, d, J= 5.9 Hz), 8.13 (1 H, d, J= 2.3 Hz), 7.94 - 7.98 (1 H, m),

7.88 - 7.93 (1 H, m), 3.43 - 3.53 (4 H, m), 3.20 - 3.30 (4 H, m), 2.39 (2 H, q, J= 7.2 Hz), 2.04 (6 H, s), 0.66 (3 H, t, J= 7.4 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 417.3.

EXAMPLE 158

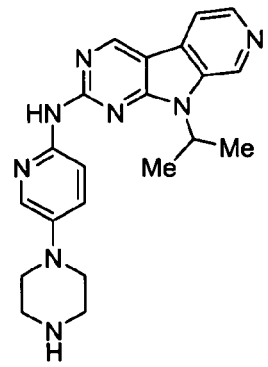


205

9-cyclopentyl-N-(5-(3-(dimethylamino)-8-azabicyclo[321]oct-8-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **205** was prepared using chemistry similar to that described in example 1.^{1}H NMR (500 MHz, *DMSO-d_6*) δ 11.41 (1 H, br. s.), 10.65 (1 H, br. s.), 9.71 (1 H, s), 9.47 (1 H, s), 8.75 - 8.79 (1 H, m), 8.71 - 8.74 (1 H, m), 8.04 (1 H, d, J= 2.4 Hz), 7.92 - 7.98 (1 H, m), 7.88 (1 H, d, J= 10.3 Hz), 5.43 (1 H, quin, J= 8.7 Hz), 4.46 - 4.51 (2 H, m), 3.62 - 3.72 (1 H, m), 2.62 (6 H, d, J= 4.9 Hz), 2.37 - 2.47 (2 H, m), 2.06 - 2.18 (4 H, m), 1.99 - 2.05 (2 H, m), 1.90 - 1.97 (2 H, m), 1.80 - 1.90 (4 H, m), 1.71 - 1.80 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 483.3.

EXAMPLE 159

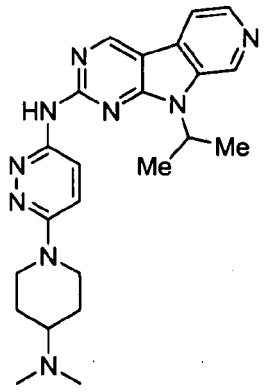


206

9-(1-methylethyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **206** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 9.71 (1 H, s), 9.54 (3 H, br. s.), 8.76 (1 H, d, J= 6.1 Hz), 8.72 (1 H, d, J= 6.1 Hz), 8.14 (1 H, d, J= 2.7 Hz), 8.03 (1 H, d, J= 9.3 Hz), 7.93 (1 H, d, J= 9.3 Hz), 5.35 (1 H, dt, J= 13.9, 6.9 Hz), 3.45 - 3.51 (4 H, m), 3.22 - 3.28 (4 H, m), 1.72 (6 H, d, J= 7.1 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 389.2.

EXAMPLE 160

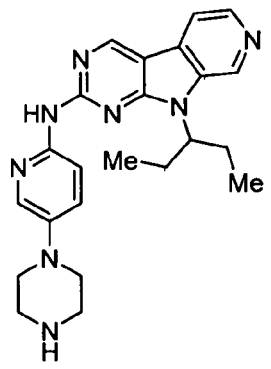


207

***N*-(6-(4-(Dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(1-methylethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **207** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 10.18 (1 H, s), 9.26 (1 H, s), 9.09 (1 H, s), 8.44 (1 H, d, J= 5.1 Hz), 8.22 (1 H, d, J= 9.5 Hz), 8.04 (1 H, d, J= 5.1 Hz), 7.44 (1 H, d, J= 9.8 Hz), 5.24 (1 H, dt, J= 13.7, 6.8 Hz), 4.30 (2 H, d, J= 12.5 Hz), 2.88 (2 H, t, J= 11.9 Hz), 2.33 - 2.44 (1 H, m), 1.86 (2 H, d, J= 10.0 Hz), 1.66 (6 H, d, J= 6.8 Hz), 1.36 - 1.49 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 432.2.

EXAMPLE 161

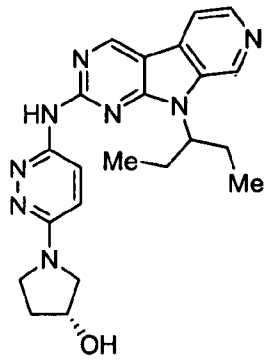


208

9-(1-Ethylpropyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **208** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 11.28 (1 H, br. s.), 9.73 (1 H, s), 9.58 (1 H, s), 9.52 (2 H, br. s.), 8.78 (1 H, d, J= 5.9 Hz), 8.73 (1 H, d, J= 6.1 Hz), 8.14 (1 H, d, J= 2.7 Hz), 8.02 (1 H, br. s.), 7.92 (1 H, br. s.), 4.83 - 4.95 (1 H, m), 3.45 - 3.52 (4 H, m), 3.18 - 3.30 (4 H, m), 2.28 - 2.42 (2 H, m), 2.00 - 2.13 (2 H, m), 0.72 (6 H, t, J=7.3 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 417.3.

EXAMPLE 162

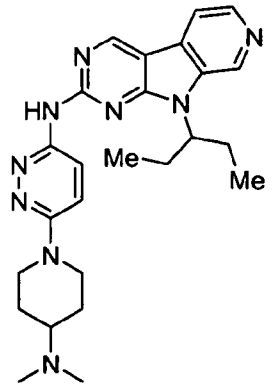


209

(3*R*)-1-(6-((9-(1-Ethylpropyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-amino)-3-pyridazinyl)-3-pyrrolidinol

Compound **209** was prepared using chemistry similar to that described in example 18. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 11.44 (1 H, br. s.), 9.75 (1 H, s), 9.62 (1 H, s), 8.78 (1 H, d, J= 6.2Hz), 8.73 (1 H, d, J= 6.1Hz), 8.48 (1 H, d, J= 10.0 Hz), 7.92 (1 H, d, J= 10.0 Hz), 4.82 - 4.91 (1 H, m), 4.47 - 4.56 (1 H, m), 3.65 - 3.84 (3 H, m), 3.57 - 3.64 (1 H, m), 2.25 - 2.41 (2 H, m), 1.92 - 2.17 (4 H, m), 0.70 (6 H, t, J= 14.6Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 419.2.

EXAMPLE 163

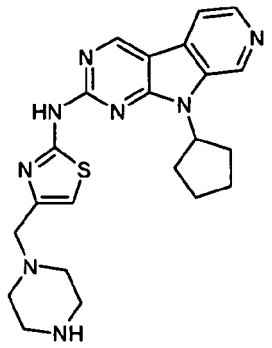


210

***N*-(6-(4-(Dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(1-ethylpropyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **210** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 10.18 (1 H, br. s.), 9.28 (1 H, s), 9.06 (1 H, s), 8.44 (1 H, d, J= 5.1 Hz), 8.20 (1 H, d, J= 9.8 Hz), 8.05 (1 H, d, J= 5.1 Hz), 7.45 (1 H, d, J= 9.8 Hz), 4.75 (1 H, br. s.), 4.29 (2 H, d, J= 13.0 Hz), 2.88 (2 H, t, J= 11.6 Hz), 2.25 - 2.37 (3 H, m), 2.19 (6 H, s), 1.93 - 2.03 (2 H, m), 1.81 - 1.88 (2 H, m), 1.36 - 1.47 (2 H, m), 0.67 (6 H, t, J=7.3 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 460.3.

EXAMPLE 164

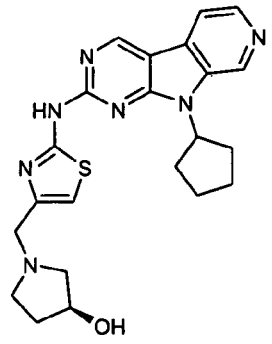


211

9-Cyclopentyl-*N*-(4-(1-piperazinylmethyl)-1,3-thiazol-2-yl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **211** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 12.47 (1 H, br. s.), 9.71 (1 H, s), 9.44 (1 H, s), 9.02 (2 H, br. s.), 8.73 (1 H, d, J= 6.1 Hz), 8.65 (1 H, d, J= 6.1 Hz), 7.41 (1 H, s), 5.39 - 5.53 (1 H, m), 4.15 (2 H, s), 3.30 (4 H, br. s.), 3.17 (4 H, br. s., J= 7.6 Hz), 2.53 - 2.62 (2 H, m), 2.08 - 2.20 (4 H, m), 1.77 - 1.89 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 435.2.

EXAMPLE 165

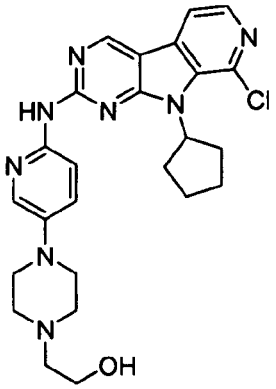


212

(3*S*)-1-((2-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1,3-thiazol-4-yl)methyl)-3-pyrrolidinol

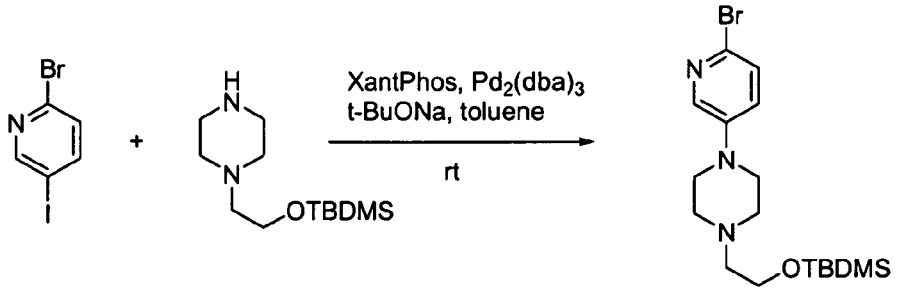
Compound **212** was prepared using chemistry similar to that described in example 18. ^{1}H NMR (500 MHz, *MeOD-d$_3$*) δ 9.28 (1 H, br. s.), 8.94 (1 H, br. s.), 8.43 (1 H, br. s.), 8.09 (1 H, br. s.), 6.94 (1 H, br. s.), 5.49 - 5.62 (1 H, m), 4.34 - 4.44 (1 H, m), 3.67 - 3.83 (2 H, m), 2.93 - 3.01 (1 H, m), 2.83 - 2.91 (1 H, m), 2.68 - 2.77 (1 H, m), 2.60 - 2.66 (1 H, m), 2.48 - 2.57 (2 H, m), 2.08 - 2.27 (5 H, m), 1.88 - 2.00 (2 H, m), 1.76 (1 H, br. s.) ppm; LCMS-ESI (POS), M/Z, M+1: Found 436.1.

EXAMPLE 166



213

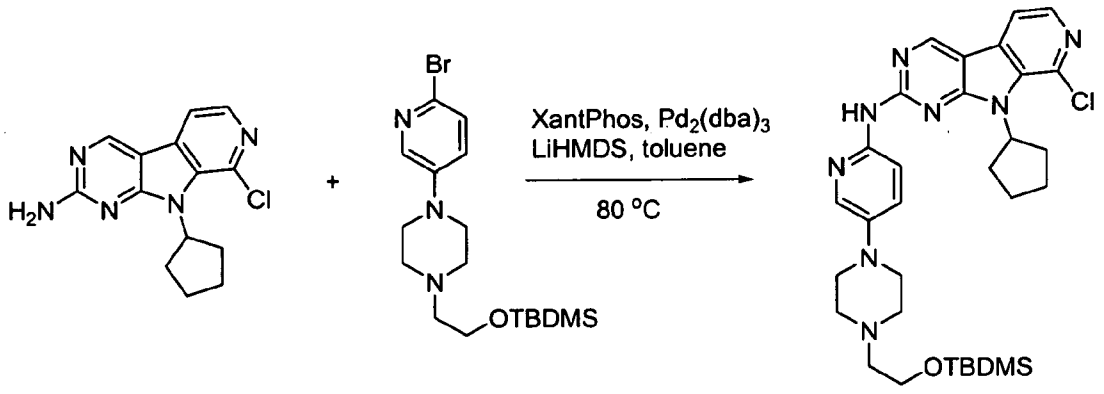
2-(4-(6-((8-Chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol



246 **216**

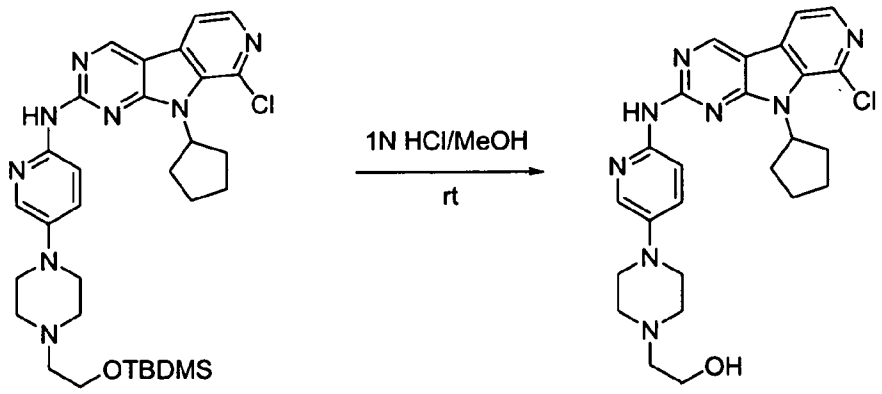
1-(6-Bromo-3-pyridinyl)-4-(2-((tert-butyl(dimethyl)silyl)oxy)ethyl)piperazine (216); 2-Bromo-5-iodopyridine (0.383 g, 1.35 mmol), compound **246** (see example 170) (0.330 g, 1.35 mmol), and sodium 2-methylpropan-2-olate (0.195 g, 2.02 mmol) were combined in 10 mL of anhydrous toluene. N_2 was bubbled briefly through the solution before adding $Pd_2(dba)3$ (0.0309 g, 0.0337 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0391 g, 0.0675 mmol). The solution was then stirred at room temperature overnight. After 17 hours, more 2-bromo-5-iodopyridine (0.383 g, 1.35 mmol), $Pd_2(dab)_3$ (0.0309 g, 0.0337 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0391 g, 0.0675 mmol) and sodium 2-methylpropan-2-olate (0.195 g, 2.02 mmol) were added. The solution was stirred at

room temperature for 48 hours. NH_4Cl (300 mg) was added and the solution was stirred at room temperature for 10 min. The product was purified on CombiFlash column (dry loaded), eluting with a gradient of 20% ethyl acetate/hexane to ethyl acetate. The fractions containing the product were combined and concentrated under vacuum to give compound **216** (100mg, 19%) as a tan colored solid. ^1H NMR (500 MHz, *CDCl3*) δ ppm 8.01 (1 H, d, J=3.2 Hz), 7.29 (1 H, d, J=8.8 Hz), 7.07 (1 H, dd, J=8.8, 3.2 Hz), 3.79 (2 H, t, J=6.1 Hz), 3.15 - 3.24 (4 H, m), 2.67 - 2.75 (4 H, m), 2.60 (2 H, t, J=6.1 Hz), 0.90 (9 H, s), 0.07 (6 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 400.1.



194 **216** **217**

N-(5-(4-(2-((tert-Butyl(dimethyl)silyl)oxy)ethyl)-1-piperazinyl)-2-pyridinyl)-8-chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (217): Compound **217** was prepared from compounds **194** and **216** using methods described in example 152. LCMS-ESI (POS), M/Z, M+1: Found 607.4.

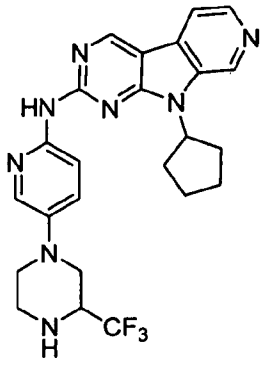


217 **213**

2-(4-(6-((8-Chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol (213): Compound **217** (0.094 g, 0.15 mmol) was combined with 10 mL of methanol and 4 mL of 1N HCl. The solution was stirred at room

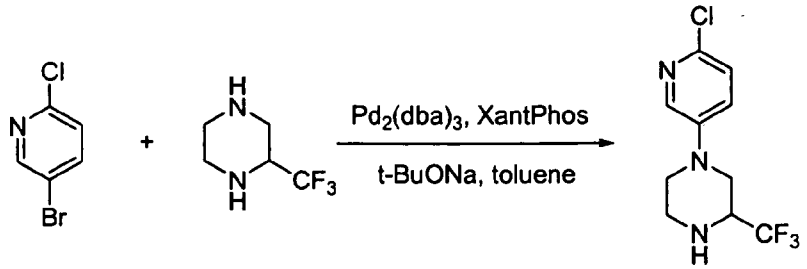
temperature overnight. The solution was concentrated under vacuum and the residue obtained was purified on CombiFlash column (dry loaded), eluting with a gradient of 2% methanol/0.1% NH_4OH(~28% in water)/DCM to 10%methanol/0.5%NH_4OH(~28% in water)/DCM. The fractions containing the product were combined and concentrated under vacuum to give a yellow solid. The solid was partially dissolved in methanol and then collected on filter paper. Washed the solid off of the filter paper with DCM/methanol through a fritted funnel and then concentrated under vacuum to give compound **213** (0.065 g, 85% yield) as a yellow solid. ^{1}H-NMR(500 MHz, *DMSO-d_6*) δ 9.92 (1 H, s), 9.33 (1 H, s), 8.22 (1 H, d, J= 5.1 Hz), 8.10 (1 H, d, J= 4.9 Hz), 8.04 (1 H, d, J= 2.9 Hz), 8.02 (1 H, d, J= 9.0 Hz), 7.46 (1 H, dd, J= 9.0, 2.9 Hz), 5.95 - 6.05 (1 H, m), 4.43 (1 H, t, J= 5.4 Hz), 3.54 (2 H, q, J= 6.1 Hz), 3.12 - 3.19 (4 H, m), 2.55 - 2.65 (6 H, m), 2.45 (2 H, t, J= 6.4 Hz), 1.98 - 2.08 (4 H, m), 1.65 - 1.75 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 493.1.

EXAMPLE 167



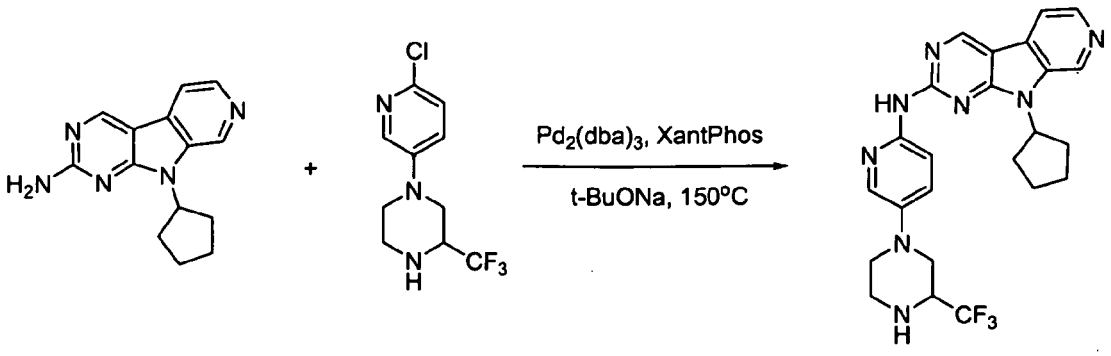
218

4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-(trifluromethyl)piperazine



219 **220**

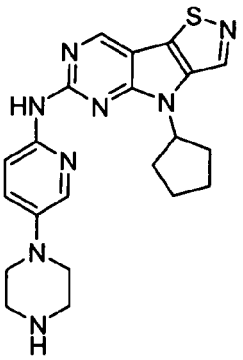
1-(6-Chloropyridin-3-yl)-3-(trifluoromethyl)piperazine (220): Compound **220** was prepared using methods described in example 1 using compound **219**. ^{1}H NMR (500 MHz, *$CDCl_3$*) δ 7.97 (s, 1 H) 7.09 - 7.18 (m, 2 H) 3.52 - 3.60 (m, 1 H) 3.34 - 3.48 (m, 2 H) 3.09 - 3.22 (m, J= 11.98 Hz, 1 H) 2.91 - 3.01 (m, 1 H) 2.75 - 2.88 (m, 2 H) 1.84 (s, 1 H) ppm.



4 220 218

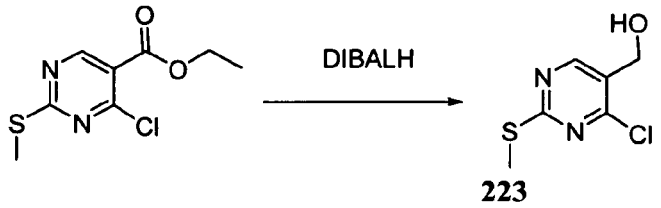
4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-(trifluromethyl)piperazine (218): Compound **218** was prepared from compounds **4** and **220** using methods described in example 1. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 9.84 (s, 1 H) 9.28 (s, 1 H) 9.00 (s, 1 H) 8.44 (d, J= 4.89 Hz, 1 H) 8.21 (d, J= 9.05 Hz, 1 H) 8.08 (d, J= 2.93 Hz, 1 H) 8.04 (d, J= 5.14 Hz, 1 H) 7.54 (dd, J= 9.05, 2.93 Hz, 1 H) 5.29 - 5.47 (m, 1 H) 3.62 (d, J= 11.25 Hz, 1 H) 3.49 - 3.59 (m, 1 H) 3.46 (d, J= 11.49 Hz, 1 H) 2.98 - 3.10 (m, J= 9.78 Hz, 1 H) 2.79 - 2.95 (m, 2 H) 2.65 - 2.79 (m, 2 H) 2.29 - 2.45 (m, 2 H) 1.95 - 2.18 (m, 4 H) 1.77 (d, J= 5.38 Hz, 2 H) ppm.

EXAMPLE 168



221

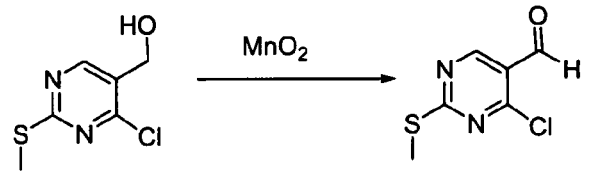
4-Cyclopentyl-*N*-(5-(1-piperazinyl)-2-pyridinyl)-4H-isothiazolo[5',4':4,5]pyrrolo[2,3-d]pyrimidin-6-amine



223

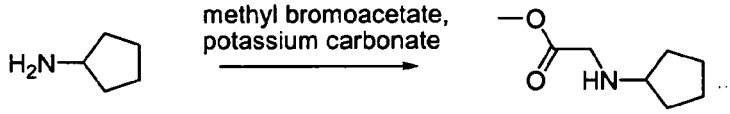
(4-Chloro-2-(methylthio)pyrimidin-5-yl)methanol (223): To ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (20.0 g, 86 mmol) in dichloromethane (400 mL) at -78

°C was added diisobutylaluminum hydride, 1.0 M in toluene (172 mL, 172 mmol). The reaction was allowed to warm to 0 °C over 2 h. To the reaction was added a 20% Rochelle's (1600 mL) and diethyl ether (750 mL). The emulsion was stirred for 30 min. The organics were sequestered and the aqueous was extracted further with diethyl ether (2 x 500 mL). The combined organics were washed with water (500 mL), brine (500 mL), dried over $MgSO_4$, and concentrated in vacuo and filtered through a plug of silica eluting with 1:1; ethyl acetate:CH_2Cl_2 to obtain compound **223** (9.6 g, 59% yield). ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 8.55 (s, 1 H) 4.75 (d, J=5.87 Hz, 2 H) 2.58 (s, 3 H) 2.06 - 2.25 (m, J=5.14 Hz, 1 H) ppm.



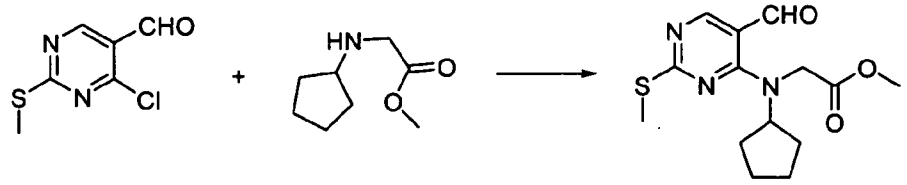
223 **224**

4-chloro-2-(methylthio)pyrimidine-5-carbaldehyde (224): Manganese(IV) oxide, <5 micron, activated (38.1g , 439 mmol) was added to a solution of compound **223** (16.73 g, 87.8 mmol) in chloroform (800 mL). The reaction was stirred overnight, filtered through Celite, and the filtrate was concentrated in vacuo to yield compound **224** (13.7 g, 82.8% yield). ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 10.31 (s, 1 H) 8.88 (s, 1 H) 2.65 (s, 2 H) ppm.



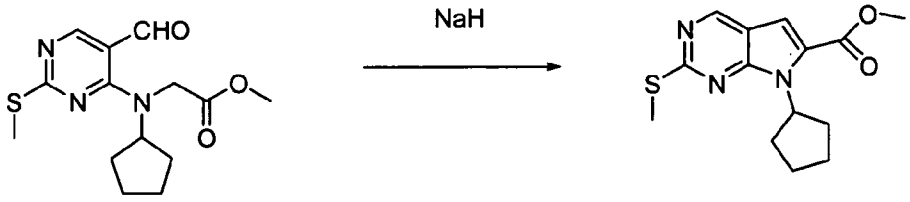
225

Methyl 2-(cyclopentylamino)acetate (225): A solution of methyl bromoacetate (17.4 mL, 188 mmol) in THF (40 mL) was dropwise added to a solution of cyclopentylamine (18.6 mL, 188 mmol) and triethylamine (26.1 mL, 188 mmol) in THF (150 mL) at 0 °C. Following addition, the reaction was allowed to reach room temperature and was stirred overnight. The triethylammonium salts were filtered and rinsed with scant THF. The combined filtrates were concentrated *in vacuo*. The desired product was distilled from the residuals under reduced pressure to yield 20.2 g of compound **225** (68% yield). ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 3.73 (s, 3 H) 3.41 (s, 2 H) 3.00 - 3.13 (m, J=12.90, 6.39, 6.39 Hz, 1 H) 1.77 - 1.87 (m, 2 H) 1.67 - 1.74 (m, 2 H) 1.48 - 1.59 (m, 2 H) 1.29 - 1.41 (m, 2 H) ppm.



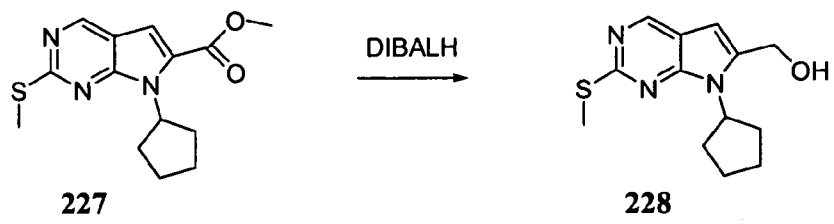
224 225 226

Methyl 2-(cyclopentyl(5-formyl-2-(methylthio)pyrimidin-4-yl)amino)acetate (226): Triethylamine (10.9 mL, 78.2 mmol) was added to a solution of compound **224** (12.3 g, 65.2 mmol) and compound **225** (12.8 g, 81.5 mmol) in THF (200 mL). The reaction was stirred at room temperature. After 6 h, the reaction contents were poured into saturated sodium bicarbonate and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was crystallized from ethyl acetate and hexanes to afford methyl 2-(cyclopentyl(5-formyl-2-(methylthio)pyrimidin-4-yl)amino)acetate **(226)** (17.55 g, 87.0% yield).



226 227

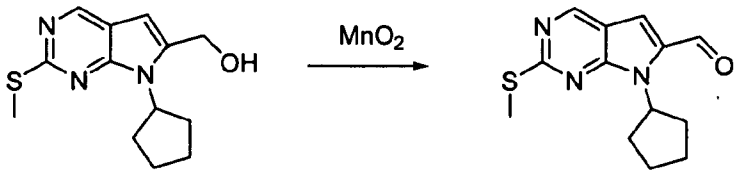
Methyl 7-cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate (227): Sodium hydride (3.85 g, 167 mmol)(freshly washed with hexane) was added to a solution of compound **226** (12.95 g, 41.9 mmol) in benzene (150 mL). The reaction was stirred at 70 °C. After 1 h, the reaction contents were poured into water (300 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Silica gel chromatography (gradient elution 0 to 50% ethyl acetate in hexanes) afforded compound **227** (4.24 g, 34.8% yield).



227 228

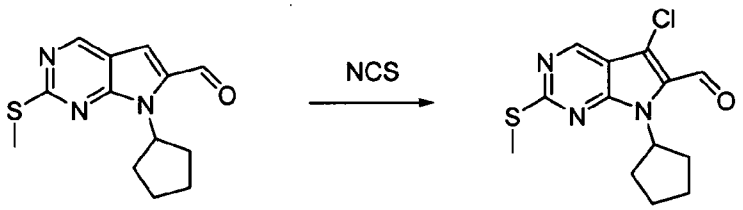
(7-Cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)methanol (228): DIBAL-H (1.0 M in toluene) (33.8 mL, 33.8 mmol) was added dropwise to a solution of compound **227** (4.93 g, 16.9 mmol) in dichloromethane (85 mL) at -78 °C . The reaction was stirred for

20 minutes, then warmed to 0 °C and quenched with 400 mL of 0.5 M Rochelle's salt saturated with NaCl. The mixture was stirred for 3 h then extracted with ethyl acetate (4 x 250 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to provide 4.36 g of crude. The crude material was taken up in dichloromethane and methanol, plated onto silica gel, and flashed through a plug of silica using 30% ethyl acetate in hexanes, then switching to 10% methanol in DCM to provide compound **228** (3.37 g, 75.6% yield). ^{1}H NMR (500 MHz, *CDCl$_3$*) δ 8.60 (s, 1 H) 6.29 (s, 1 H) 4.83 - 4.95 (m, J= 17.30, 8.59, 8.59 Hz, 1 H) 4.79 (d, J= 5.87 Hz, 2 H) 2.62 (s, 3 H) 2.47 - 2.58 (m, 2 H) 1.97 - 2.15 (m, 5 H) 1.67 - 1.81 (m, 2 H) ppm.



228 **229**

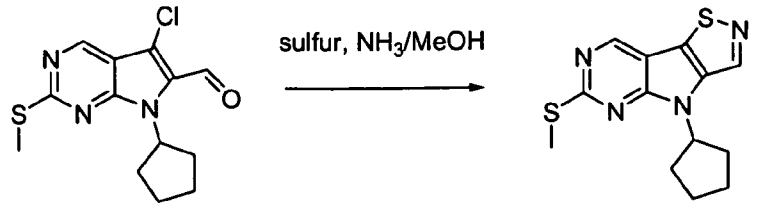
7-Cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carbaldehyde (229): Manganese dioxide (5.56 g, 64.0 mmol) was added to a solution of compound **228** (3.37 g, 12.8 mmol) in dichloromethane (250 mL). After 16 h, the reaction contents were filtered through Celite and organics were removed *in vacuo* to provide compound **229** (3.10 g, 92.7% yield).



229 **230**

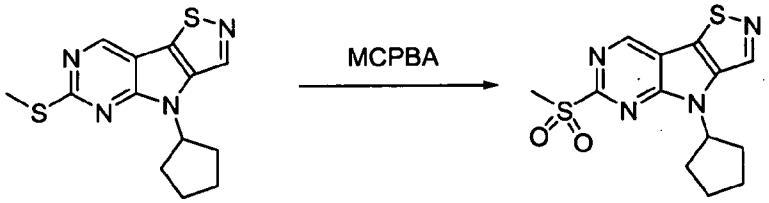
5-Chloro-7-cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carbaldehyde (230): Compound **229** (3.10 g, 11.9 mmol) and *N*-chlorosuccinimide (1.74 g, 13.0 mmol) were dissolved in DMF (30 mL) and stirred at 100 °C. After 1 h, the temperature of the reaction was reduced to 65°C and 0.35 eq of NCS were added. After 30 min, the reaction contents were poured into water (10 x) and saturated bicarbonate was added (300 mL). The aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organics were dried with sodium sulfate and concentrated *in vacuo*. Silica gel chromatography (gradient elution 0 to 7% ethyl acetate in hexanes) afforded 5-chloro-7-cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carbaldehyde (**230**) (1.37 g, 39% yield). ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm

10.17 (s, 1 H) 8.91 (s, 1 H) 5.73 - 5.96 (m, 1 H) 2.63 (s, 3 H) 2.29 - 2.47 (m, 2 H) 1.97 - 2.16 (m, 4 H) 1.63 - 1.83 (m, 2 H) ppm.



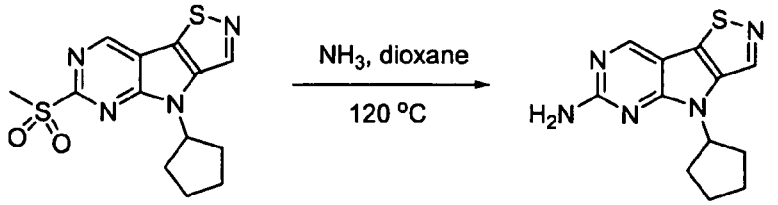
230 231

4-Cyclopentyl-6-(methylsulfanyl)-4H-isothiazolo[5',4':4,5]pyrrolo[2,3-d]pyrimidine (231): To sulfur (0.238 g, 0.926 mmol) and 5-chloro-7-cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carbaldehyde (1.37 g, 4.63 mmol) was added saturated methanolic ammonia (15 mL). The reaction was sealed and stirred at 80 °C overnight. The reaction was cooled to 0 °C and an aliquot was removed and partitioned between dichloromethane and saturated sodium bicarbonate. The organics were removed *in vacuo* and partitioned between dichloromethane (100 mL) and saturated sodium bicarbonate (200 mL). The aqueous was extracted further with dichloromethane (100 mL). The combined organics were dried with Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography (gradient elution 0 to 25% ethyl acetate in hexanes) afforded compound **231** (1.30 g, 96.6% yield). ^{1}H NMR (500 MHz, *CDCl*$_3$) δ 8.97 (s, 1 H) 8.62 (s, 1 H) 5.36 - 5.52 (m, 1 H) 2.69 (s, 3 H) 2.21 - 2.34 (m, 2 H) 1.97 - 2.18 (m, 4 H) 1.78 - 1.93 (m, 2 H) ppm.



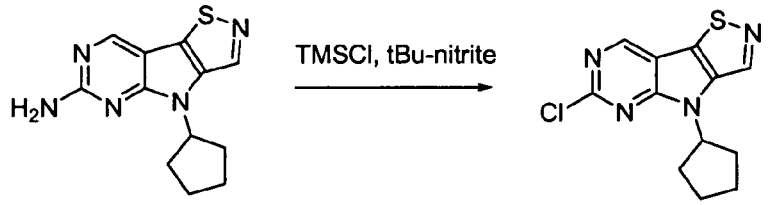
231 232

4-Cyclopentyl-6-(methylsulfonyl)-4H-isothiazolo[5',4':4,5]pyrrolo[2,3-d]pyrimidine (232): To reactant **231** (1.30 g, 4.48 mmol) in dichloromethane (25 mL) at 0 °C was added MCPBA (50%) (3.42 g, 9.85 mmol). The reaction was allowed to stir overnight while warming to room temperature. The reaction contents were poured into saturated sodium bicarbonate (150 mL) and extracted with dichloromethane (3 x 75 mL). Silica gel chromatography (gradient elution 20 to 60% ethyl acetate in hexanes) afforded compound **232** (1.30 g, 90.1% yield).



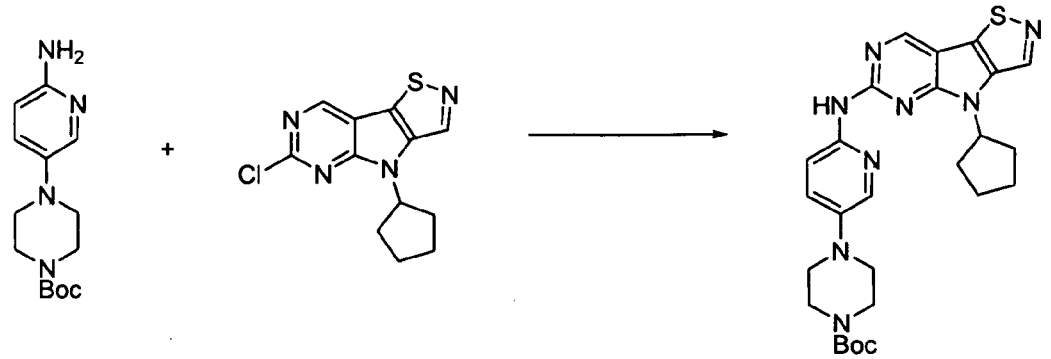
232 233

4-cyclopentyl-pyrimidino[4',5':2,3]4H-pyrrolo[2,3-d]isothiazole-6-amine (233): In a glass bomb, a solution of compound **232** (1.30 g, 4.06 mmol) in dioxane (35 mL) was saturated with ammonia gas.. The bomb was sealed and the reaction was stirred at 120 °C. After 16 h, LCMS indicated complete consumption of starting material. Solvent was removed *in vacuo.* Silica gel chromatography (gradient elution 20 to 50% THF in hexanes) afforded 430 mg of compound **233** (41% yield).



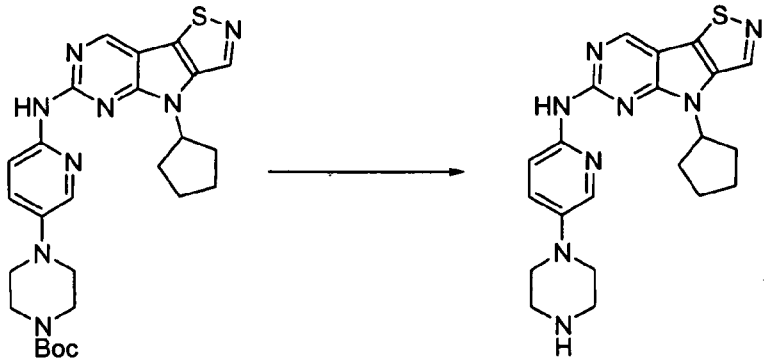
233 234

6-Chloro-4-cyclopentyl-pyrimidino[4',5':2,3]4H-pyrrolo[2,3-d]isothiazole (234): To a solution of compound **233** (0.100 g, 0.39 mmol) in dichloromethane (10 mL) at 0 °C was added dropwise trimethylsilyl chloride (0.15 mL, 1.2 mmol) followed by addition of *tert*-butyl nitrite (0.2 g, 1.9 mmol). The reaction was stirred at room temperature for 5 days. The reaction contents were poured into saturated sodium bicarbonate (20 mL). The aqueous layer was extracted with dichloromethane (1 x 20 mL). Silica gel chromatography (gradient elution 0 to 30% THF in hexanes) afforded compound **234** (0.025 g, 23% yield) which was carried on without further characterization.



5 234 235

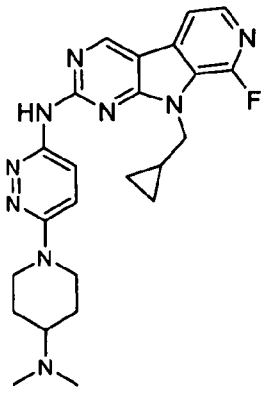
1,1-Dimethylethyl 4-(6-((4-cyclopentyl-4H-isothiazolo[5',4':4,5]pyrrolo[2,3-d]pyrimidin-6-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (235): In a screw cap vial were combined compound **5** (0.075 g, 0.27 mmol), compound **234** (0.025 g, 0.090 mmol) and DMSO (0.200 mL). The reaction was sealed and stirred at 100 °C over 4 d. DMSO was removed under high vacuum. Silica gel chromatography (gradient elution 0 to 10% methanol in DCM) afforded 15 mg of compound **235** (32% yield).



235 **221**

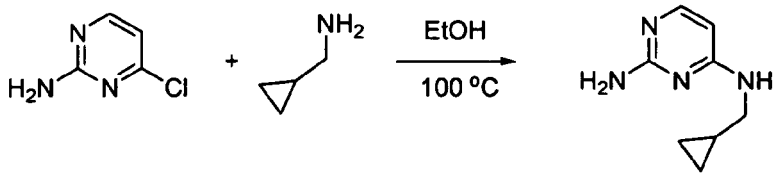
4-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-pyrimidino[4',5':2,3]4H-pyrrolo[2,3-d]isothiazole-6-amine (221): Compound **221** was prepared using methods described in Example 1. ^{1}H NMR (500 MHz, *CD_3OD*) δ 9.57 (s, 1 H) 9.00 (s, 1 H) 8.13 (d, J= 2.45 Hz, 1 H) 8.06 (dd, J= 9.78, 2.69 Hz, 1 H) 7.24 (d, J= 9.54 Hz, 1 H) 5.53 (quin, J= 8.44 Hz, 1 H) 3.38 - 3.48 (m, 8 H) 2.21 - 2.40 (m, 4 H) 2.06 - 2.18 (m, 2 H) 1.83 - 1.95 (m, 2 H) ppm. LCMS-ESI (POS), M/Z, M+1: Found 421.0, Calculated 421.2.

EXAMPLE 169



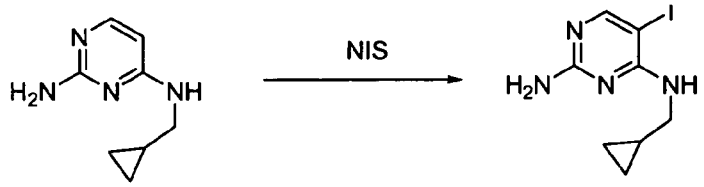
236

9-Cyclopentyl-8-fluoro-N-(6-(4-dimethylaminopiperidine-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine



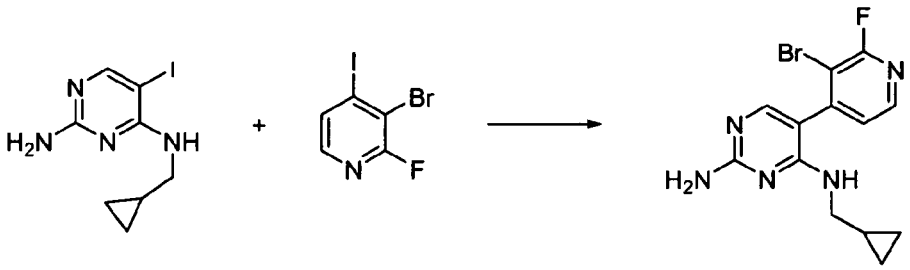
237

***N*4-(cyclopropylmethyl)pyrimidine-2,4-diamine (237):** To cyclopropylmethanamine (3.62 g, 50.9 mmol) in ethanol (90 mL) was added solid 4-chloropyrimidin-2-amine (6.00 g, 46.3 mmol). The reaction was stirred at reflux (100 °C oil bath) for 16 h. The reaction was cooled to room temperature and solvent was removed *in vacuo*. The product **237** obtained in quantitative yield. LCMS-ESI (POS), M/Z, M+1: Found 165.0, Calculated 165.1.



237 238

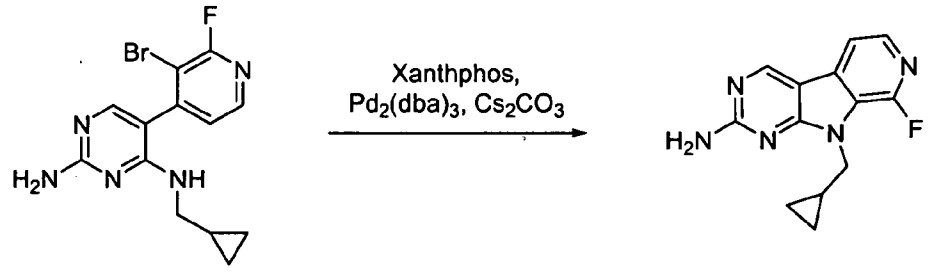
N4-(Cyclopropylmethyl)-5-iodopyrimidine-2,4-diamine (238): N-iodosuccinimide (11.5 g, 50.9 mmol) was added to a solution of compound **237** (7.60 g, 46.3 mmol) in AcOH (90 mL). The reaction was warmed to 80 °C and stirred for 1.5 h. Solvent was removed *in vacuo*. The residue was taken up in dichloromethane (200 mL) and water. The aqueous layer was brought to pH 12 with 5 N NaOH and organics were sequestered. The aqueous was extracted further with dichloromethane (2 x 100 mL). The combined organics were treated with solid sodium thiosulfate, dried with $MgSO_4$ and concentrated *in vacuo*. Silica gel chromatography (gradient elution 10 to 75% ethyl acetate in hexanes) afforded compound **238** (8.0 g, 60% yield).



238 240

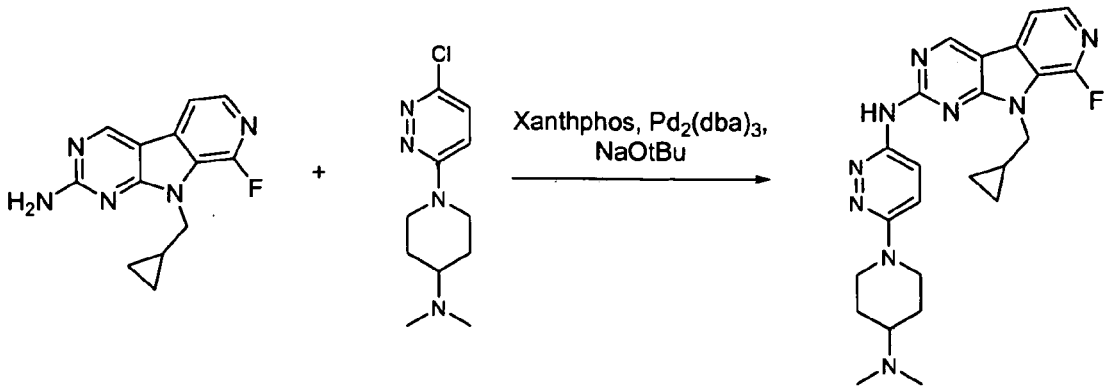
5-(3-Bromo-2-fluoropyridin-4-yl)-N4-(cyclopropylmethyl)pyrimidine-2,4-diamine (240): Isopropylmagnesium chloride, 2 M solution in THF (0.814 mL, 1.63 mmol) was added dropwise over 15 minutes to a degassed solution of 3-bromo-2-fluoro-4-iodopyridine (0.468 g, 1.55 mmol) in Et_2O (0.150 mL) and THF (0.850) cooled at -78 °C. The solution was stirred for 0.5 h. Zinc chloride, 1.0 M solution in diethyl ether (0.776 mL, 0.776 mmol) was then

added dropwise to the reaction over 10 minutes. The reaction was allowed to reach room temperature. The reaction warmed to room temperature within 15 min. A solution of compound **238** (0.150 g, 0.517 mmol) and tetrakis(triphenylphosphine)palladium (0.0418 g, 0.0362 mmol) in THF (0.50 mL) was added to the reaction. The reaction was equipped with a reflux condenser and stirred in a 60 °C oil bath. After 2 h the reaction was removed from heat and allowed to stand overnight. Saturated NH_4Cl (0.5 mL) and 12% 2-propanol in CH_2Cl_2 (2 mL) were added. The organics were sequestered and the aqueous was extracted with 12% 2-propanol in CH_2Cl_2 (4 x 4 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Silica gel chromatography (elution 3% methanol in DCM with 0.175 % NH_4OH additive) afforded compound **240** (0.140 g, 80.1% yield). ^1H NMR (500 MHz, *CDCl3*) δ ppm 0.22 (d, J= 4.40 Hz, 2 H) 0.46 - 0.59 (m, 2 H) 0.96 - 1.07 (m, 1 H) 3.21 - 3.36 (m, 2 H) 4.51 (br. s., 1 H) 5.11 (br. s., 2 H) 7.16 (d, J= 4.89 Hz, 1 H) 7.69 (s, 1 H) 8.22 (d, J= 4.89 Hz, 1 H) ppm.



240 **241**

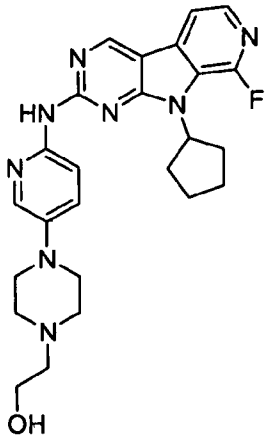
9-(Cyclopropylmethyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (241): To a vacuum to argon purged vial containing 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.017 g, 0.030 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.014 g, 0.015 mmol), cesium carbonate (0.19 g, 0.59 mmol) and compound **240** (0.100 g, 0.30 mmol) was added degassed dioxane (2.00 mL). The reaction was stirred at 100 °C. After 4 h, the reaction was cooled and applied directly to silica. Silica gel chromatography (gradient elution 40 to 90% ethyl acetate in hexanes) afforded compound **241** (0.060 g, 79% yield). ^1H NMR (500 MHz, *CDCl3*) δ ppm 0.45 - 0.57 (m, 4 H) 1.34 - 1.47 (m, 1 H) 4.32 (d, J=7.09 Hz, 2 H) 5.46 (br. s., 2 H) 7.68 (dd, J=5.26, 2.81 Hz, 1 H) 8.02 (dd, J=5.13, 1.71 Hz, 1 H) 8.93 (s, 1 H).



241 236

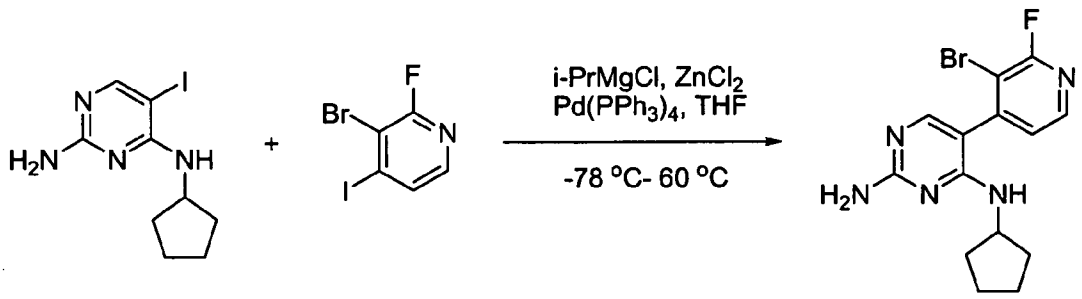
9-Cyclopentyl-8-fluoro-N-(6-(4-dimethylaminopiperidine-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine (236): To tris(dibenzylideneacetone)dipalladium (0) (0.015 g, 0.016 mmol), Xantphos (0.019 g, 0.032 mmol), NaOtBu (0.025 g, 0.26 mmol), 1-(6-chloropyridazin-3-yl)-N,N-dimethylpiperidin-4-amine (0.051 g, 0.21 mmol), and compound **241** (0.0550 g, 0.21 mmol) was added degassed dioxane (1.0 mL). The reaction vessel was sealed and stirred at 105 °C. After 13 h, the reaction contents were poured into saturated sodium bicarbonate (5 mL). The aqueous layer was extracted with 10% methanol in dichloromethane (3 x 10 mL). The combined organics were dried with sodium sulfate and concentrated *in vacuo*. Silica gel chromatography (0.175% NH_4OH 3% methanol in DCM to 100% 1% NH_4OH, 7% methanol, CH_2Cl_2) yielded compound **236** (0.038 g, 39% yield). ^1H NMR (500 MHz, *DMSO-d_6*) δ 0.41 - 0.55 (m, 4 H) 1.29 - 1.50 (m, 3 H) 1.85 (d, J=11.98 Hz, 2 H) 2.20 (s, 6 H) 2.34 (tt, J=10.85, 3.58 Hz, 1 H) 2.90 (t, J=11.62 Hz, 2 H) 4.25 - 4.37 (m, 4 H) 7.44 (d, J=10.03 Hz, 1 H) 7.98 - 8.09 (m, 2 H) 8.24 (d, J=9.78 Hz, 1 H) 9.34 (s, 1 H) 10.35 (s, 1 H) ppm. LCMS-ESI (POS), M/Z, M+1: Found 462.0, Calculated 462.2.

EXAMPLE 170



242

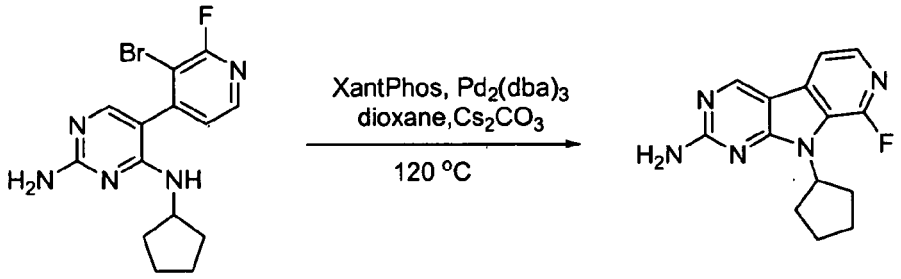
2-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol



243 244

5-(3-Bromo-2-fluoro-4-pyridinyl)-N4-cyclopentyl-2,4-pyrimidinediamine (244): In a dry 3 neck 2 L flask equipped with a dry addition funnel, thermometer and stir bar was added 3-bromo-2-fluoro-4-iodopyridine (83.4 g, 276 mmol) followed by 300 mL of anhydrous THF under an atmosphere of nitrogen. The solution was cooled to -70°C in 2-propanol/dry ice bath. A solution of isopropylmagnesium chloride 2.0 M in diethyl ether (145 mL, 290 mmol) was added drop wise over a period of 30 minutes. The solution was then stirred for 30 minutes before zinc (II) chloride 0.5 M in THF (276 mL, 138 mmol) was cannulated in. The solution was warmed to room temperature and stirred for 1hour. The addition funnel was replaced with a reflux condenser and N4-cyclopentyl-5-iodopyrimidine-2,4-diamine (**243**, see example 200) (28.00 g, 92.1 mmol) was added, followed by $Pd(PPh_3)_4$ (5.32 g, 4.60 mmol). The solution was heated over night at a gentle reflux. After concentrating the solution to 1/10th of the volume under vacuum, it was cooled in an ice bath. To this was added 100 mL of cold saturated NH_4Cl, followed by 500 mL of water. 500mL of 12% isopropanol/DCM was then added and the solution was stirred at room temperature for 1hour before being filtered through

filter paper. The filter cake was washed in succession with water, DCM and 12% 2-propanol /DCM. The filtrate was partitioned in a separation funnel and the aqueous layer was washed with 12% 2-propanol /DCM. The organics were dried over MgSO4 and then concentrated under vacuum. The residue obtained was partially dissolved in DCM with sonication and filtered off to give compound **244** (26.45g, 81.6%) as a light yellow solid. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.18 (1 H, d, J= 4.9 Hz), 7.52 (1 H, s), 7.26 (1 H, dd, J= 4.9, 0.7 Hz), 6.34 (2 H, s), 6.12 (1 H, d, J= 7.6 Hz), 4.42 (1 H, sxt, J= 7.4 Hz), 1.76 - 1.96 (2 H, m), 1.55 - 1.68 (2 H, m), 1.31 - 1.53 (4 H, m)) ppm; LCMS-ESI (POS), M/Z, M+1: Found 352.0.



244 **245**

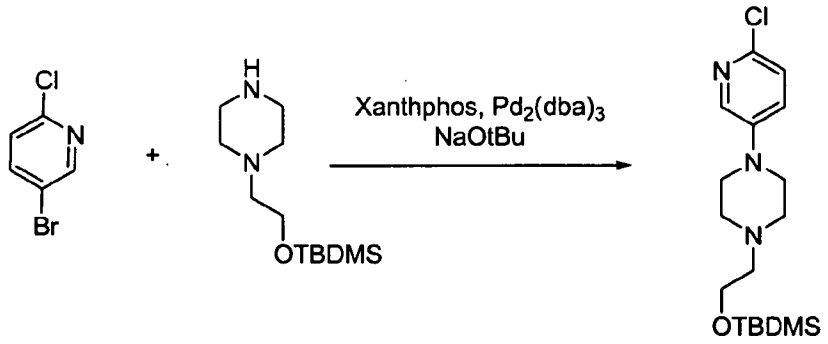
9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine(245): Compound **244** (0.143 g, 0.41 mmol), and cesium carbonate (0.40 g, 1.2 mmol) were combined in 5mL of anhydrous 1,4-dioxane. Nitrogen was bubbled through the solution briefly before adding $Pd_2(dba)_3$ (0.037 g, 0.041 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.047 g, 0.081 mmol). The solution was heated at 120 °C with microwave irradiation for 1hour. The solution was purified on CombiFlash column (dry loaded) eluting with a gradient of 2%methanol/0.1% NH_4OH(~28% in water)/DCM to 7%methanol/0.35%NH_4OH(~28% in water)/DCM. The fractions containing the pure product were combined and concentrated under vacuum to give compound **245** (94mg, 85%) as a light brownish solid. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 9.10 (1 H, s), 7.94 (1 H, dd, J= 5.2, 1.5 Hz), 7.91 (1 H, dd, J= 5.1, 2.9 Hz), 7.10 (2 H, br. s.), 5.38 - 5.49 (1 H, m), 2.10 - 2.23 (2 H, m), 1.93 - 2.08 (4 H, m), 1.64 - 1.79 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 272.0.



246

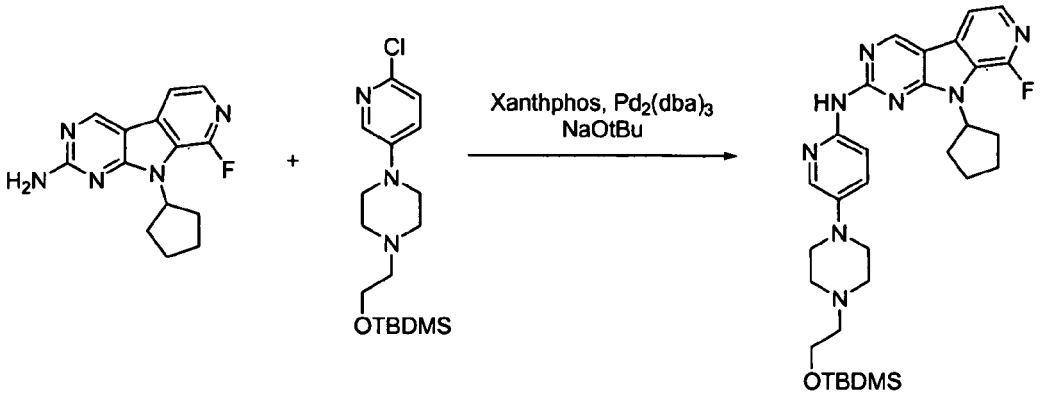
1-(2-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)ethyl)piperazine (246): To 1-(2-hydroxyethyl)-piperazine (3.36 g, 25.8 mmol) in dichloromethane (25 mL) was added *tert*-butyldimethylsilylchloride (3.89 g, 25.8 mmol). The reaction mixture was stirred at room

temperature. The reaction mixture was stirred overnight, then diluted 1 x with CH_2Cl_2 and extracted against 0.5 N NaOH (100 mL). The aqueous was extracted further with 10 % methanol in CH_2Cl_2 (3 x 100 mL). The combined organics were dried with Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography (gradient elution 0 to 100% B (7% methanol in DCM + 1% NH_4OH additive) against A (3% methanol in DCM + 0.175% NH_4OH additive) afforded compound **246** (4.71 g, 74.7% yield). ^1H NMR (500 MHz, *CDCl3*) δ 0.06 (s, 6 H) 0.90 (s, 9 H) 2.36 - 2.59 (m, 6 H) 2.89 (t, J= 4.77 Hz, 4 H) 3.76 (t, J= 6.48 Hz, 2 H) ppm.



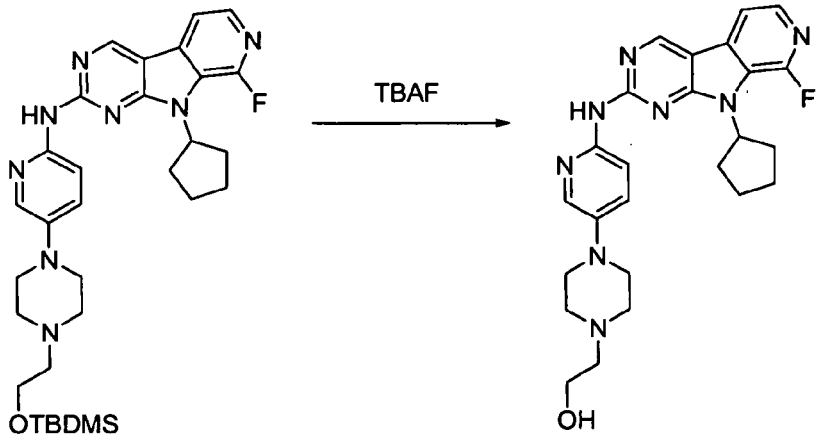
246 **247**

1-(6-chloro-3-pyridinyl)-4-(2-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)ethyl)-piperazine (247): 5-Bromo-2-chloropyridine (3.15 g, 16.4 mmol), compound **246** (4.00 g, 16.4 mmol), $Pd_2(dba)_3$ (0.749 g, 0.818 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.947 g, 1.64 mmol) and sodium *tert*-butoxide (1.82 g, 19.0 mmol) were combined in a screw cap vial and solvated under argon atmosphere with degassed toluene (44 mL). The reaction was briefly sparged with argon, then sealed and stirred at 100 °C. After 3 h, the reaction contents were poured into saturated sodium bicarbonate (100 mL) and extracted with 10% methanol in dichloromethane (3 x 200 mL). The combined organics were dried with sodium sulfate and concentrated in vacuo. Silica gel chromatography (gradient elution 0 to 100% ethyl acetate in hexanes switching to 3% methanol in DCM) afforded compound **247** (5.40 g, 92.7% yield). 1H NMR (500 MHz, *CDCl3*) δ 0.08 (s, 6 H) 0.91 (s, 9 H) 2.60 (t, J= 5.87 Hz, 2 H) 2.70 (br. s., 4 H) 3.20 (d, J= 4.40 Hz, 4 H) 3.80 (t, J= 6.11 Hz, 2 H) 7.17 (d, J= 1.71 Hz, 2 H) 8.02 (s, 1 H) ppm.



245 **247** **248**

9-Cyclopentyl-N-(5-(4-(2-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)ethyl)-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (248): To tris(dibenzylideneacetone)dipalladium (0) (0.0289 g, 0.0316 mmol), xantphos (0.0366 g, 0.0632 mmol), NaOtBu (0.0486 g, 0.506 mmol), compound **247** (0.150 g, 0.421 mmol), and compound **245** (0.114 g, 0.421 mmol) was added degassed dioxane (2.0 mL). The reaction vessel was sealed and stirred at 105 °C overnight. The reaction was loaded directly to silica. Silica gel chromatography (gradient elution 1.5 to 5% 2 M methanolic NH_3 in DCM) afforded compound **248** (0.120 g, 48.2% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 0.09 (s, 6 H) 0.83 - 1.00 (m, 9 H) 1.75 - 1.90 (m, 2 H) 2.05 - 2.25 (m, 4 H) 2.36 - 2.53 (m, 2 H) 2.63 (br. s., 2 H) 2.75 (br. s., 4 H) 3.22 (br. s., 4 H) 3.82 (br. s., 2 H) 5.54 (quin, J= 9.00 Hz, 1 H) 7.38 (dd, J= 9.00, 2.74 Hz, 1 H) 7.72 (dd, J= 5.09, 3.13 Hz, 1 H) 8.00 - 8.04 (m, 1 H) 8.06 (d, J= 2.74 Hz, 1 H) 8.10 (s, 1 H) 8.36 (d, J= 9.00 Hz, 1 H) 9.08 (s, 1 H) ppm.

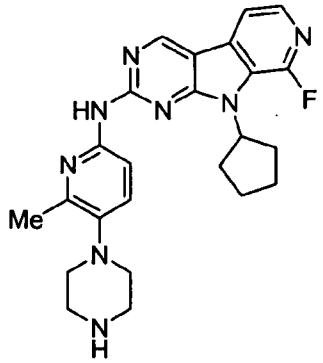


248 **242**

2-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol (242): To compound **248** (0.115 g, 0.19 mmol) in THF (1.0 mL) was added tetrabutylammonium fluoride, 1.0 M in THF (0.49 mL,

0.49 mmol). The reaction was stirred at room temperature. After 1 h, the reaction contents were poured into water. The aqueous layer was brought to pH 12 with 5 N NaOH and extracted with 10% methanol in dichloromethane (3 x 25 mL). The combined organics were dried with Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography (gradient elution 3 to 7.5% 2M methanolic NH_3 in DCM) afforded compound **242** (0.070 g, 75% yield). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 1.68 - 1.80 (m, 2 H) 1.92 - 2.05 (m, 2 H) 2.05 - 2.17 (m, 2 H) 2.25 - 2.40 (m, 2 H) 2.45 (t, J= 6.11 Hz, 2 H) 2.54 - 2.62 (m, 4 H) 3.00 - 3.27 (m, 4 H) 3.54 (q, J= 5.95 Hz, 2 H) 4.43 (t, J= 5.26 Hz, 1 H) 5.45 (quin, J= 9.05 Hz, 1 H) 7.47 (dd, J= 9.17, 2.81 Hz, 1 H) 7.93 - 8.07 (m, 3 H) 8.11 (d, J= 9.05 Hz, 1 H) 9.32 (s, 1 H) 9.89 (s, 1 H) ppm.

EXAMPLE 171

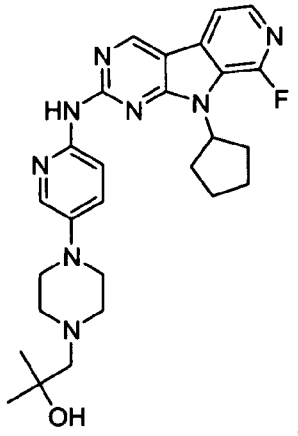


249

9-Cyclopentyl-8-fluoro-N-(6-methyl-5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

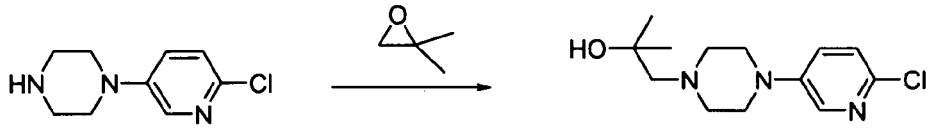
Compound **249** was prepared using methods described in Example 170 and isolated as the HCl salt. ^{1}H NMR (500 MHz, *D_2O*) δ ppm 8.97 (1 H, s), 8.03 (1 H, d, J=9.0 Hz), 7.87 (1 H, dd, J=5.1, 2.4 Hz), 7.79 (1 H, d, J=4.4 Hz), 7.12 (1 H, d, J=9.0 Hz), 5.35 (1 H, qd, J=8.7, 8.6 Hz), 3.47 - 3.55 (4 H, m), 3.23 - 3.32 (4 H, m), 2.65 (3 H, s), 2.17 - 2.28 (2 H, m), 1.97 - 2.17 (5 H, m), 1.73 - 1.87 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 447.3.

EXAMPLE 172



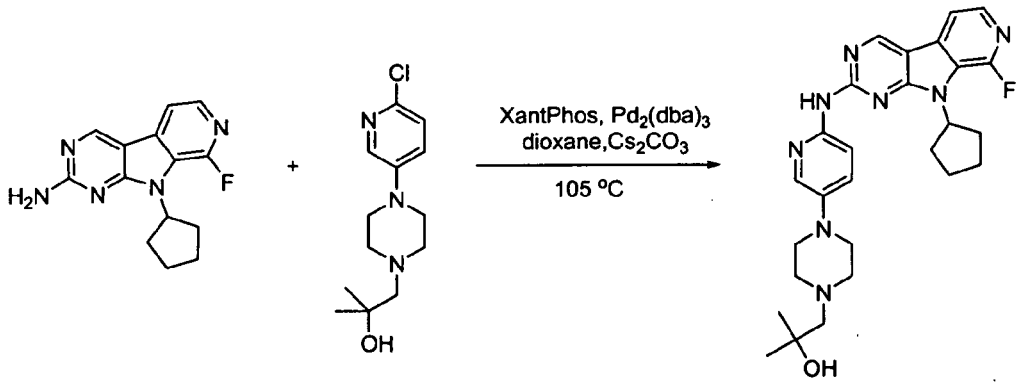
250

1-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-methyl-2-propanol



251

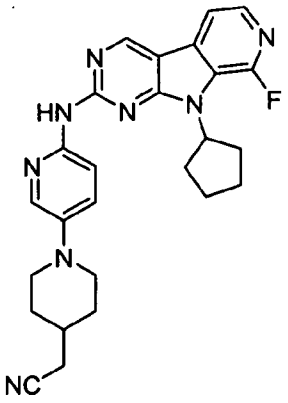
1-(4-(6-chloro-3-pyridinyl)-1-piperazinyl)-2-methyl-2-propanol (251): To 1-(6-chloropyridin-3-yl)piperazine (0.600 g, 3.04 mmol) in methanol (1.5 mL) was added dropwise isobutylene oxide (0.274 mL, 3.04 mmol). The reaction was left to stir at room temperature overnight. An additional 0.15 equivalents of isobutylene oxide were added and the reaction was placed in a 55 °C oil bath overnight. Solvent was removed *in vacuo*. Silica gel chromatography (gradient elution 2 to 10% methanol in DCM) afforded compound **251** (0.450 g, 55.0% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 0.95 - 1.50 (m, 7 H) 2.23 - 3.61 (m, 9 H) 7.12 - 7.24 (m, 2 H) 8.03 (br. s., 1 H) ppm.



245 251 250

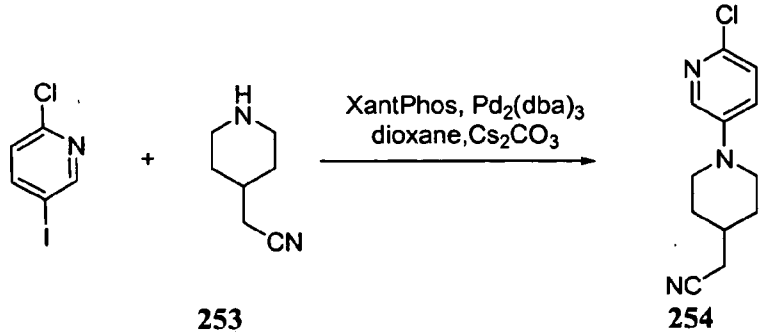
1-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-methyl-2-propanol (250): To tris(dibenzylideneacetone)dipalladium (0) (0.0190 g, 0.0207 mmol), Xantphos (0.0240 g, 0.0415 mmol), cesium carbonate (0.126 g, 0.387 mmol), 1-(4-(6-chloropyridin-3-yl)piperazin-1-yl)-2-methylpropan-2-ol **(251)** (0.0746 g, 0.276 mmol), and compound **245** (0.0750 g, 0.276 mmol) was added degassed dioxane (1.1 mL). The reaction was stirred at 105 °C overnight. After 16 h, the reaction was cooled to room temperature and partitioned between dichloromethane (30 mL) and water. The aqueous was brought to pH 12 w/ 5 N NaOH and extracted further with dichloromethane (15 mL) and 10% methanol in dichloromethane (10 mL). The combined organics were dried with sodium sulfate and concentrated *in vacuo*. Silica gel chromatography (1% to 5 % 2M methanolic NH_3 in DCM) afforded compound **250** (0.135 g, 96.8% yield). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 1.13 (s, 6 H) 1.67 - 1.81 (m, 2 H) 1.96 - 2.06 (m, 2 H) 2.07 - 2.16 (m, 2 H) 2.27 (s, 2 H) 2.33 (d, J= 8.56 Hz, 2 H) 2.65 - 2.74 (m, 4 H) 3.10 - 3.17 (m, 4 H) 4.14 (s, 1 H) 5.46 (quin, J= 9.05 Hz, 1 H) 7.47 (dd, J= 9.17, 2.81 Hz, 0 H) 7.97 - 8.07 (m, 3 H) 8.12 (d, J= 9.05 Hz, 0 H) 9.33 (s, 1 H) 9.90 (s, 1 H) ppm.

EXAMPLE 173



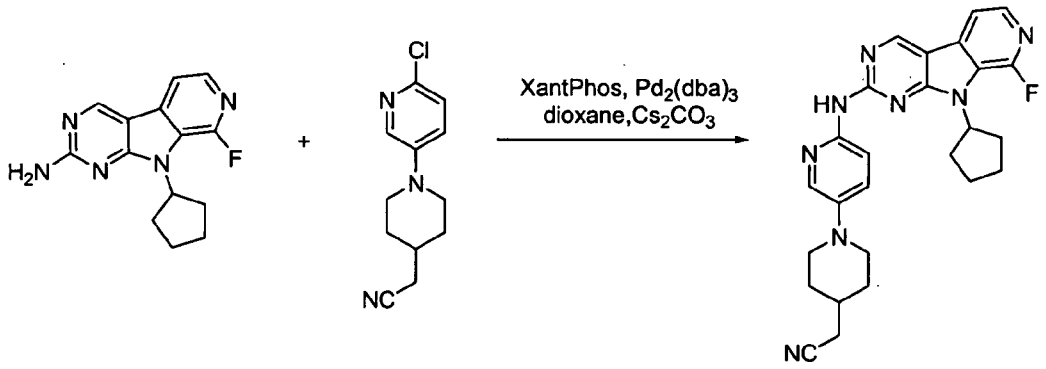
252

(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetonitrile



253 **254**

(1-(6-Chloro-3-pyridinyl)-4-piperidinyl)acetonitrile (254): 2-Chloro-5-iodopyridine (0.278 g, 1.16 mmol), 2-(piperidin-4-yl)acetonitrile hydrochloride (**253**) [Vidaluc, J.-L. et al., Novel *J. Med. Chem.* **1994,** 37, (5), 689-695] (0.186 g, 1.16 mmol), $Pd_2(dba)_3$ (0.0531 g, 0.0580 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0671 g, 0.116 mmol) and cesium carbonate (0.945 g, 2.90 mmol) were combined in a screw cap vial and solvated under argon atmosphere with degassed dioxane (4.5 mL). The reaction was briefly sparged with argon, then sealed and stirred at 105 °C. After 3 h, the reaction was poured into water (30 mL) and extracted with 10% methanol in CH_2Cl_2 (3 x 20 mL). The combined organics were dried with sodium sulfate and concentrated *in vacuo*. Silica gel chromatography (gradient elution 10 to 50% ethyl acetate in hexanes) afforded compound **254** (0.110 g, 40.2% yield). ^{1}H NMR (400 MHz, *DMSO-d6*) δ 1.23 - 1.44 (m, J=11.98, 11.98, 11.84, 3.72 Hz, 2 H) 1.68 - 1.90 (m, 3 H) 2.54 (d, 2 H) 2.75 (td, J=12.42, 2.15 Hz, 2 H) 3.77 (d, J=12.52 Hz, 2 H) 7.26 (d, J=9.00 Hz, 1 H) 7.42 (dd, J=8.80, 3.33 Hz, 1 H) 8.06 (d, J=3.13 Hz, 1 H) ppm.

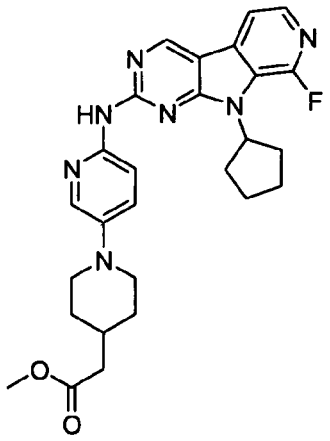


245 **254** **252**

(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetonitrile (252): To tris(dibenzylideneacetone)dipalladium (0) (0.0147 g, 0.0160 mmol), xantphos (0.0186 g, 0.0321 mmol), Cs_2CO_3 (0.0975 g, 0.299 mmol), 2-(1-(6-chloropyridin-3-yl)piperidin-4-yl)acetonitrile (0.0504 g, 0.214 mmol), and compound **245** (0.0580 g, 0.214 mmol) was added degassed (Ar) dioxane (1.0 mL). The reaction was stirred at 105 °C overnight. After 16 h, the reaction was cooled to room temperature and loaded directly onto silica gel. Crystallization from THF and HCl salt formation provided compound **252** (55 mg). ^{1}H NMR (400 MHz, *DMSO-d6*) δ 1.43 (d, J= 10.56 Hz, 2 H) 1.66 - 1.81 (m, 2 H) 1.86 (d, J= 11.35 Hz, 3 H) 2.05 (d, J= 6.26 Hz, 2 H) 2.15 (br. s., 2 H) 2.19 - 2.31 (m, 2 H) 2.59 (d, J= 5.87 Hz, 2 H) 2.85 (t, J= 11.74 Hz, 2 H) 3.75 (d, J= 12.13 Hz, 2 H) 5.53 (quin, J= 9.10 Hz, 1 H) 7.68 (d, J= 9.39 Hz, 1 H) 8.00 (br. s., 1 H) 8.15 (d, J= 5.09 Hz, 1 H)

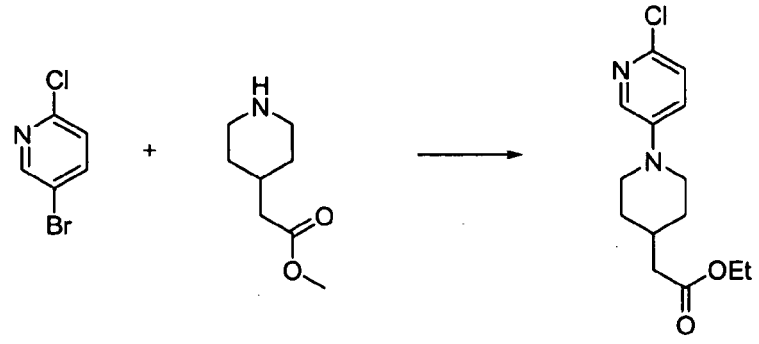
8.20 (dd, J= 9.39, 2.74 Hz, 1 H) 8.30 (dd, J= 4.89, 2.93 Hz, 1 H) 9.55 (s, 1 H) 11.80 (br. s., 1 H) ppm.

EXAMPLE 174



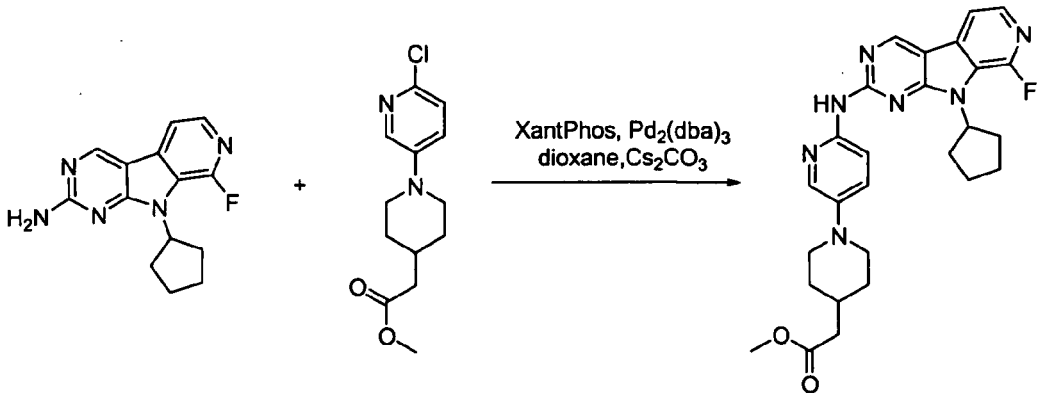
258

Methyl (1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetate



255

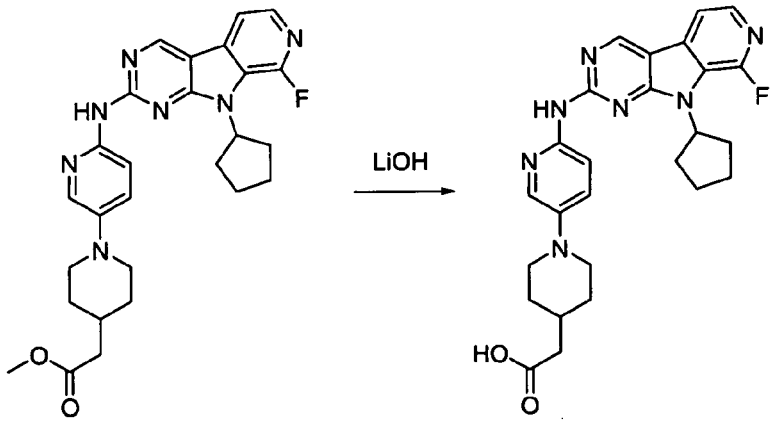
Ethyl (1-(6-chloro-3-pyridinyl)-4-piperidinyl)acetate (255): Compound **255** was prepared using methods described in example 173. ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 1.27 (qd, J=12.26, 3.91 Hz, 2 H) 1.72 (d, J=12.52 Hz, 2 H) 1.78 - 1.93 (m, J=11.05, 7.38, 7.38, 3.72, 3.72 Hz, 1 H) 2.29 (d, J=7.04 Hz, 2 H) 2.72 (td, J=12.32, 2.35 Hz, 2 H) 3.60 (s, 3 H) 3.72 (d, J=12.52 Hz, 2 H) 7.25 (d, J=9.00 Hz, 1 H) 7.40 (dd, J=9.00, 3.13 Hz, 1 H) 8.04 (d, J=3.13 Hz, 1 H) ppm.



245 255 258

Methyl (1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetate (258): Compound **258** was prepared using methods described for Example 173 and isolated as the HCl salt. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 1.39 (br. s., 2 H) 1.71 - 1.86 (m, 4 H) 1.93 (d, J= 8.80 Hz, 1 H) 2.05 (t, J= 6.72 Hz, 2 H) 2.15 (d, J= 7.58 Hz, 2 H) 2.20 - 2.31 (m, 2 H) 2.34 (d, J= 6.85 Hz, 2 H) 2.86 (br. s., 2 H) 3.63 (s, 3 H) 3.71 (d, J= 12.47 Hz, 2 H) 5.54 (quin, J= 9.11 Hz, 1 H) 7.69 (br. s., 1 H), 8.01 (br. s., 1 H) 8.13 - 8.18 (m, 1 H) 8.20 (dd, J= 9.54, 2.20 Hz, 1 H) 8.30 (dd, J= 4.52, 2.81 Hz, 1 H) 9.56 (s, 1 H) ppm. LCMS-ESI (POS), M/Z, M+1: Found 504.2, Calculated 504.2.

EXAMPLE 175

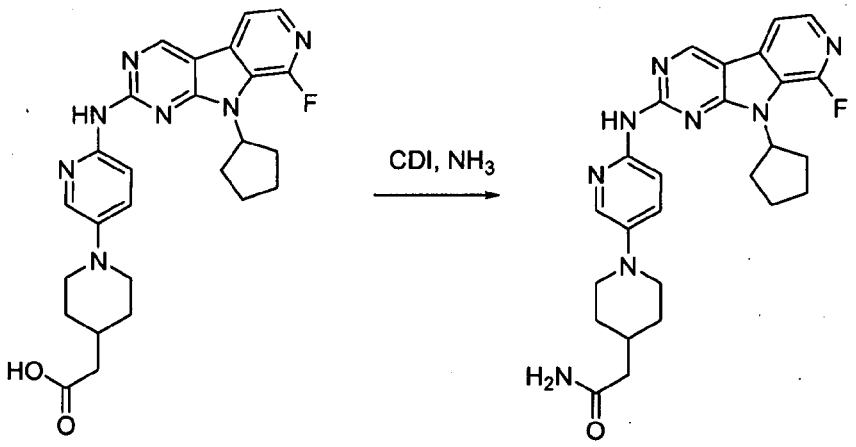


258 259

(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetic acid (259): Compound **258** (0.100 g, 0.20 mmol) was suspended in dioxane (4.8 mL) and methanol (4.8 mL). A solution of lithium hydroxide, monohydrate (0.0092 g, 0.22 mmol) in 2.0 mL of water was added to the suspension. The reaction was warmed to 70 °C. After 1 hour, solvent was removed *in vacuo*. The residue was dissolved in water (3 mL). Dichloromethane was added (1 mL) and the pH was brought to ca.

pH 10 with dilute NaOH. The organics were removed and the aqueous was brought to ca. pH 4 with dilute HCl. The resulting precipitate was filtered. Purification by RP-HPLC on C18 column (10-90% CH_3CN in water with 0.1% TFA) provided compound **259** (5 mg) as a TFA salt. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 1.28 - 1.41 (m, J= 12.17, 12.01, 12.01, 3.18 Hz, 2 H) 1.68 - 1.94 (m, 5 H) 1.99 - 2.09 (m, 2 H) 2.09 - 2.19 (m, 2 H) 2.21 - 2.34 (m, 4 H) 2.81 (t, J= 11.49 Hz, 2 H) 3.71 (d, J= 12.23 Hz, 2 H) 5.53 (quin, J= 9.11 Hz, 1 H) 7.72 (d, J= 9.05 Hz, 1 H) 7.98 (br. s., 1 H) 8.06 (d, J= 8.56 Hz, 1 H) 8.11 - 8.18 (m, 1 H) 8.25 (dd, J= 4.65, 2.93 Hz, 1 H) 9.51 (s, 1 H) 11.43 (br. s., 1 H) ppm. LCMS-ESI (POS), M/Z, M+1: Found 490.1, Calculated 490.2.

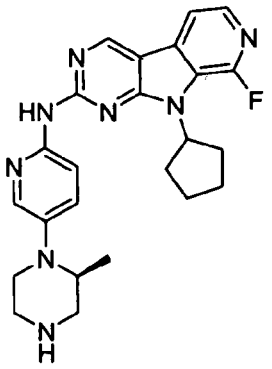
EXAMPLE 176



259 **260**

2-(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetamide (260): Compound **259** (0.077 g, 0.16 mmol) was suspended in DMF (1.5 mL) and 1,1'-carbonyldiimidazole (0.028 g, 0.17 mmol) was added. The reaction was stirred at 70 °C. After 1 h, the suspension was cooled to 0 °C and ammonia gas was sparged therein. The tube was sealed and warmed to 70 °C. After 1 h, the reaction was diluted in water (30 mL) and filtered. Purification by reversed phase HPLC (10-90% acetonitrile in water with 0.1% TFA) provided compound **260** (0.025 g, 26% yield) as a TFA salt. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 1.25 - 1.39 (m, 2 H) 1.70 - 1.84 (m, 4 H) 1.89 (dt, J= 7.27, 3.58 Hz, 1 H) 2.05 (d, J= 7.09 Hz, 4 H) 2.14 (br. s., 2 H) 2.27 (d, J= 8.31 Hz, 2 H) 2.80 (t, J= 10.88 Hz, 2 H) 3.70 (d, J= 12.23 Hz, 2 H) 5.52 (quin, J= 9.05 Hz, 1 H) 6.80 (br. s., 1 H) 7.31 (br. s., 1 H) 7.74 (br. s., 1 H) 7.98 (br. s., 1 H) 8.05 (br. s., 1 H) 8.13 (d, J= 3.91 Hz, 1 H) 8.21 - 8.28 (m, 1 H) 9.51 (s, 1 H) 11.36 (br. s., 1 H) ppm.

EXAMPLE 177

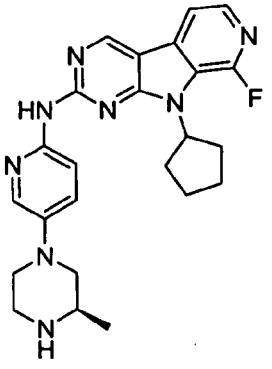


261

9-Cyclopentyl-8-fluoro-N-(5-((2S)-2-methyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Tile compound **261** was prepared using methods described in Example 170 and isolated as the HCl salt. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ 0.91 (d, J= 6.36 Hz, 3 H) 1.43 (s, 9 H) 1.67 - 1.81 (m, 2 H) 2.01 (br. s., 2 H) 2.05 - 2.16 (m, 2 H) 2.33 (br. s., 2 H) 2.91 - 3.02 (m, 1 H) 3.63 (d, J= 11.74 Hz, 1 H) 3.75 - 3.96 (m, 2 H) 5.45 (quin, J= 8.99 Hz, 1 H) 7.49 (dd, J=8.93, 2.57 Hz, 1 H) 7.95 - 8.07 (m, 3 H) 8.14 (d, J= 9.05 Hz, 1 H) 9.33 (s, 1 H) 9.92 (s, 1 H) ppm.

EXAMPLE 178



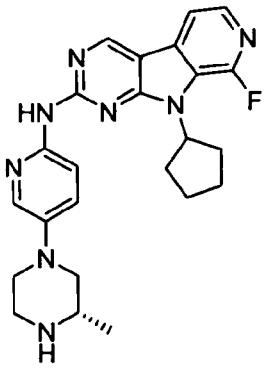
262

9-Cyclopentyl-8-fluoro-N-(5-((3R)-3-methyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **262** was prepared using methods described in example 170 and isolated as the HCl salt. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ 1.35 (d, J= 6.60 Hz, 3 H) 1.62 - 1.86 (m, 2 H) 1.97 - 2.10 (m, 2 H) 2.10 - 2.20 (m, 2 H) 2.21 - 2.34 (m, 2 H) 2.93 (dd, J= 12.47, 11.00 Hz, 1 H) 3.15 (d, J= 6.85 Hz, 2 H) 3.37 - 3.46 (m, 2 H) 3.78 (d, J= 8.31 Hz, 1 H) 3.84 (d, J= 11.98 Hz, 1 H)

5.53 (quin, J= 9.05 Hz, 1 H) 7.82 (d, J= 9.78 Hz, 1 H) 8.09 (s, 2 H) 8.14 (d, J= 3.91 Hz, 1 H) 8.22 - 8.33 (m, 1 H) 9.43 (br. s., 1 H) 9.54 (s, 1 H) 9.61 (br. s., 1 H) 11.54 (br. s., 1 H) ppm.

EXAMPLE 179

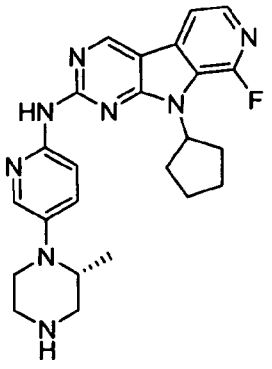


263

9-cyclopentyl-8-fluoro-N-(5-((3S)-3-methyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **263** was prepared using methods described in example 170 and isolated as the HCl salt. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 1.33 (d, J= 6.60 Hz, 3 H) 1.69 - 1.82 (m, 2 H) 2.04 (t, J= 6.72 Hz, 2 H) 2.14 (d, J= 5.87 Hz, 2 H) 2.21 - 2.33 (m, 2 H) 2.91 (dd, J= 12.47, 11.00 Hz, 1 H) 3.08 - 3.20 (m, 2 H) 3.77 (d, J= 9.05 Hz, 1 H) 3.83 (d, J= 11.98 Hz, 1 H) 5.52 (quin, J= 9.05 Hz, 1 H) 7.81 (d, J= 8.80 Hz, 1 H) 8.00 - 8.10 (m, 2 H) 8.13 (d, J= 4.16 Hz, 1 H) 8.22 - 8.29 (m, 1 H) 9.42 (br. s., 1 H) 9.53 (s, 1 H) 9.57 (d, J= 9.29 Hz, 1 H) 11.50 (br. s., 1 H) ppm.

EXAMPLE 180

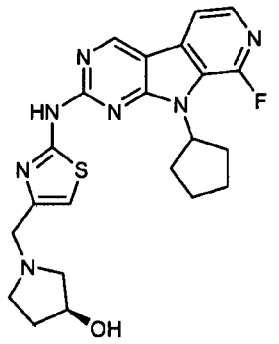


264

9-Cyclopentyl-8-fluoro-*N*-(5-((2R)-2-methyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **264** was prepared using methods described in example 170 and isolated as the HCl salt. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 1.15 (d, J= 6.85 Hz, 3 H) 1.67 - 1.83 (m, 2 H) 1.95 - 2.08 (m, 2 H) 2.15 (br. s., 2 H) 2.25 (d, J= 6.60 Hz, 2 H) 3.06 - 3.17 (m, 1 H) 3.18 - 3.36 (m, 3 H) 3.45 - 3.54 (m, 1 H) 4.06 - 4.20 (m, 1 H) 5.52 (quin, J= 9.05 Hz, 1 H) 7.80 (d, J= 9.29 Hz, 1 H) 8.01 - 8.12 (m, 2 H) 8.12 - 8.20 (m, 1 H) 8.28 (dd, J= 4.77, 3.06 Hz, 1 H) 9.31 (br. s., 1 H) 9.55 (s, 1 H) 9.74 (br. s., 1 H) 11.69 (br. s., 1 H) ppm.

EXAMPLE 181

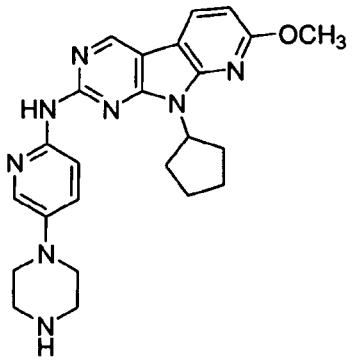


265

(3S)-1-((2-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1,3-thiazol-4-yl)methyl)-3-pyrrolidinol

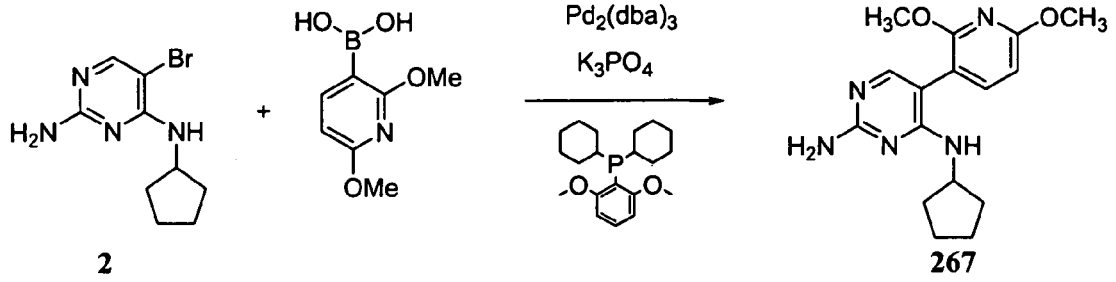
Compound **265** was prepared using methods described in example 170. ^{1}H NMR (500 MHz, *$CDCl_3$*) δ 10.48 (2 H, br. s.), 9.30 (1 H, s), 8.08 (1 H, dd, J= 5.3, 1.8 Hz), 7.79 (1 H, dd, J= 5.1, 2.9 Hz), 6.83 (1 H, s), 5.64 - 5.74 (1 H, m), 4.35 - 4.43 (1 H, m), 3.84 - 3.98 (2 H, m), 3.03 - 3.11 (1 H, m), 2.88 - 2.96 (1 H, m), 2.69 - 2.77 (1 H, m), 2.41 - 2.59 (3 H, m), 2.11 - 2.29 (5 H, m), 1.76 - 1.94 (3 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 454.1.

EXAMPLE 182



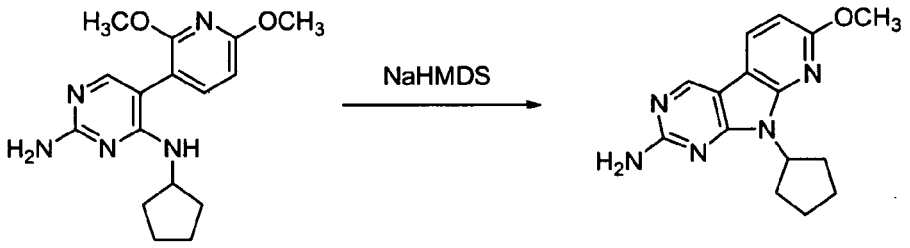
266

9-Cyclopentyl-7-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



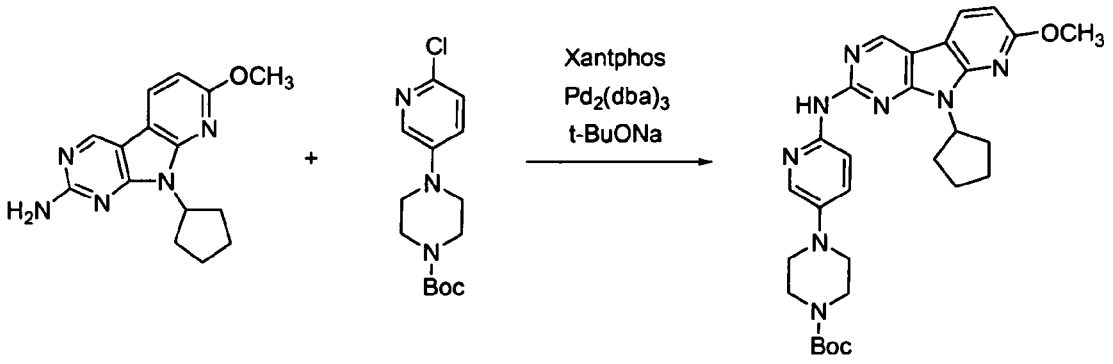
2 267

N4-Cyclopentyl-5-(2,6-dimethoxypyridin-3-yl)pyrimidine-2,4-diamine (267): Compound **2** (2.00 g, 7.78 mmol), 2,6-dimethoxypyridin-3-ylboronic acid (2.13 g, 11.7 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.214 g, 0.233 mmol), and dicyclohexyl(2,6-dimethoxyphenyl)phosphine (0.156 g, 0.467 mmol), were dissolved in *n*-butanol (2.5 mL). The reaction was purged with argon and and heated at 100°C for 19 hours. The resulting solution was added to 80 mL water and extracted with ethyl acetate (2X 150 mL). The combined organics were dried ($MgSO_4$) and evaporated to give an orange oil. Silica gel chromatography (gradient elution dichloromethane + 2.5% TEA/0-5% methanol) afforded compound **267** as an off-white solid (1.29 g, 53%).



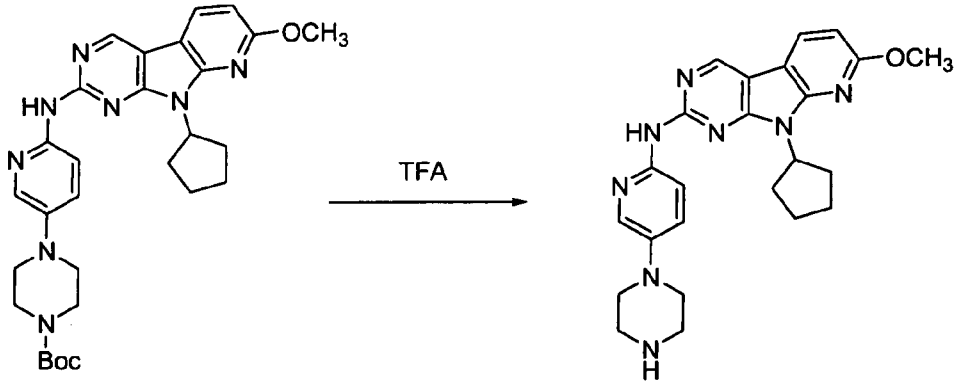
267 268

9-cyclopentyl-7-methoxy-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (268): A 10 mL reaction vessel was charged with N4-cyclopentyl-5-(2,6-dimethoxypyridin-3-yl)pyrimidine-2,4-diamine (**267**) (50.0 mg, 159 μmol) dissolved in dry pyridine (1 mL) under argon. Sodium bis(trimethylsilyl)amide in THF (1.0M, 0.349 mL, 349 μmol) was added and the reaction heated with microwave energy (300W) for 12 minutes at 150°C. The solvent was removed *in vacuo*. Silica gel chromatography of the residue (gradient elution dichloromethane/0-5% methanol) afforded compound **268** as an off-white solid (28 mg, 62%)



268 5 269

tert-Butyl 4-(6-((9-cyclopentyl-7-methoxy-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (269): A 10 mL reaction vessel was charged with compound **268** (100 mg, 353 μmol), compound **5** (126 mg, 424 μmol), and sodium *t*-butoxide (102 mg, 1059 μmol), followed by dioxane (3 mL). The reaction was purged with argon. 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (40.8 mg, 70.6 μmol) and tris(dibenzylideneacetone)dipalladium (0) (32.3 mg, 35.3 μmol) were added and the reaction was again purged with argon. The reaction was heated with microwave energy (300W) at 120°C for 90 minutes. The resulting solution was diluted with ethyl acetate (75 mL) and added to water (75 mL). The layers were separated and the aqueous phase extracted with ethyl acetate (75 mL) and dichloromethane (75 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a brown oil. Silica gel chromatography (gradient elution hexanes/50-100% ethyl acetate) afforded a tan solid, which was recrystallized from boiling ethyl acetate to give compound **269** as a white solid (120 mg, 62%)

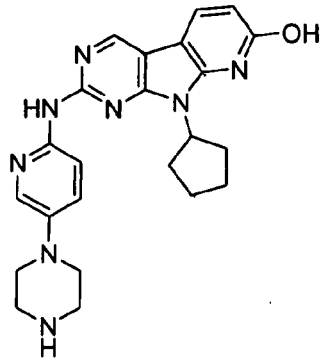


269 266

9-cyclopentyl-7-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[3',2':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (266): Compound **269** (120 mg, 220 μmol) was dissolved in dichloromethane (4 mL). Trifluoroacetic acid (0.400 mL, 2203 μmol) was added and the reaction stirred at room temperature for 70 minutes. The reaction was added to aqueous K_2CO_3 (10%, 30 mL) and extracted thrice with dichloromethane. The combined organics were dried

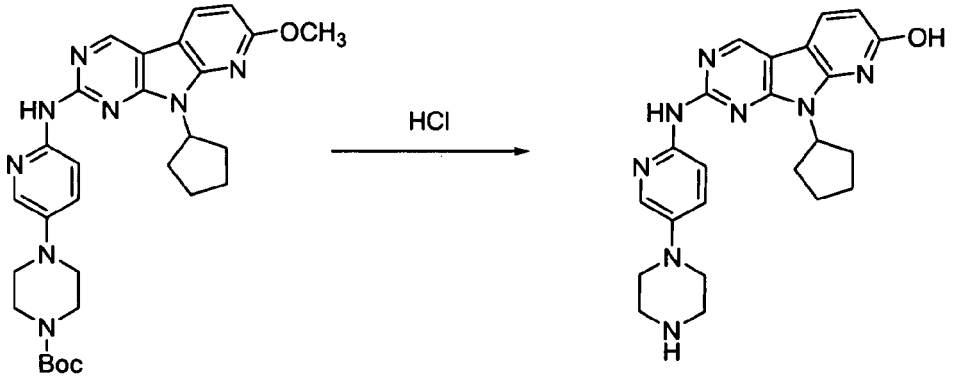
($MgSO_4$) and evaporated to give a pale yellow solid, 82 mg. This residue was dissolved in dioxane (2 mL) and methanol (2 mL) and 1 mL of a saturated solution of HCl in dioxane was added. ethyl acetate (30 mL) followed by diethyl ether (30 mL) were added to precipitate the HCl salt, which was collected and dried *in vacuo* to give compound **266** as a yellow solid (77 mg, 84%). ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 9.24 - 9.36 (m, 4 H) 9.19 (s, 1 H) 8.52 (s, 1 H) 7.97 (s, 1 H) 7.92 - 7.96 (m, 1 H) 7.44 - 7.54 (m, 1 H) 6.83 (d, *J*=8.56 Hz, 1 H) 5.31 - 5.43 (m, 1 H) 3.94 (s, 3 H) 3.33 - 3.41 (m, 4 H) 3.21 (br. s., 4 H) 1.95 - 2.11 (m, 4 H) 1.70 (none, 2 H) ppm.

EXAMPLE 183



270

9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-ol

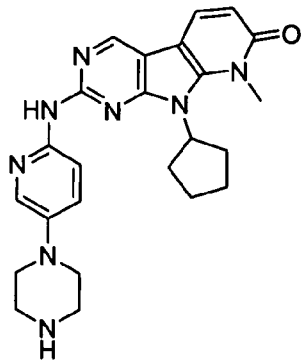


269 **270**

9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[3',2':4,5]-pyrrolo[2,3-d]pyrimidin-7-ol (270): A 10 mL reaction tube vessel was charged with compound **269** (56.0 mg, 103 μmol) and concentrated hydrochloric acid (2.00 mL, 103 μmol).). The reaction was heated with microwave energy (300W) at 120°C for 1 hour, then an additional 30 minutes at 140°C. The resulting solution was filtered through a 0.45 μM filter and washed with water. The solvent was removed *in vacuo*, and the residue coevaporated with water (10 mL) and then

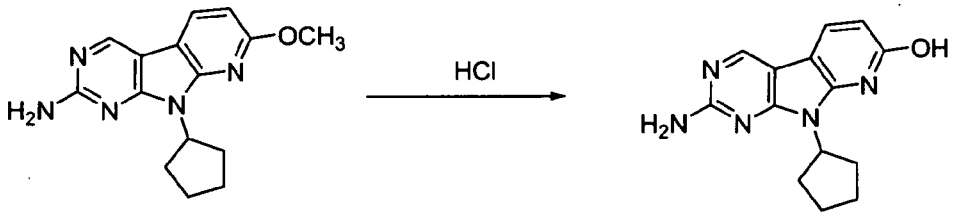
methanol (2X, 10 mL) to give compound **270** as a yellow solid (48 mg). ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 11.63 - 11.91 (m, 2 H) 9.40 (br. s., 4 H) 9.19 (s, 1 H) 8.50 (d, J= 8.61 Hz, 1 H) 8.04 (d, J= 2.74 Hz, 1 H) 7.99 (dd, J= 9.39, 2.74 Hz, 1 H) 7.51 (d, J= 9.39 Hz, 1 H) 6.69 - 6.78 (m, 1 H) 5.35 (quin, J= 8.71 Hz, 1 H) 3.37 - 3.51 (m, 4 H) 3.20 - 3.34 (m, 4 H) 2.06 - 2.18 (m, 2 H) 1.93 - 2.06 (m, 2 H) 1.66 - 1.82 (m, 2 H) ppm.

EXAMPLE 184



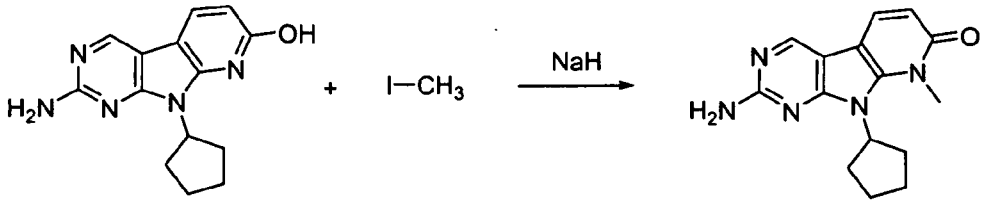
271

9-Cyclopentyl-8-methyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one



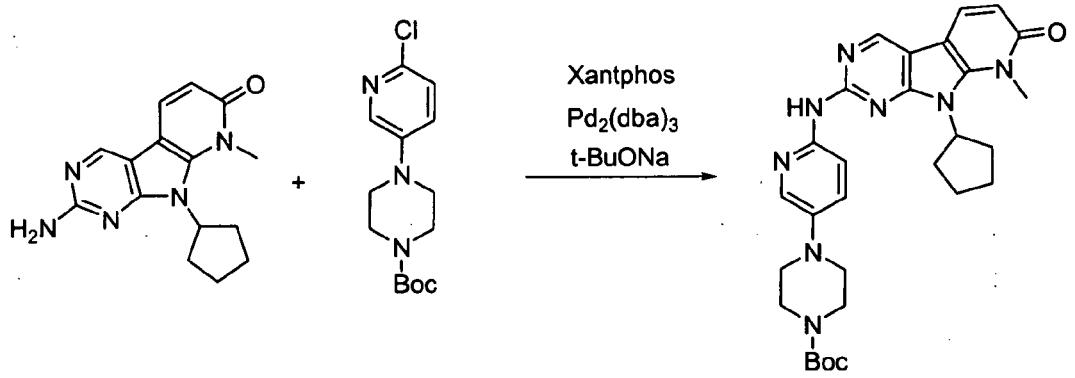
268 **272**

2-Amino-9-cyclopentyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-ol (272): Compound **268** (150 mg, 529 μmol) was dissolved in conc. hydrochloric acid (2 mL). The reaction was heated with microwave energy (300W) for 40 min. at 140°C. The resulting solution was added to aqueous $NaHCO_3$ (20 mL, 50% sat.) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give an orange tar. Silica gel chromatography (gradient elution hexanes + 2.5% TEA/0-100% ethyl acetate+2.5% TEA) afforded compound **272** as a tan solid, 120 mg (84%).



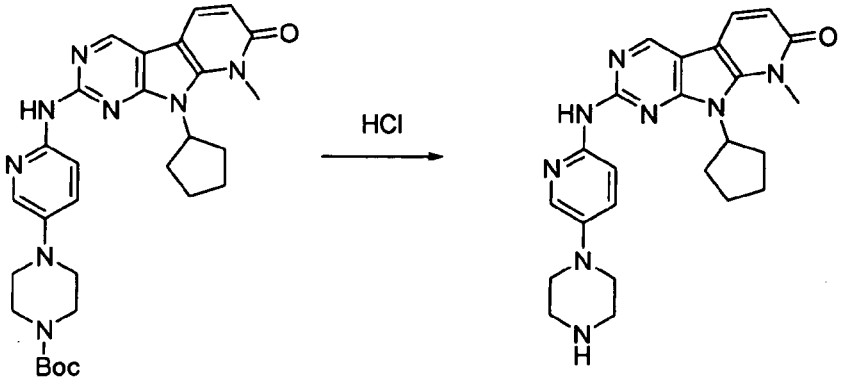
272 **273**

2-Amino-9-cyclopentyl-8-methyl-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one (273): Compound **272** (100 mg,0.37 mmol) was dissolved in dry DMF (1 mL). Sodium hydride, 60% dispersion in oil (16.0 mg, 0.4 mmol) was added and the reaction stirred at 60°C for 20 minutes. Iodomethane (26.5 µl, 423 µmol) was the added and the reaction stirred at 60°C for 2 hr. The solution was allowed to cool and added to water (10 mLl) and aqueous K_2CO_3 (saturated, 2 mL), and extracted with ethyl acetate (2X 30 mL), and dichloromethane+10% methanol (2X 30 mLl). The combined organics were dried ($MgSO_4$) and evaporated to give an orange solid. Silica gel chromatography (gradient elution hexanes + 2.5% TEA/0-70% ethyl acetate+2.5% TEA) afforded compound **273** as a white solid, 64 mg (61%).



273 **5** **274**

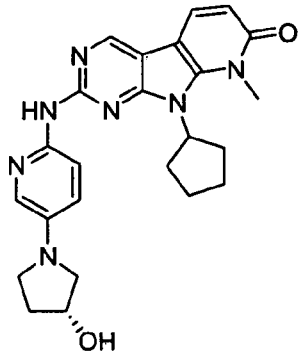
tert-Butyl 4-(6-((9-cyclopentyl-8-methyl-7-oxo-8,9-dihydro-7H-pyrido[3',2':4,5]-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (274): A 10 mL reaction vessel was charged with compound **273** (61.0 mg, 215 µmol), compound **5** (70.5 mg, 237 µmol), and sodium *t*-butoxide (62.1 mg, 646 µmol), followed by dioxane (3 mL). The reaction was purged thoroughly with argon. 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (24.9 mg, 43.1 µmol) and tris(dibenzylideneacetone)dipalladium (0) (19.7 mg, 21.5 µmol) were added, and the reaction was again purged with argon. The reaction was heated with microwave energy (300W) at 120°C for 90 minutes. The resulting solution was diluted with ethyl acetate (75 mL) and added to water (75 mL). The layers were separated layers and the aqueous phase extracted with ethyl acetate (75 mL), followed by dichloromethane (75 mL). The combined organics were dried ($MgSO_4$) and evaporated to give the product as a tan solid. Recrystallization from boiling ethyl acetate gave compound **274** as a white solid (74 mg, 63%).



274 271

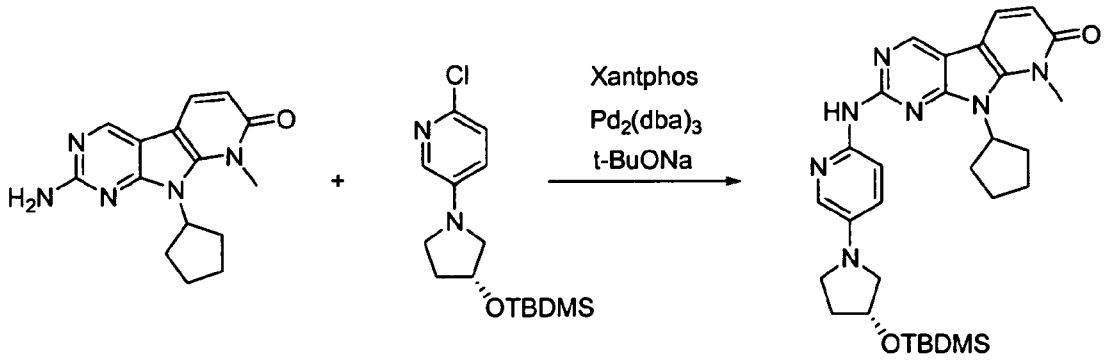
9-Cyclopentyl-8-methyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one (271): Compound **274** (51 mg) was dissolved in 2 mL dioxane. Dioxane (1 mL) saturated at room temperature with HCl was added, followed by 1 mL methanol to aid solution. The reaction was stirred at room temperature for 80 min. The solution was then added dropwise to diethyl ether (8 mL) and the resulting precipitate was collected and dried *in vacuo* to give compound **271** as a yellow solid (26 mg, 62%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 11.75 (br. s., 1 H) 9.36 (br. s., 2 H) 9.20 (s, 1 H) 8.53 (d, J= 8.31 Hz, 1 H) 7.91 - 8.01 (m, 2 H) 7.49 (d, J= 9.29 Hz, 1 H) 6.83 (d, J= 8.56 Hz, 1 H) 5.37 (quin, J= 8.56 Hz, 1 H) 3.35 - 3.43 (m, 5 H) 1.94 - 2.13 (m, 4 H) 1.64 - 1.79 (m, 2 H) ppm.

EXAMPLE 185



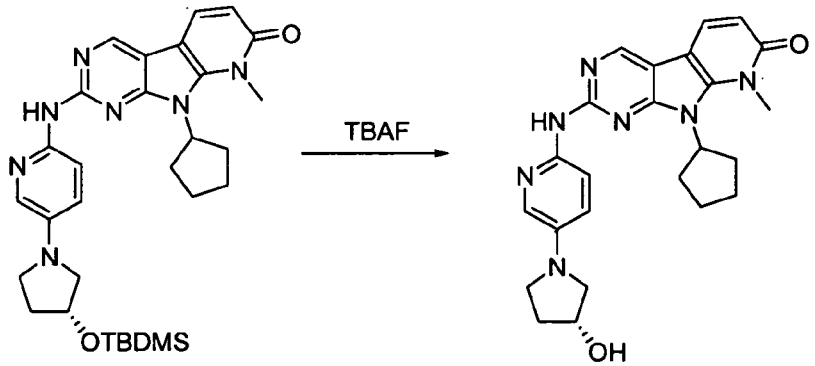
275

9-Cyclopentyl-2-((5-((3R)-3-hydroxy-1-pyrrolidinyl)-2-pyridinyl)amino)-8-methyl-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one



273 276

9-Cyclopentyl-2-((5-((3R)-3-(tert-butyldimethylsilyloxy)pyrrolidin-1-yl)-2-pyridinyl)amino)-8-methyl-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]-pyrimidin-7-one (276): A 10 mL reaction vessel was charged with compound **273** (55 mg, 193 μmol), (R)-5-(3-(*t*-butyldimethylsilyloxy)pyrrolidin-1-yl)-2-chloropyridine (60.3 mg, 193 μmol), tris(dibenzylideneacetone)dipalladium (0) (13 mg, 14 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (17 mg, 29 μmol), and sodium *t*-butoxide (22 mg, 231 μmol) in 2 mL dry dioxane. The reaction was purged with argon and heated with microwave energy (300W) for 2 hours at 120°C. The resulting solution was taken up in ethyl acetate (40 mL) and washed with water (30 mL) , and brine (30 mL). The organics were dried ($MgSO_4$) and evaporated to give a brown oil. Silica gel chromatography (gradient elution hexanes + 2.5% TEA/0-50% ethyl acetate+2.5% TEA) afforded compound **276** as a yellow solid (53 mg, 49%).

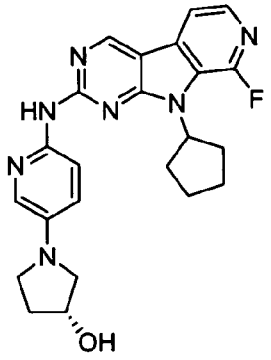


276 275

9-Cyclopentyl-2-((5-((3R)-3-hydroxy-1-pyrrolidinyl)-2-pyridinyl)amino)-8-methyl-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one (275): Compound **276** (53.0 mg, 94.7 μmol) was dissolved in THF (2 mL).). Tetrabutylammonium fluoride, 1.0M in THF (0.500 mL, 500 μmol) was added and the reaction was stirred at room temperature for 4.5 hours. The solvent was evaporated to give an orange oil. Preparative reverse phase HPLC (gradient elution 0.1% TFA in water/10-70% acetonitrile) afforded a yellow solid. This residue

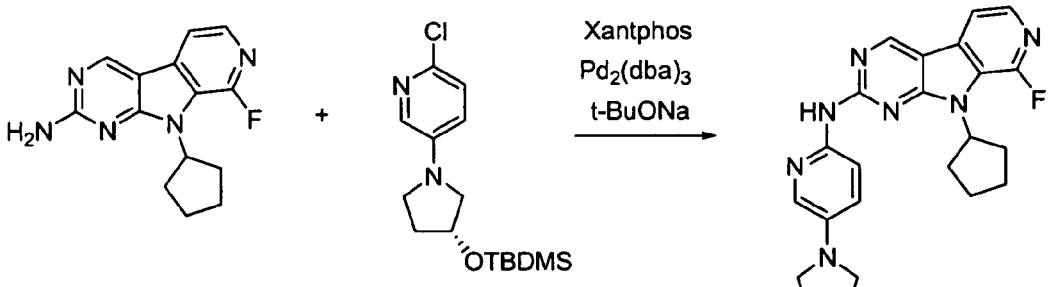
was added to aqueous $NaHCO_3$ (saturated, 10 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow solid. This product was taken up in methanol (2 mL) and 1 mL methanol (saturated at room temperature with HCl) was added. 20 mL diethyl ether was added to precipitate the product, which was washed with ether and dried *in vacuo* to give compound **275** as yellow solid (21 mg, 50%). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 9.21 (s, 2 H) 8.56 (d, J= 8.56 Hz, 2 H) 7.63 (d, J= 2.69 Hz, 4 H) 7.44 - 7.57 (m, 2 H) 6.87 (d, J= 8.56 Hz, 2 H) 5.43 (quin, J= 8.62 Hz, 1 H) 4.47 (br. s., 1 H) 4.00 (s, 3 H) 3.09 - 3.21 (m, 1 H) 2.00 - 2.22 (m, 5 H) 1.90 - 2.04 (m, 1 H) 1.66 - 1.85 (m, 2 H) ppm.

EXAMPLE 186a



277

(3R)-1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-pyrrolidinol

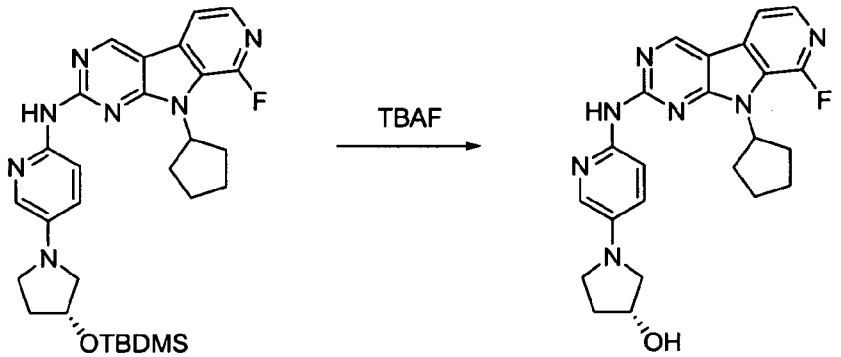


245 278

N-(5-((3R)-3-((tert-butyl(dimethyl)silyl)oxy)-1-pyrrolidinyl)-2-pyridinyl)-9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

(278): A 10 mL reaction vessel was charged with compound **245** (75.0 mg, 276 μmol), (R)-5-(3-(*t*-butyldimethylsilyloxy)pyrrolidin-1-yl)-2-chloropyridine (86.5 mg, 276 μmol), tris(dibenzylideneacetone)dipalladium (0) (19.0 mg, 20.7 μmol), 4,5-bis(diphenylphosphino)-

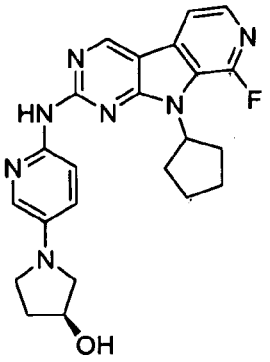
9,9-dimethyl-9H-xanthene (24.0 mg, 41.5 μmol), sodium *t*-butoxide (53.1 mg, 553 μmol), and dioxane (1.5 mL). The reaction was heated with microwave energy (300W) for 2 hours at 120°C. in the resulting solution was added to ethyl acetate (40 mL) and washed with water (30 mL) followed by brine (30 mL). The organic phase was dried ($MgSO_4$) and evaporated to give an orange oil. Silica gel chrmatography (gradient elution 35% ethyl acetate in hexanes) afforded compound **278** as a yellow solid (59 mg, 39%)



278 **277**

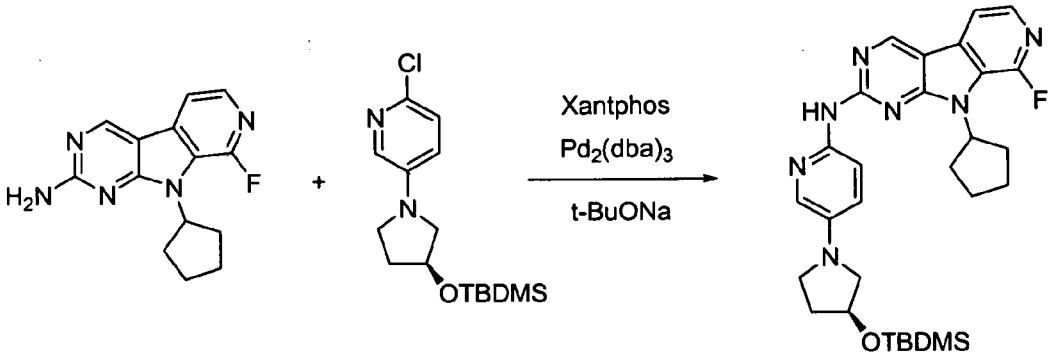
(3R)-1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-pyrrolidinol (277): Compound **278** (58 mg, 106 μmol) was dissolved in THF (2 mL). Tetrabutylammonium fluoride, 1.0M in THF (0.5 mL, 0.500 mmol) was added and the reaction stirred at room temperature for 4 hours. The solvent was removed to give an orange oil. Silica gel chromatography (gradient elution ethyl acetate+2.5% TEA/0-5% methanol) afforded a yellow solid. This residue was taken up in methanol (2 mL) and HCl in ethanol (1.0M, 0.5 mL) was added. Diethyl ether (20 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **277** as a yellow solid (23 mg , 50%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.72 (s, 1 H) 9.25 - 9.35 (m, 1 H) 7.94 - 8.11 (m, 4 H) 7.62 - 7.77 (m, 2 H) 7.05 (dd, *J*=8.93, 2.81 Hz, 1 H) 5.37 - 5.54 (m, 1 H) 4.99 (d, *J*=3.91 Hz, 1 H) 4.44 (br. s., 1 H) 3.46 (dd, *J*=10.03, 4.89 Hz, 2 H) 3.05 - 3.16 (m, 1 H) 2.26 - 2.42 (m, 3 H) 1.96 - 2.20 (m, 8 H) 1.85 - 1.96 (m, 2 H) 1.66 - 1.83 (m, 3 H) ppm.

EXAMPLE 186b



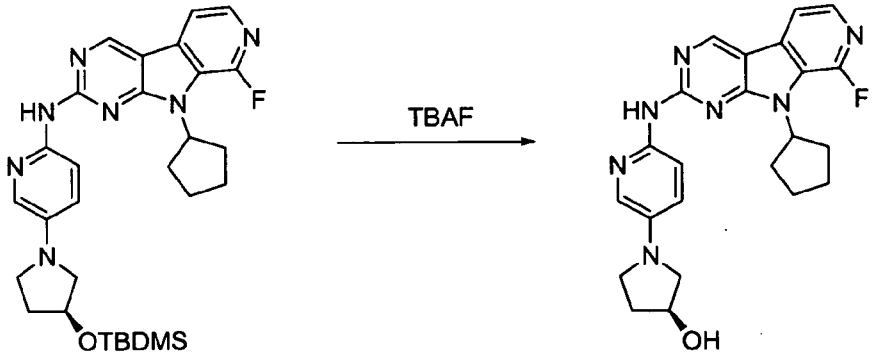
279

(3S)-1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-pyrrolidinol



245 280

N-(5-((3S)-3-((tert-butyl(dimethyl)silyl)oxy)-1-pyrrolidinyl)-2-pyridinyl)-9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (280): Compound **280** was prepared from compound **245** and (S)-5-(3-(tert-butyldimethylsilyloxy)-pyrrolidin-1-yl)-2-chloropyridine using methods described in Example 186a.

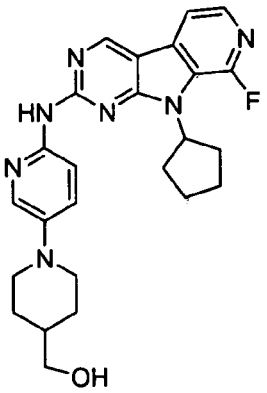


280 279

(3S)-1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-pyrrolidinol (279): Compound **279** was prepared from compound **280** using methods described in Example 186a. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ 9.44 - 9.57

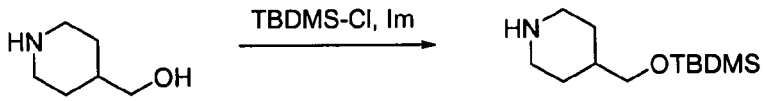
(m, 1 H) 8.22 - 8.33 (m, 1 H) 8.09 - 8.19 (m, 1 H) 7.63 - 7.73 (m, 3 H) 5.45 - 5.59 (m, 1 H) 4.39 - 4.53 (m, 1 H) 3.45 - 3.53 (m, 2 H) 3.39 (none, 3 H) 3.11 - 3.21 (m, 1 H) 3.11 - 3.22 (m, 1 H) 2.20 - 2.34 (m, 2 H) 1.88 - 2.20 (m, 6 H) 1.68 - 1.87 (m, 2 H) ppm

EXAMPLE 187



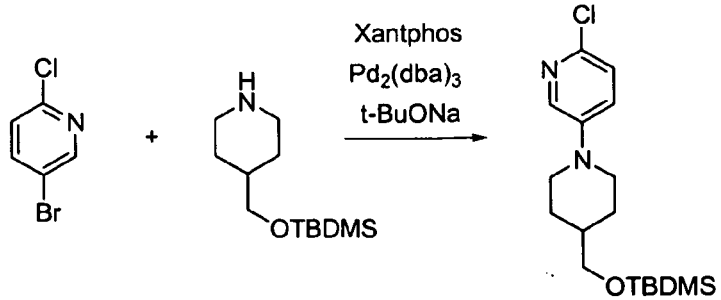
283

(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)methanol



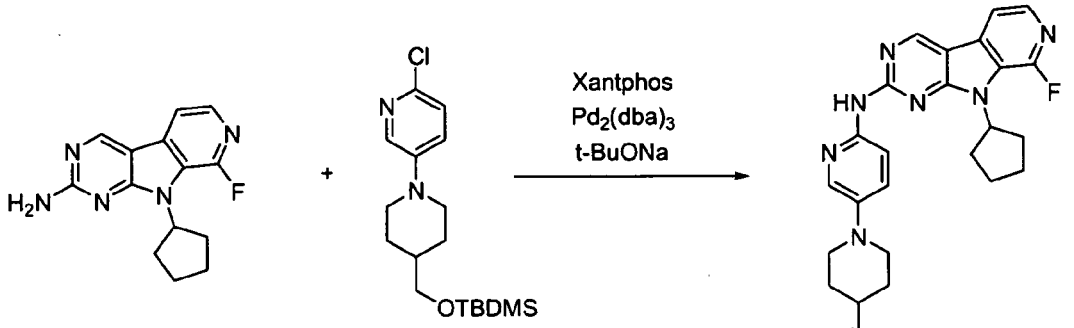
284

4-((*t*-butyldimethylsilyloxy)methyl)piperidine (284): Piperidin-4-ylmethanol (2.50 g, 21.7 mmol), *t*-butylchlorodimethylsilane (4.13 g, 23.9 mmol), and imidazole (1.48 g, 21.7 mmol) were dissolved in dichloromethane (25 mL) and stirred at room temperature for 18 hours. The reaction was added to aqueous $NaHCO_3$ (200 mL, 50% saturated) and extracted with dichloromethane (3X 150 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow oil. Silica gel chromatography (gradient elution dichloromethane+2.5% TEA/0-10% methanol) gave a soft white solid, which was then added to 0.5 M NaOH (100 mL) and extracted with dichloromethane+10% methanol (3X 100 mL). The combined organics were dried ($MgSO_4$) and evaporated to give compound **284** as a pale yellow oil (4.75 g).



284 **281**

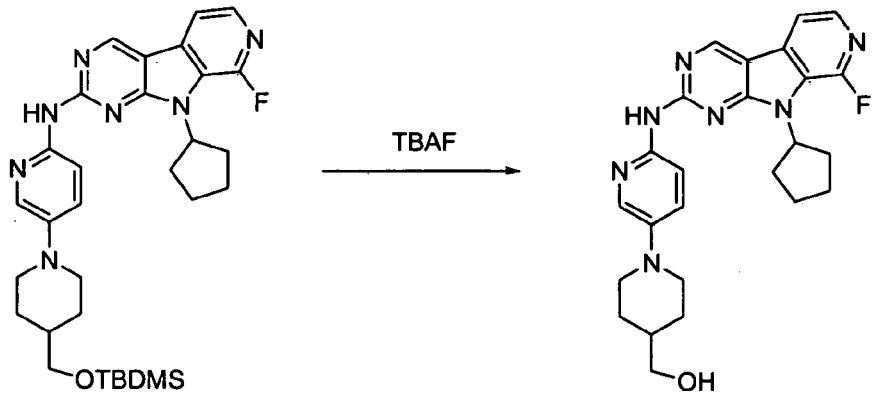
5-(4-((*t*-butyldimethylsilyloxy)methyl)piperidin-1-yl)-2-chloropyridine (281): 5-Bromo-2-chloropyridine (1.00 g, 5.20 mmol), 4-((*t*-butyldimethylsilyloxy)-methyl)piperidine (**284**), (1.19 g, 5.20 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.0952 g, 0.104 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.180 g, 0.312 mmol), and sodium *t*-butoxide (0.749 g, 7.79 mmol) were dissolved in 40 mL dioxane under argon. . The reaction was heated at 80°C for 17 hours. The resulting solution was cooled an taken up in ethyl acetate (125 mL) and washed with aqueous K_2CO_3, (10%, 100 mL) water (100 mLl), and brine (100 mL). The organic phase was dried ($MgSO_4$) and evaporated to give an orange oil. Silica gel chromatography (gradient elution hexanes/0-10% ethyl acetate) afforded compound **281** as a white solid (158 mg , 9%).



245 **281** **282**

N-(5-(4-(((tert-Butyl(dimethyl)silyl)oxy)methyl)-1-piperidinyl)-2-pyridinyl)-9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

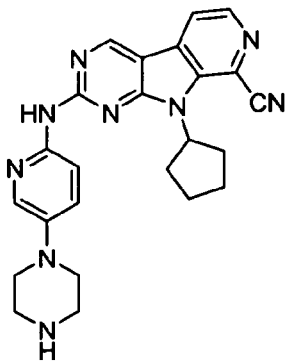
(282): A 10 mL reaction vessel was charged with compound **245** (100 mg, 369 μmol), compound **281** (126 mg, 369 μmol), tris(dibenzylideneacetone)dipalladium (0) (25.3 mg, 27.6 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (32.0 mg, 55.3 μmol), sodium *t*-butoxide (70.8 mg, 737 μmol), and dioxane (1.5 mL).). The reaction was purged with argon and heated with microwave energy (300W) for 2 hours at 120°C. The resulting solution was added to ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$) and evaporated to give an orange oil. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-35% ethyl acetate+2.5% TEA) afforded compound **282** as a yellow solid (121 mg, 57%).



282 283

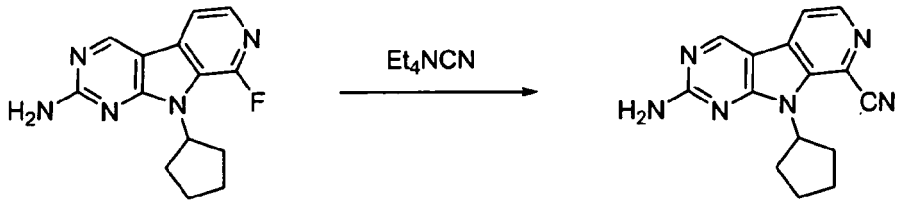
(1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-amino)-3-pyridinyl)-4-piperidinyl)methanol (283): Compound **282** (118 mg, 205 μmol) was dissolved in dry THF (3 mL). Tetrabutylammonium fluoride, 1.0M in THF (0.75 mL, 750 μmol) was added and the reaction was stirred at room temperature for 80 minutes. The resulting solution was added to aqueous K_2CO_3 (10%, 30 mL) and extracted with dichloromethane+10% methanol (2X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give an orange oil. Silica gel chromatography (gradient elution ethyl acetate+2.5% TEA/0-5% methanol) afforded a yellow solid. This residue was taken up in methanol (1.5 mL) and HCl in ethanol (1.0M, 0.5 mL) was added. Diethyl ether (20 mL) was added to precipitate the product as a yellow solid, which was filtered and dried *in vacuo* to give compound **283** as a yellow solid (26 mg, 27%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.87 (s, 1 H) 9.27 - 9.37 (m, 1 H) 8.11 (d, J= 9.05 Hz, 1 H) 7.99 - 8.06 (m, 4 H) 7.48 (dd, J= 9.17, 2.81 Hz, 1 H) 5.46 (quin, J= 9.11 Hz, 1 H) 4.50 (t, J= 5.26 Hz, 2 H) 3.70 (d, J= 11.98 Hz, 2 H) 2.61 - 2.71 (m, 2 H) 2.35 (d, J= 12.72 Hz, 2 H) 2.10 (br. s., 2 H) 1.95 - 2.06 (m, 2 H) 1.77 (t, 4 H) 1.45 - 1.59 (m, 1 H) 1.28 (qd, J= 12.23, 3.67 Hz, 2 H) ppm.

EXAMPLE 188



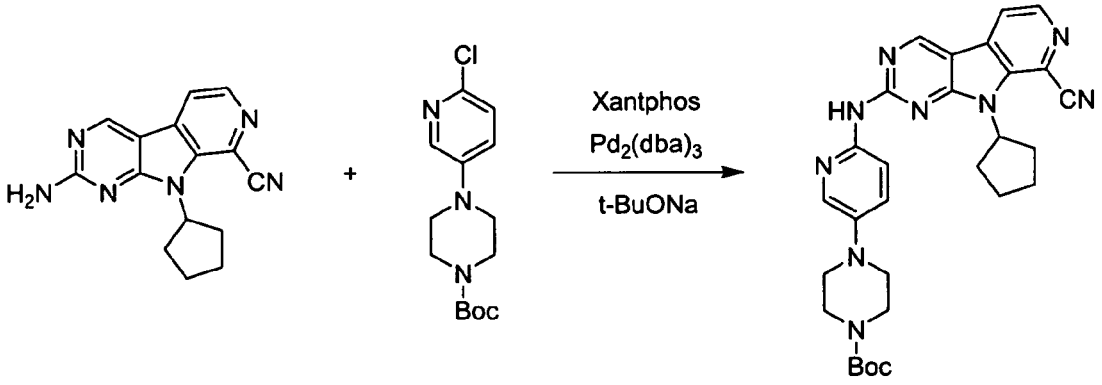
286

9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidine-8-carbonitrile



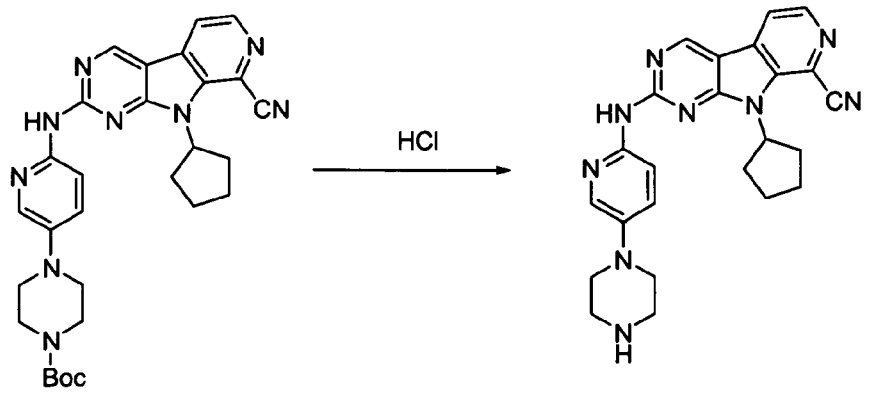
245 287

8-Cyano-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (287): Compound **245** (150 mg, 553 μmol) and tetraethylammonium cyanide (130 mg, 829 μmol) were dissolved in DMSO (3 mL) and heated at 150°C for 5.5 hours. The reaction was cooled and taken up in ethyl acetate (40 mL). This solution was washed with aqueous K_2CO_3 (30 mL), water (30 mL), and brine (30 mL). The organic phase was dried ($MgSO_4$) and evaporated to give an orange solid. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-70% ethyl acetate+2.5% TEA) afforded compound **287** as a tan solid (104 mg, 68%).



287 5 288

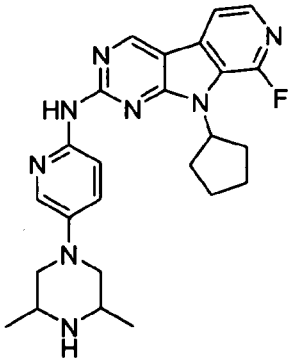
tert-Butyl 4-(6-((8-cyano-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (288): A 10 mL reaction vessel was charged with compound **287** (75.0 mg, 269 μmol), compound **5** (80.2 mg 269 μmol), tris(dibenzylideneacetone)dipalladium (0) (19.7 mg, 21.6 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (24.9 mg, 43.1 μmol), sodium *t*-butoxide (51.8 mg, 539 μmol), and dioxane (2.5 mL). The reaction was purged with argon and heated with microwave energy (300W) for 2 hours at 120°C. The solvent was evaporated *in vacuo*. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA/0-5% methanol) afforded compound **288** as a yellow solid (44 mg, 30%).



288 286

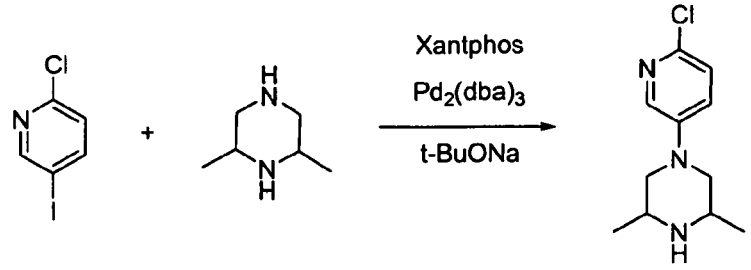
9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidine-8-carbonitrile (286): Compound **288** (44.0 mg, 81.5 μmol) was suspended in 3 mL methanol. Mmethanol saturated at room temperature with HCl (1 mL) was added, and the reaction stirred at room temperature for 2.5 hours. The solventswere removed *in vacuo*. The residue was taken up in methanol (10 mL) and stripped again to give compound **286** as a yellow solid (37 mg, 91%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.68 - 1.80 (m, 2 H) 2.01 - 2.20 (m, 4 H) 2.64 (none, 2 H) 3.25 - 3.34 (m, 4 H) 3.34 - 3.44 (m, 5 H) 5.62 - 5.73 (m, 1 H) 7.60 - 7.73 (m, 1 H) 7.98 - 8.07 (m, 1 H) 8.09 - 8.16 (m, 1 H) 8.39 - 8.48 (m, 1 H) 8.58 - 8.65 (m, 1 H) 8.67 - 8.80 (m, 2 H) 9.40 - 9.49 (m, 1 H) 10.32 - 10.51 (m, 1 H) ppm.

EXAMPLE 189



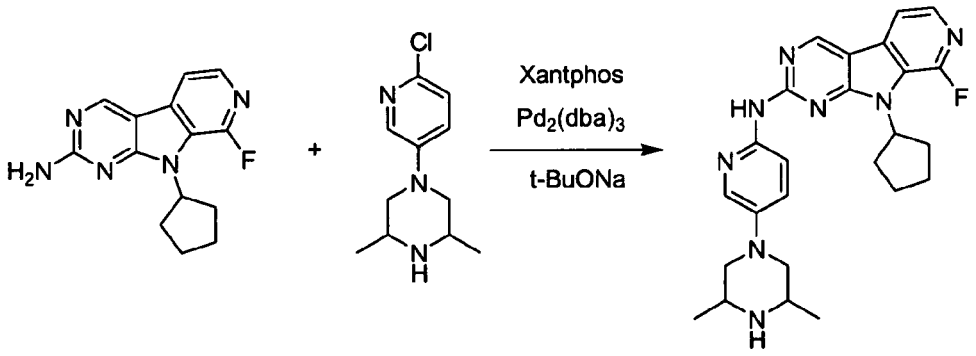
289

9-Cyclopentyl-N-(5-(3,5-dimethyl-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



290

1-(6-chloropyridin-3-yl)-3,5-dimethylpiperazine (290): 2-chloro-5-iodopyridine (1.00 g, 4176 μmol), 2,6-dimethylpiperidine (477 mg, 4.18 mmol) , tris(dibenzylideneacetone)-dipalladium (0) (191 mg, 209 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (242 mg, 418 μmol), and sodium *t*-butoxide (803 mg, 8.35 mmol) were dissolved in 20 mL dioxane. The reaction was purged with argon and heated at 80°C for 4.5 hours. The solvent was removed *in vacuo*. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA/0-5% methanol) afforded compound **290** as an orange solid (545 mg, 58%).

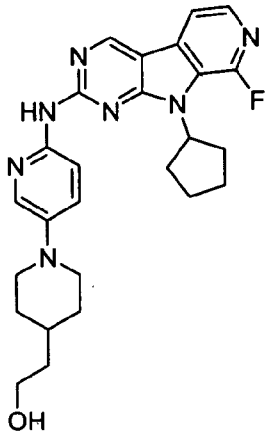


245 **290** **289**

9-Cyclopentyl-N-(5-(3,5-dimethyl-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (289): A 10 mL reaction vessel was charged with compound **245** (80.0 mg, 295 μmol), 1-(6-chloropyridin-3-yl)-3,5-dimethylpiperazine (66.6 mg, 295 μmol), tris(dibenzylideneacetone)dipalladium (0) (20.3 mg, 22.1 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (25.6 mg, 44.2 μmol), sodium *t*-butoxide (56.7 mg, 590 μmol), and dioxane (2.5 mL). The reaction was purged with argon and heated with microwave energy (300W) for 3.5 hours at 120°C. The reaction was taken up in ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$) and evaporated to give an orange oil. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA, 0-8% methanol) afforded a yellow solid. This residue was taken up in 2 mL methanol (2 mL) and 1M ethanolic HCl (1 mL) was added, followed by the addition of diethyl ether (20 mL).

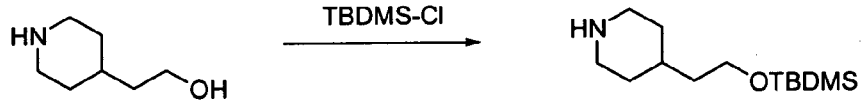
The resulting precipitate was collected and dried *in vacuo* to give compound **289** as a yellow solid (91 mg, 67%) ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.54 - 9.67 (m, 2 H) 9.47 - 9.54 (m, 1 H) 9.05 - 9.23 (m, 1 H) 8.19 - 8.30 (m, 1 H) 8.06 - 8.17 (m, 3 H) 7.94 - 8.04 (m, 1 H) 7.81 - 7.94 (m, 1 H) 5.45 - 5.58 (m, 1 H) 3.81 - 3.94 (m, 2 H) 3.34 - 3.48 (m, 2 H) 2.75 - 2.91 (m, 2 H) 2.23 - 2.35 (m, 2 H) 2.10 - 2.20 (m, 2 H) 2.05 (none, 2 H) 1.68 - 1.86 (m, 2 H) 1.34 (d, *J*=6.60 Hz, 7 H) ppm.

EXAMPLE 190



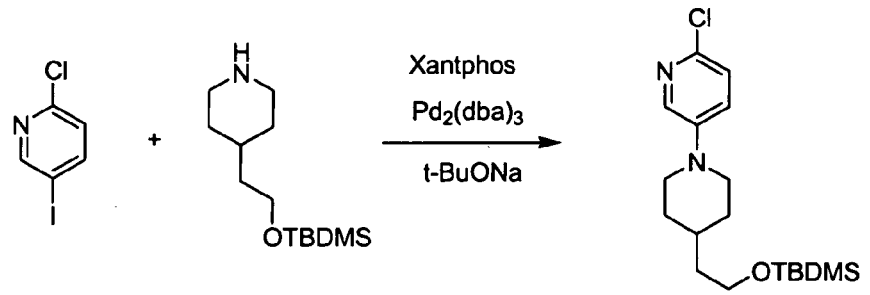
291

2-(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)ethanol



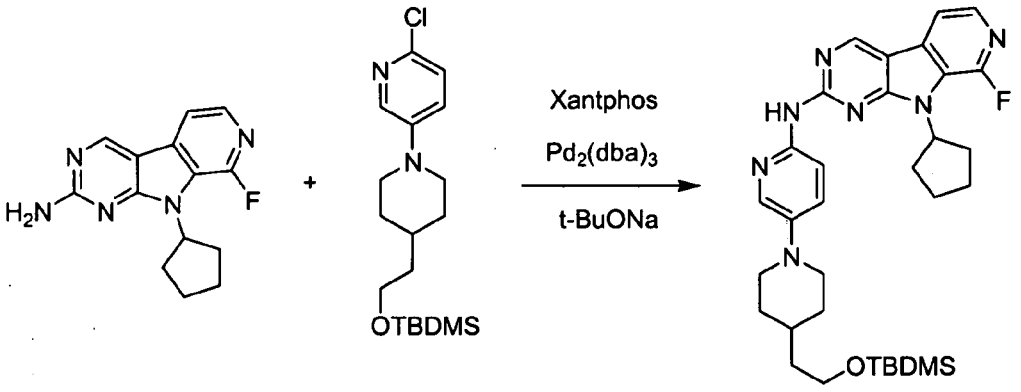
292

4-(2-(*t*-Butyldimethylsilyloxy)ethyl)piperidine (292): 2-(piperidin-4-yl)ethanol (2.00 g, 15.5 mmol), *t*-butylchlorodimethylsilane (2.57 g, 17.0 mmol), and imidazole (1.05 g, 15.5 mmol) were taken up in dichloromethane (15 mL) and stirred for 22 hours. . This solution was added to aqueous K_2CO_3 (80 mL) and extracted with dichloromethane (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a pale yellow oil. Silica gel chromatography (gradient elution dichloromethane+2.5% TEA/0-10% methanol) afforded a white solid. This solid was added to aqueous K_2CO_3 (60 mL) and extracted with dichloromethane+10% methanol (3X 30 mL), the organics dried ($MgSO_4$) and evaporated to give compound **292** as a yellow oil (3.24 g, 86%).



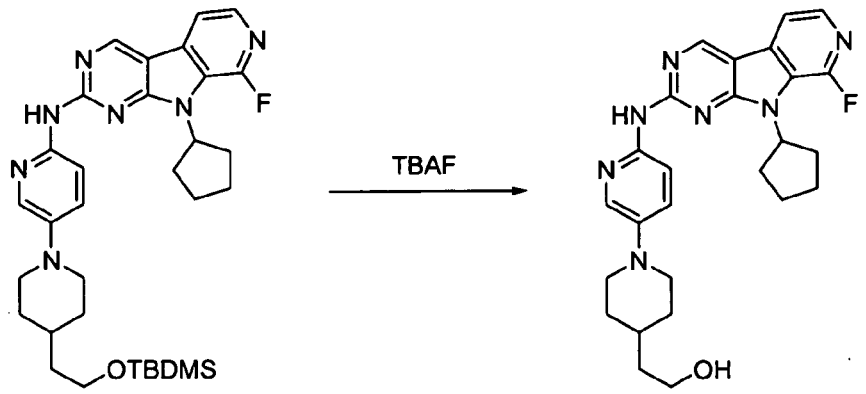
292 293

5-(4-(2-(*t*-Butyldimethylsilyloxy)ethyl)piperidin-1-yl)-2-chloropyridine (293): 2-chloro-5-iodopyridine (1.00 g, 4.18 mmol), compound **292** (1.02 g, 4.18 mmol), Tris(dibenzylideneacetone)dipalladium (0) (0.191 g, 0.209 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.242 g, 0.418 mmol), and sodium *t*-butoxide (0.803 g, 8.35 mmol) were dissolved in 20 mL dioxane. The reaction was purged with argon and heated at 80°C for 16 hours. The solvent was removed *in vacuo* and silica gel chromatography (gradient elution hexanes/0-10% ethyl acetate) afforded compound **293** as a beige solid (597 mg, 40%).



245 293 294

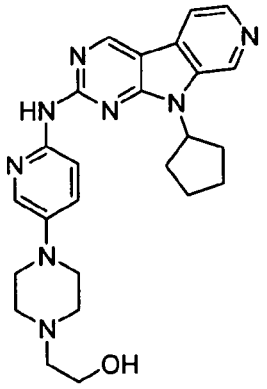
N-(5-(4-(2-((tert-butyl(dimethyl)silyl)oxy)ethyl)-1-piperidinyl)-2-pyridinyl)-9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (294): A 10 mL microwave reaction tube was charged with compound **245** (80.0 mg, 295 µmol), 5-(4-(2-(*t*-butyldimethylsilyloxy)ethyl)piperidin-1-yl)-2-chloropyridine (**293**) (105 mg, 295 µmol), tris(dibenzylideneacetone)dipalladium (0) (20.3 mg, 22.1 µmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (25.6 mg, 44.2 µmol), sodium t-butoxide (56.7 mg, 590 µmol), and dioxane (3 mL). The reaction was purged with argon and heated with microwave energy (300W) for 3.5 hours at 120°C. The reaction was taken up in ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$) and evaporated to give an orange oil. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-100% ethyl acetate+2.5% TEA) afforded compound **294** as a yellow solid (113 mg, 65%).



294 291

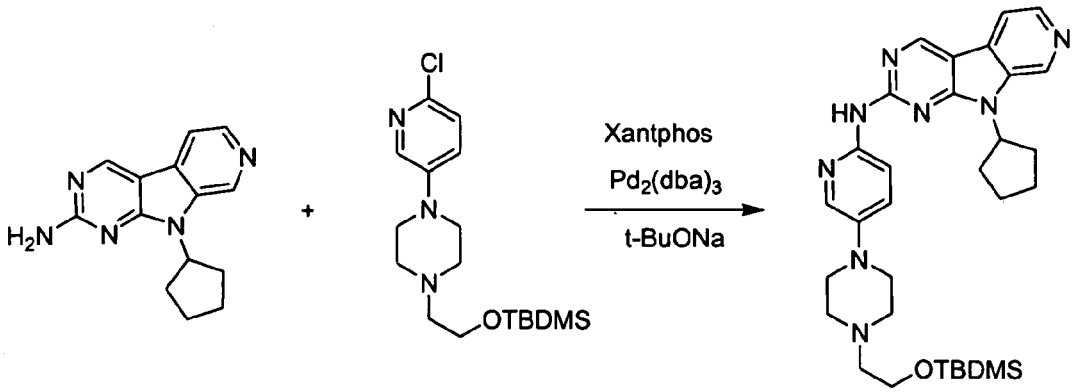
2-(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)ethanol (291): Compound **294** (78 mg, 132 μmol) was dissolved in dry THF (3 mL). Tetrabutylammonium fluoride, 1.0M in THF (1.00 mL, 1.00 mmol) was added and the reaction stirred at room temperature for 4 hours. The solvent was removed *in vacuo* and silica gel chromatography (gradient elution hexanes+2.5% /0-100% ethyl acetate+2.5% TEA) afforded compound **291** as a beige solid (44 mg, 70%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 11.60 - 11.85 (m, 2 H) 9.49 (s, 2 H) 8.19 - 8.24 (m, 2 H) 8.13 - 8.19 (m, 2 H) 8.05 - 8.10 (m, 2 H) 7.96 - 8.04 (m, 2 H) 7.61 - 7.71 (m, 2 H) 5.48 (s, 1 H) 3.64 (d, *J*=11.98 Hz, 2 H) 3.44 (t, *J*=6.48 Hz, 2 H) 2.71 - 2.90 (m, 2 H) 2.20 (br. s., 2 H) 2.09 (br. s., 2 H) 2.00 (br. s., 2 H) 1.66 - 1.82 (m, 4 H) 1.52 - 1.66 (m, 1 H) 1.37 (d, *J*=6.60 Hz, 2 H) 1.28 (none, 2 H) ppm.

EXAMPLE 191



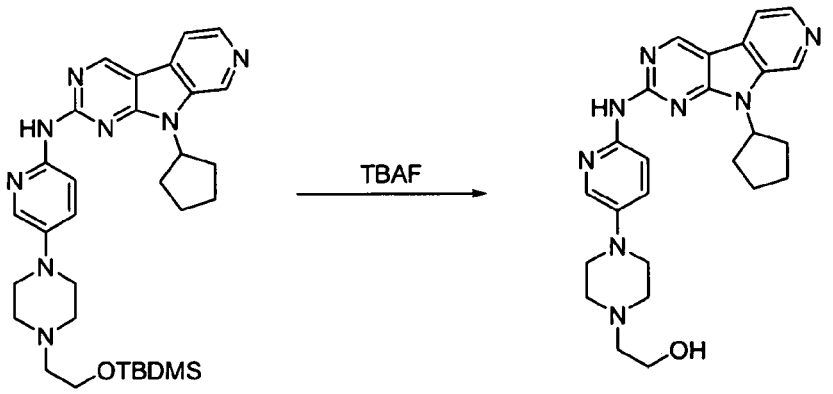
295

2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol



4 247 296

N-(5-(4-(2-((tert-butyl(dimethyl)silyl)oxy)ethyl)-1-piperazinyl)-2-pyridinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (296): A 10 mL reaction vessel was charged with compound **4** (153 mg, 604 μmol), compound **247** (215 mg, 604 μmol), tris(dibenzylideneacetone)-dipalladium (0) (41.5 mg, 45.3 μmol), sodium t-butoxide (69.7 mg, 725 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (52.4 mg, 90.6 μmol), and dioxane (3 mL). The reaction was purged with argon and heated with microwave energy at 120°C for 3.5 hours. The solvent was removed *in vacuo* and silica gel chromatography (gradient elution hexanes+2.5%/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA/0-5% methanol) afforded compound **296** as a yellow solid (85 mg, 25%).

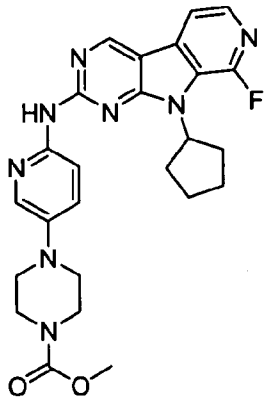


296 295

2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol (295): Compund **296** (85.0 mg, 148 μmol) was dissolved in dry THF (3 mL).). Tetrabutylammonium fluoride, 1.0M in THF (1.00 mL, 1.00mmol) was added and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and silica gel chromatography (gradient elution hexanes+2.5%/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA/0-5% methanol) afforded a yellow solid. This residue was taken up in methanol (3 mL) and 1M ethanolic HCl (1 mL). Diethyl ether (20 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give

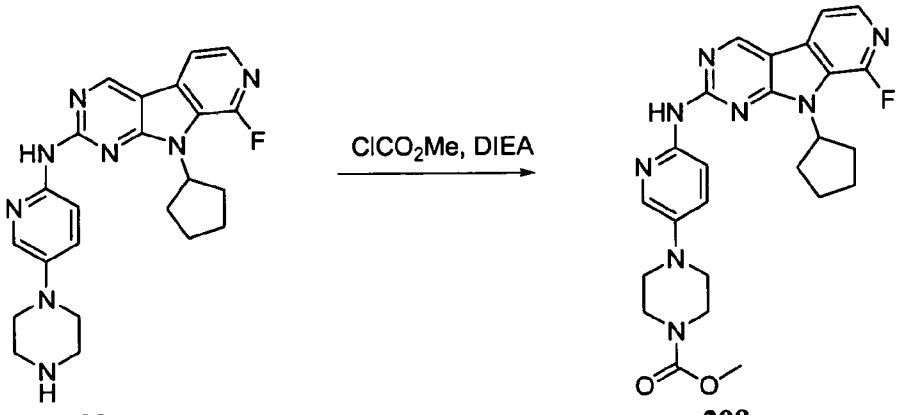
compound **295** as a yellow solid (54 mg, 79%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 10.75 - 10.97 (m, 2 H) 9.70 (s, 2 H) 9.47 (s, 1 H) 8.74 (d, *J*=3.67 Hz, 2 H) 8.16 (d, *J*=2.45 Hz, 1 H) 7.99 - 8.10 (m, 1 H) 7.84 - 7.99 (m, 1 H) 5.30 - 5.52 (m, 1 H) 3.81 - 3.96 (m, 4 H) 3.62 - 3.72 (m, 2 H) 3.20 - 3.36 (m, 6 H) 2.39 - 2.49 (m, 2 H) 2.02 - 2.20 (m, 4 H) 0.88 (d, *J*=6.85 Hz, 2 H) ppm.

EXAMPLE 192



298

Methyl 4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate

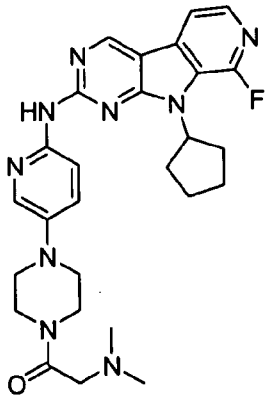


92 **298**

Methyl 4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (298): Compound **92** (68.9 mg, 0.159 mmol) was partially dissolved in DMF (2 mL) and DIEA (0.200 mL, 1.15 mmol).). Methyl chloroformate (0.0122 mL, 0.159 mmol) was added and the reaction stirred at room temperature 16 for hours. The reaction mixture was diluted with dichloromethane+10% methanol (30 mL) and added to aqueous K_2CO_3 (10%, 30 mL). The layers were separated and the aqueous phase extracted with dichloromethane+10% methanol (2X 30 mL) The combined organics were dried ($MgSO_4$) and evaporated to give a yellow oil. Preparative reverse phase

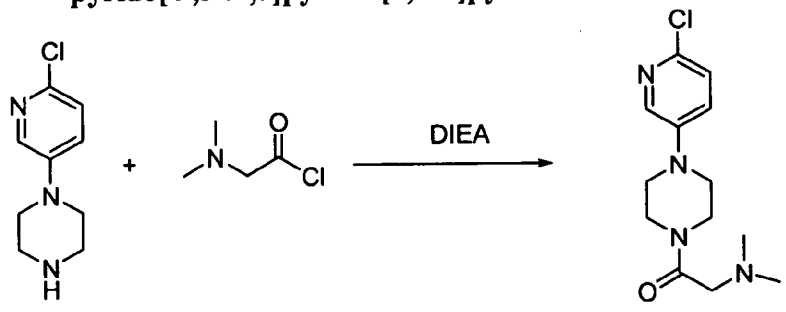
HPLC (gradient elution 0.1% TFA in water/10-70% acetonitrile) afforded a yellow oil. This residue was taken up in aqueous K_2CO_3 and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow solid. This was taken up in methanol (2 mL) and 1M HCl in ethanol (0.5 mL) was added. Diethyl ether (10 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **298** as a yellow solid (24 mg, 31%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.54 - 9.66 (m, 1 H) 8.30 - 8.39 (m, 1 H) 8.12 - 8.25 (m, 2 H) 7.98 - 8.09 (m, 1 H) 7.68 - 7.84 (m, 1 H) 5.51 - 5.65 (m, 1 H) 3.71 (s, 4 H) 3.57 - 3.66 (m, 5 H) 3.20 - 3.34 (m, 5 H) 2.25 - 2.40 (m, 2 H) 2.14 - 2.25 (m, 2 H) 2.02 - 2.14 (m, 2 H) 1.83 (none, 2 H) ppm.

EXAMPLE 193



299

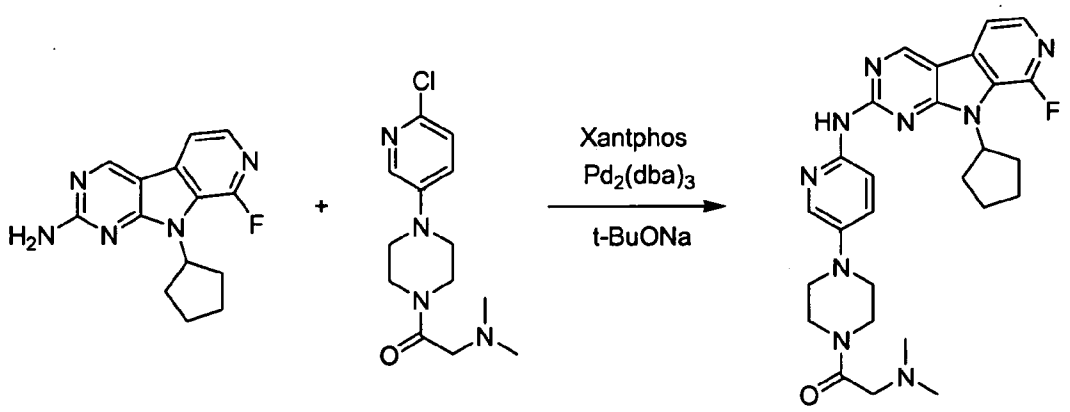
9-Cyclopentyl-N-(5-(4-((dimethylamino)acetyl)-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



300

1-(4-(6-chloropyridin-3-yl)piperazin-1-yl)-2-(dimethylamino)ethanone (300): 1-(6-chloropyridin-3-yl)piperazine (250 mg, 1265 μmol) and dimethylaminoacetyl chloride hydrochloride, 85% (260 mg, 1644 μmol) were dissolved in DMF (6 mL) and DIEA (661 μl, 3794 μmol).). The reaction was stirred at room temperature for 4 hours and then 20 hours at 60°C. The resulting solution was taken up in ethyl acetate 80 mL) and washed with aqueous K_2CO_3 (10%, 70 mL), water (70 mL), and brine (70 mL). The organic phase was dried ($MgSO_4$) and evaporated to give a brown oil. Silica gel chromatography (gradient elution

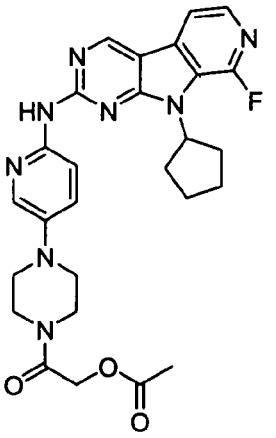
dichloromethane/0-10% 2M NH_3 in methanol) afforded compound **300** as an orange tar (174 mg, 49%).



245 **300** **299**

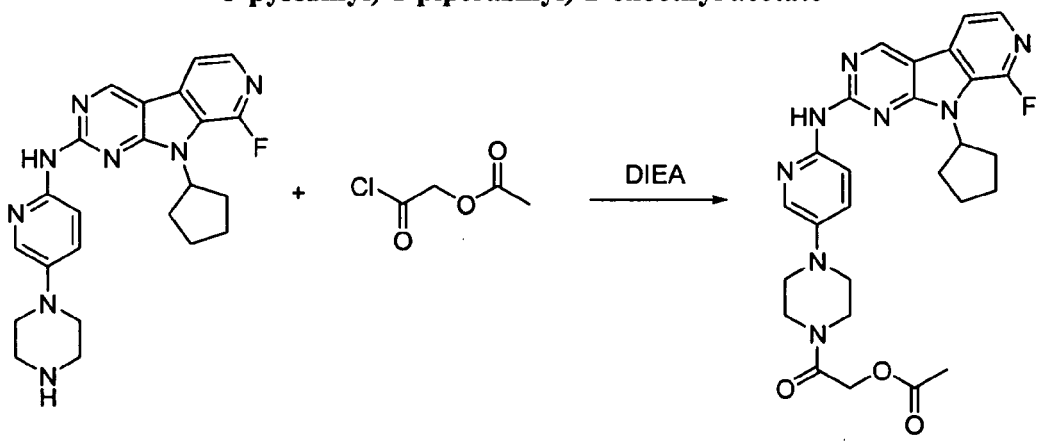
9-Cyclopentyl-N-(5-(4-((dimethylamino)acetyl)-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (299): A 10 mL reaction vessel was charged with compound **245** (100 mg, 369 μmol), compound **300** (109 mg, 387 μmol), tris(dibenzylideneacetone)dipalladium (0) (25.3 mg, 27.6 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (32.0 mg, 55.3 μmol), sodium *t*-butoxide (70.8 mg, 737 μmol), and dioxane (2.5 mL). The reaction was purged with argon and heated with microwave energy (300W) for 2.5 hours at 120°C. The reaction was added to aqueous K_2CO_3 (10 %, 30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give an orange oil. Preparative reverse phase HPLC (gradient elution 0.1% TFA in water/10-70% acetonitrile) afforded. a yellow oil. This residue was taken up in aqueous K_2CO_3 (30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow solid. This was taken up in methanol (2 mL) and 1M HCl in ethanol (0.5 mL) was added. Diethyl ether (10 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **299** as a yellow solid (32 mg, 17%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.43 - 9.61 (m, 1 H) 9.27 - 9.40 (m, 1 H) 8.01 - 8.12 (m, 1 H) 7.91 - 8.01 (m, 1 H) 7.75 - 7.91 (m, 3 H) 7.62 - 7.75 (m, 1 H) 5.27 - 5.42 (m, 1 H) 4.14 - 4.28 (m, 3 H) 3.10 - 3.18 (m, 3 H) 3.06 (none, 3 H) 2.68 (d, *J*=4.65 Hz, 8 H) 2.06 - 2.18 (m, 2 H) 1.93 - 2.06 (m, 2 H) 1.80 - 1.93 (m, 3 H) 1.48 - 1.69 (m, 3 H) ppm.

EXAMPLE 194



301

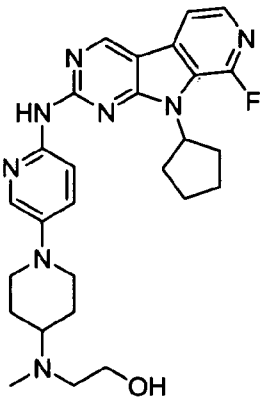
2-(4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethyl acetate



92 301

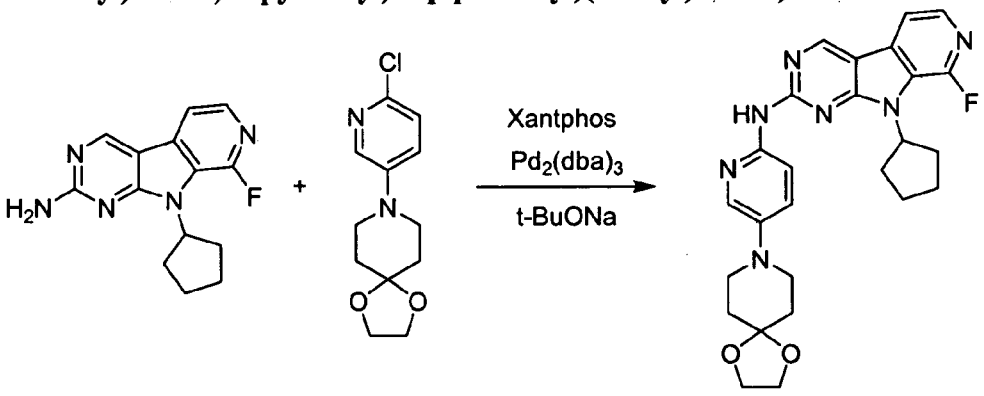
2-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethyl acetate (301): Compound **92** (75.0 mg, 173 μmol) was partially dissolved in DMF (2 mL) and DIEA (0.200 mL, 1148 μmol). Acetoxyacetyl chloride (0.0196 mL, 182 μmol) was added and the reaction was stirred at room temperature 16 for hours. The reaction was added to aqueous K_2CO_3 (10 %, 30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give an orange oil. Preparative reverse phase HPLC (gradient elution 0.1% TFA in water/10-70% acetonitrile) afforded a yellow oil. This residue was taken up in aqueous K_2CO_3 (30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow solid. This was taken up in methanol (2 mL) and 1M HCl in ethanol (0.5 mL) was added. Diethyl ether (10 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **301** as a yellow solid (24 mg, 26%). LCMS M+1 found 533.2 calculated 533.2

EXAMPLE 195



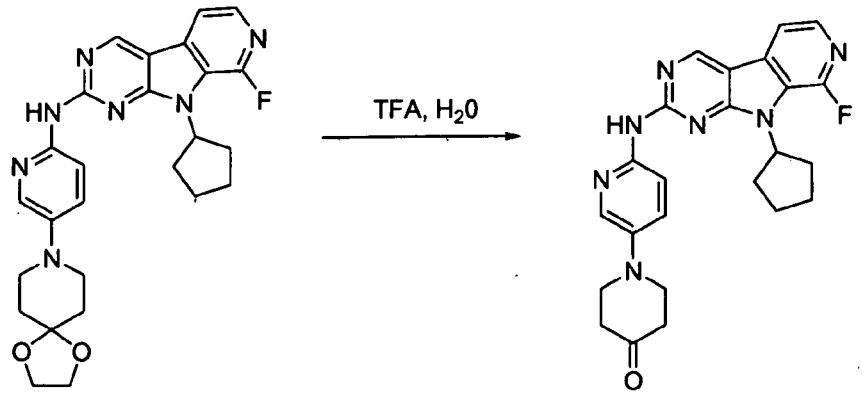
302

2-((1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)(methyl)amino)ethanol



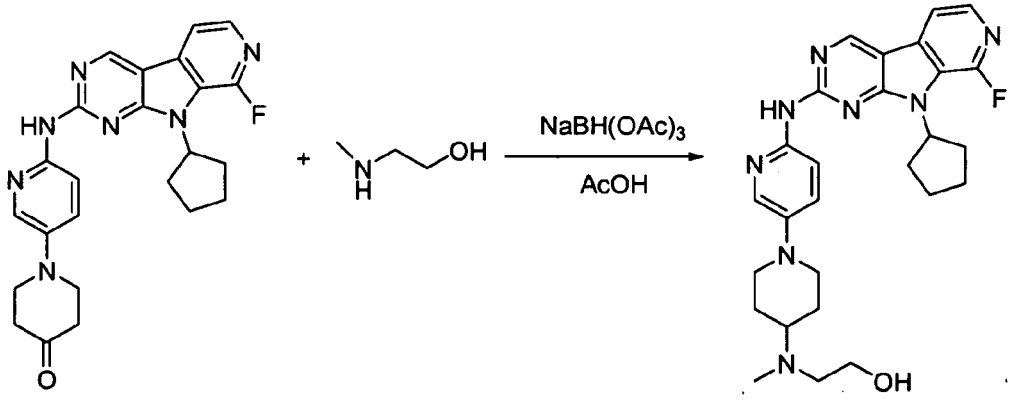
245 303 304

9-Cyclopentyl-N-(5-(1,4-dioxa-8-azaspiro[45]dec-8-yl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (304): A 35 mL reaction vessel was charged with compound **245** (300 mg, 1.10 mmol), compound **303** (see example 436) [Schön, U. et al. *Tetrahedron Lett.* **2007,** 48, (14), 2519-2525] (310 mg, 1.22 mmol), tris(dibenzylideneacetone)dipalladium (0) (75.9 mg, 82.9 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (96.0 mg, 0.166 mmol), sodium *t*-butoxide (213 mg, 2.21 mmol), and dioxane (10 mL). The reaction was purged with argon and heated with microwave energy (300W) for 3 hours at 120°C. The reaction was added to aqueous K_2CO_3 (10%, 30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow solid. Silica gel chromatography (gradient elution hexanes+2.5% TEA/50-100% ethyl acetate+2.5% TEA) afforded compound **304** as a yellow solid (228 mg, 42%).



304 305

1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinone (305): Compound **245** (200 mg, 0.41 mmol) was dissolved in a solution of water (0.150 mL, 8.33 mmol) in trifluoroacetic acid (3.00 mL, 38.9 mmol). The solution was stirred at room temperature for 2 hours and then poured into aqueous K_2CO_3 (10%, 30 mL). This was extracted with dichloromethane+10% methanol (3X 30 mL), and the combined organics were dried ($MgSO_4$) and evaporated to give a yellow solid. Silica gel chromatography (gradient elution hexanes+2.5% TEA/50-100% ethyl acetate+2.5% TEA) afforded compound **305** as a yellow solid (156 mg, 86%).

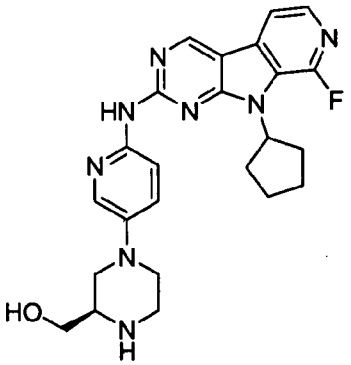


305 302

2-((1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)(methyl)amino)ethanol (302): Compound **305** (75.0 mg, 168 μmol), 2-(methylamino)ethanol (20.2 μl, 253 μmol), sodium triacetoxyborohydride (53.5 mg, 253 μmol), and acetic acid (9.64 μl, 168 μmol) in dichloroethane (2 mL) were stirred at room temperature for 45 hours. . The reaction was diluted with dichloromethane+10% methanol (30 mL) and added to aqueous K_2CO_3 (10%, 30 mL). The layers were separated and the aqueous phase extracted with dichloromethane +10% methanol (2X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow oil. Silica gel chromatography (gradient elution ethyl acetate+2.5% TEA/6% 2M NH_3 in methanol) afforded a yellow solid.

This residue was taken up in methanol (2 mL) and 1M ethanolic HCl (1 mL). Diethyl ether (20 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **302** as a yellow solid (32 mg, 38%). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.48 (s, 1 H) 8.16 - 8.25 (m, 1 H) 8.11 (br. s., 1 H) 8.06 (br. s., 1 H) 7.91 - 8.01 (m, 1 H) 7.83 - 7.92 (m, 1 H) 5.42 - 5.59 (m, 1 H) 3.88 (d, *J*=11.74 Hz, 2 H) 3.81 (br. s., 2 H) 3.58 (s, 3 H) 3.48 (d, *J*=2.93 Hz, 3 H) 3.27 - 3.37 (m, 2 H) 3.18 (s, 1 H) 3.06 - 3.15 (m, 1 H) 2.80 - 2.86 (m, 1 H) 2.78 (d, *J*=4.89 Hz, 3 H) 2.25 - 2.35 (m, 1 H) 2.18 - 2.25 (m, 1 H) 2.14 (d, *J*=9.78 Hz, 2 H) 2.04 (br. s., 2 H) 1.77 (br. s., 3 H) ppm.

EXAMPLE 196



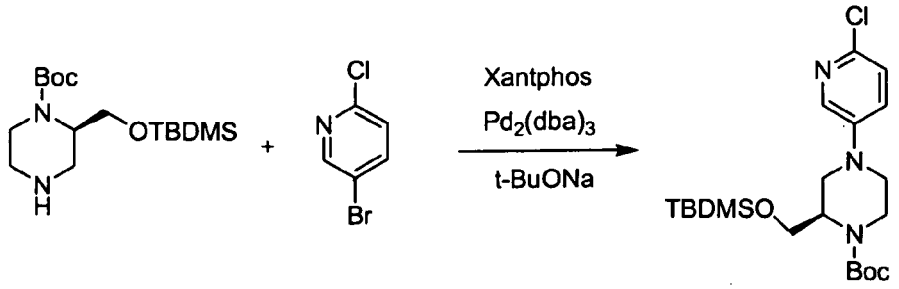
306

((2*R*)-4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol



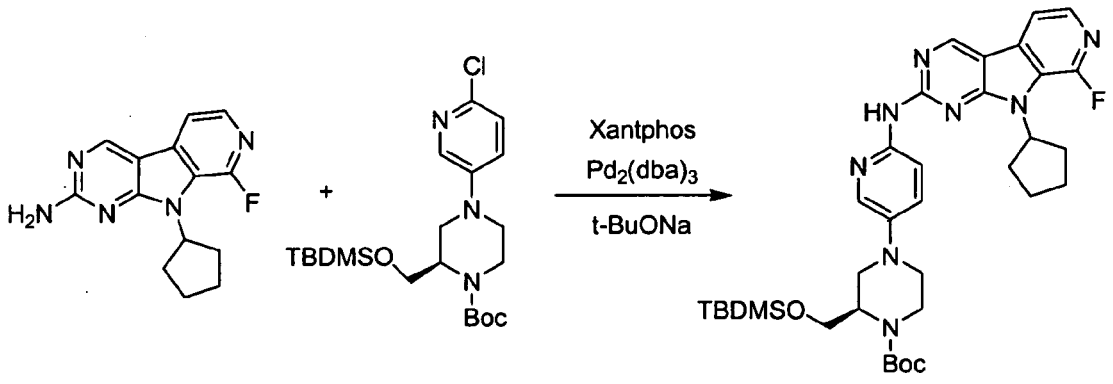
307 308

(R)-*t*-Butyl 2-((*t*-butyldimethylsilyloxy)methyl)piperazine-1-carboxylate(308): (R)-*t*-Butyl 2-(hydroxymethyl)piperazine-1-carboxylate (1.15 g, 5.32 mmol), *t*-butylchlorodimethylsilane (0.882 g, 5.85 mmol), and imidazole (0.796 g, 11.7 mmol) were stirred in dichloromethane (3 mL) for three days. The solution was added to aqueous K_2CO_3 (30 mL) and extracted with dichloromethane (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow oil. Silica gel chromatography (gradient elution hexanes/0-50% ethyl acetate) afforded compound **308** as a colorless oil(1.06 g, 60%).



308 309

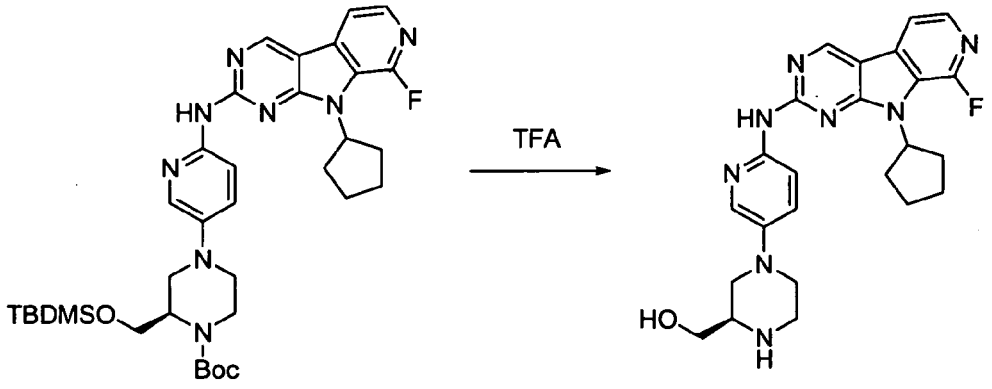
(R)-*t*-butyl 2-((*t*-butyldimethylsilyloxy)methyl)-4-(6-chloropyridin-3-yl)piperazine-1-carboxylate (309): Compound **308** (361 mg, 1091 μmol), 5-bromo-2-chloropyridine (200 mg, 1039 μmol), Tris(dibenzylideneacetone)dipalladium (0) (71.4 mg, 77.9 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (90.2 mg, 156 μmol), and sodium *t*-butoxide (200 mg, 2079 μmol) were taken up in toluene (5 mL). The reaction was purged with argon and heated at 80°C for 5 hours. The resulting solution was added to aqueous K_2CO_3 (10%, 30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give an orange tar. Silica gel chromatography (gradient elution hexanes/0-20% ethyl acetate) afforded compound **309** as a pale yellow oil (219 mg, 48%).



245 309 310

tert-Butyl (2R)-2-(((tert-butyl(dimethyl)silyl)oxy)methyl)-4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (310): A 10 mL reaction vessel was charged with compound **245** (83.0 mg, 306 μmol), compound **309** (135 mg, 306 μmol), tris(dibenzylideneacetone)dipalladium (0) (21.0 mg, 22.9 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (26.6 mg, 45.9 μmol), sodium t-butoxide (58.8 mg, 612 μmol), and dioxane (2.5 mL). The reaction was purged with argon and heated with microwave energy (300W) for 2 hours at 120°C. The resulting solution was added to aqueous K_2CO_3 (30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and

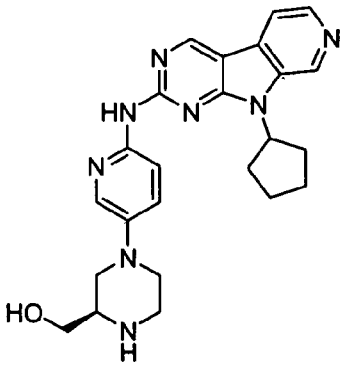
evaporated to give a yellow oil. Silica gel chromatography (gradient elution hexanes/20-100% ethyl acetate) afforded compound **310** as a colorless oil (142 mg, 69%).



310 **306**

((2R)-4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol (306): Compound **310** (140 mg, 207 μmol) was dissolved in dichloromethane (6 mL).). Trifluoroacetic acid (2.00 mL, 2.60 mmol) and 3 drops water were added and the reaction was stirred at room temperature for 3 days. The resulting solution was added dropwise with stirring to aq. K_2CO_3 (10%, 30 mL), which was then extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow oil. Silica gel chromatography (gradient elution ethyl acetate+2.5% TEA/0-100% ethyl acetate+10% 2M NH_3 in methanol) afforded the product as a yellow solid. This residue was taken up in dichloromethane (3 mL) and trifluoroacetic acid (13.3 μl, 2.0 equiv.) was added. The solvent was removed *in vacuo* to give compound **306** as a yellow solid (54 mg). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.40 (s, 1 H) 9.03 - 9.22 (m, 1 H) 8.65 - 8.82 (m, 1 H) 8.10 (d, *J*=2.93 Hz, 4 H) 7.64 - 7.78 (m, 1 H) 5.38 - 5.58 (m, 1 H) 3.70 - 3.87 (m, 3 H) 3.61 - 3.69 (m, 1 H) 3.58 (s, 1 H) 3.41 (none, 2 H) 3.15 - 3.29 (m, 1 H) 3.07 - 3.15 (m, 0 H) 2.96 - 3.07 (m, 1 H) 2.83 - 2.94 (m, 1 H) 2.26 - 2.37 (m, 2 H) 2.08 - 2.18 (m, 2 H) 1.97 - 2.08 (m, 2 H) 1.69 - 1.84 (m, 2 H) 1.14 - 1.22 (m, 1 H) ppm.

EXAMPLE 197

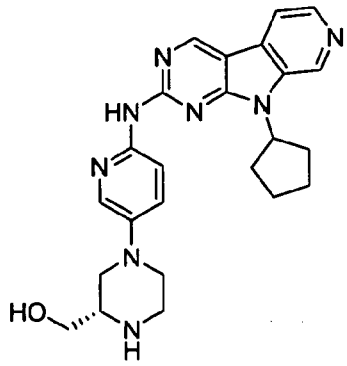


311

((2R)-4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol

Compound **311** was prepared using the methods described in Example 196 ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.50 - 9.57 (m, 1 H) 9.26 - 9.34 (m, 1 H) 9.04 - 9.15 (m, 1 H) 8.66 - 8.77 (m, 1 H) 8.60 - 8.66 (m, 1 H) 8.45 - 8.54 (m, 1 H) 8.09 - 8.19 (m, 3 H) 7.57 - 7.67 (m, 1 H) 5.31 - 5.42 (m, 1 H) 3.70 - 3.88 (m, 4 H) 3.60 - 3.70 (m, 1 H) 3.16 - 3.28 (m, 1 H) 2.96 - 3.07 (m, 1 H) 2.84 - 2.94 (m, 2 H) 2.01 - 2.19 (m, 6 H) 1.69 - 1.84 (m, 3 H) 1.10 (none, 1 H) ppm.

EXAMPLE 198

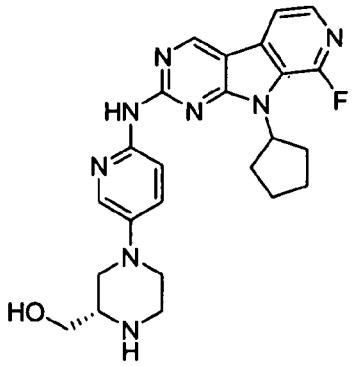


312

((2S)-4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol

Compound **312** was prepared using the methods described in Example 196. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ 9.54 (s, 1 H) 9.32 (s, 1 H) 9.10 - 9.20 (m, 1 H) 8.69 - 8.80 (m, 1 H) 8.65 (d, *J*=6.11 Hz, 1 H) 8.48 - 8.55 (m, 1 H) 8.15 (d, *J*=2.93 Hz, 2 H) 7.59 - 7.67 (m, 1 H) 5.32 - 5.43 (m, 1 H) 3.70 - 3.88 (m, 3 H) 3.60 - 3.69 (m, 1 H) 3.39 (d, 2 H) 3.16 - 3.29 (m, 1 H) 3.07 - 3.16 (m, 1 H) 2.97 - 3.07 (m, 1 H) 2.84 - 2.93 (m, 1 H) 2.38 - 2.48 (m, 2 H) 2.02 - 2.18 (m, 4 H) 1.70 - 1.83 (m, 2 H) 1.19 (s, 1 H) 1.10 (s, 1 H) ppm.

EXAMPLE 199



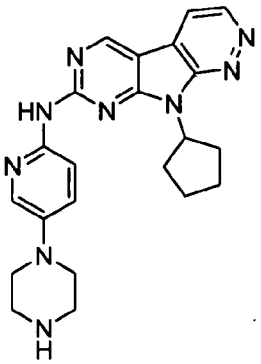
313

((2S)-4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol

Compound **313** was prepared using the methods described in Example 196.

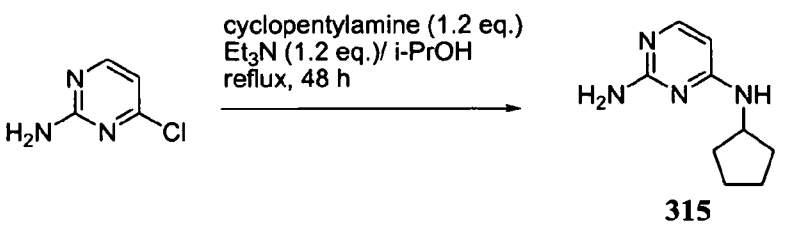
1H NMR (500 MHz, *DMSO-d_6*) δ 10.39 (none, 1 H) 9.40 (s, 1 H) 9.03 - 9.17 (m, 1 H) 8.60 - 8.80 (m, 1 H) 8.10 (d, *J*=2.45 Hz, 4 H) 7.62 - 7.77 (m, 1 H) 5.41 - 5.55 (m, 1 H) 3.68 - 3.86 (m, 3 H) 3.57 - 3.68 (m, 1 H) 3.35 - 3.42 (m, 2 H) 3.17 - 3.28 (m, 1 H) 2.97 - 3.06 (m, 1 H) 2.84 - 2.93 (m, 1 H) 2.26 - 2.40 (m, 2 H) 2.08 - 2.18 (m, 2 H) 1.97 - 2.08 (m, 2 H) 1.69 - 1.82 (m, 2 H) ppm.

EXAMPLE 200



314

9-Cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine



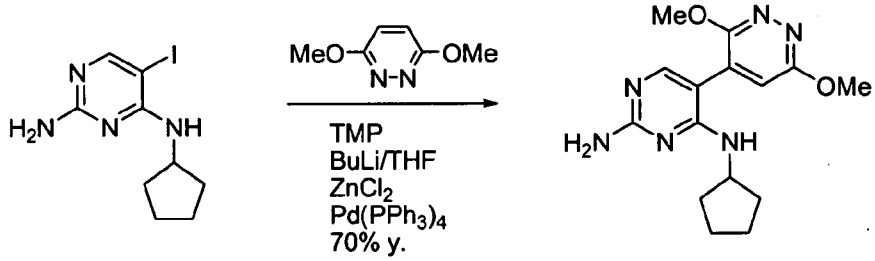
315

N4-Cyclopentyl-2,4-pyrimidinediamine (315): A mixture of 2-amino-4-chloropyrimidine (22.8 g, 176 mmol), cyclopentylamine (20.9 mL, 211 mmol) and triethylamine (29.4 mL, 211 mmol) in EtOH (200 mL) was heated at reflux (105 °C, oil bath) for 48 h. Upon workup, the volatile was removed *in vacuo*. The residue was poured into ice and saturated Na_2CO_3 aqueous solution and extracted with ethyl acetate (3 X). The combined organics were washed with saturated Na_2CO_3 aqueous solution (1 X), dried over Na_2SO_4, and concentrated in vacuo to give N4-cyclopentylpyrimidine-2,4-diamine (**315**) (26.5 g) as a light yellow solid of 92% purity. This batch of material was taken onto the next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 179.1, Calculated 179.1.



315 **243**

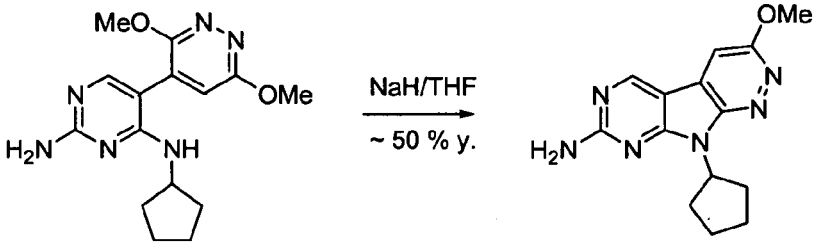
N4-Cyclopentyl-5-iodo-2,4-pyrimidinediamine (243): To a stirred solution of compound **315** (25.5 g, 143 mmol) in DMF (120 mL) was added N-iodosuccinimide (32 g, 143 mmol) in two portions at rt. The resulting mixture was stirred at rt for 2 h. Upon workup, the mixture was poured into ice and saturated Na_2CO_3 aqueous solution with some sodium sulfite and extracted with ethyl acetate (2X). The combined organics were washed with saturated Na_2CO_3 aqueous solution (3X), dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **243** (39 g, 73% yield in 2 steps). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 7.89 (1 H, s), 6.18 (2 H, s), 5.63 (1 H, d, J=7.6 Hz), 4.30 (1 H, sxt, J=7.4 Hz), 1.84 - 1.96 (2 H, m), 1.61 - 1.74 (2 H, m), 1.42 - 1.58 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 305.0.



243 **316**

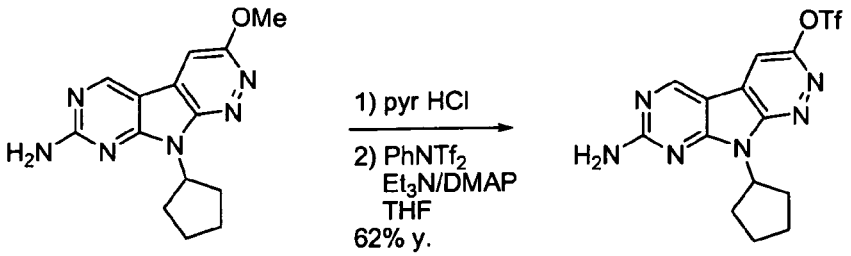
N4-Cyclopentyl-5-(3,6-dimethoxy-4-pyridazinyl)-2,4-pyrimidinediamine (316):
A solution of butyllithium (2.5m solution in hexanes) (7.5 mL, 19 mmol) was added to cold (acetonitrile-dry ice bath, -34 °C internal), stirred 2,2,6,6-tetramethylpiperidine (3.4 mL, 20 mmol). The resulting mixture was allowed to stand at 0 °C (ice-H_2O bath) for 30 min. The ice-

H_2O was then replaced with dry ice-2-propanol bath and the mixture was cooled to -0 °C. THF (24 mL) was added. A pre-cooled (ice-H_2O bath) solution of 3,6-dimethoxypyridazine (2.40 g, 17 mmol) in THF (40 mL) was added through a cannula over a period of 30 min. The internal temperature was observed fluctuating between -72 °C and -55 °C. The resulting mixture was stirred at -70 °C for 1.5 h. A solution of zinc(II) chloride (0.5 M in THF) (34 mL, 17 mmol) was added through a syringe over a period of 15 min. The internal temperature fluctuated between -73 °C and -64 °C. The cold bath was removed and the resulting mixture was allowed to warm up to rt (20.5 °C). A solution of compound **243** (1.7 g, 5.7 mmol) and tetrakis(triphenylphosphine)palladium (0.33 g, 0.29 mmol) in THF (20 mL) was added and the resulting mixture was heated at reflux for 18 h. Upon workup, the crude mixture was cooled in an ice-H_2O before poured into ice and saturated NH_4Cl aqueous solution and extracted with ethyl acetate (2 X). The combined organics were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/DCM with Et_3N) to give pure compound **316** (1.2 g, 66% yield) as an off-white solid. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 7.53 (1 H, s), 7.01 (1 H, s), 6.18 - 6.38 (3 H, m), 4.35 - 4.51 (1 H, m, J=7.3, 7.3, 7.3, 7.3, 7.0 Hz), 3.95 (3 H, s), 3.91 (3 H, s), 1.77 - 1.90 (2 H, m), 1.55 - 1.69 (2 H, m), 1.35 - 1.55 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 317.2.



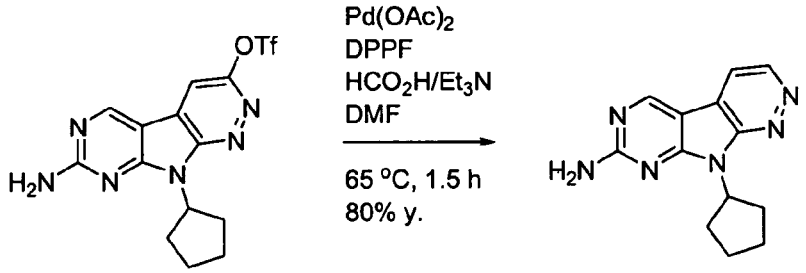
316 **317**

9-Cyclopentyl-3-methoxy-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (317): To a 35 mL microwave reaction vessel were placed with compound **316** (200 mg, 0.63 mmol) followed by THF and sodium hydride, (60% in mineral oil, 0.063 g, 1.6 mmol). The resulting mixture was stirred at room temperature for 10 min to allow gas release. Then the vessel was subjected to microwave reaction condition (60 min at 150 °C). The crude mixture was subjected to combi-flash column chromatography (methanol/DCM) to give compound **317** (0.17 g) as a light yellow solid (contaminated with mineral oil). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.97 (1 H, s), 7.57 (1 H, s), 7.28 (2 H, s), 5.28 (1 H, quin, J=8.7 Hz), 4.02 (3 H, s), 2.38 - 2.46 (2 H, m), 1.89 - 2.10 (4 H, m), 1.62 - 1.78 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 285.1.



317 318

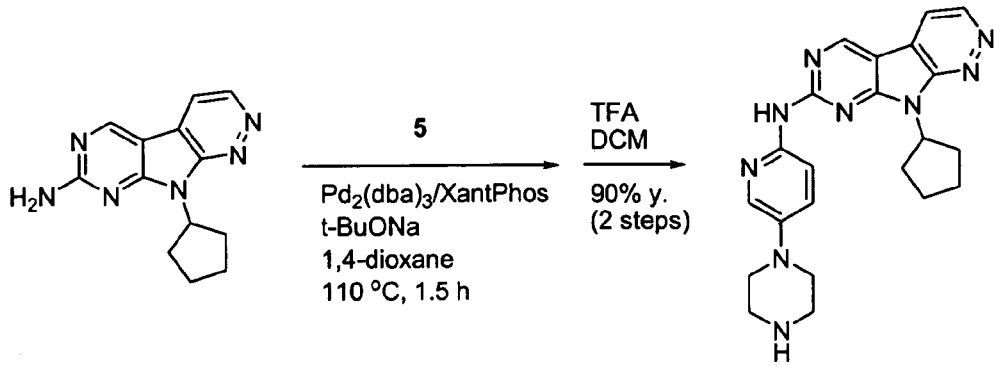
7-Amino-9-cyclopentyl-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-3-yl trifluoromethanesulfonate (318): A mixture of compound **317** (0.17 g, 0.60 mmol) and pyridine hydrochloride (0.69 g, 6.0 mmol) was heated at 200 °C (oil bath) overnight. After cooling to room temperature, the mixture was dissolved in THF (6 mL). Triethylamine (1.3 mL, 9.0 mmol) (2.0 mL), N,N-dimethylpyridin-4-amine (0.0073 g, 0.060 mmol) (catalytic amount), and N-phenyltrifluoromethanesulfonimide (0.54 g, 1.5 mmol) were added at room temperature. The resulting mixture was sonicated for 10 min and stirred for 2 h. Upon workup, the mixture was subjected to combi-flash column chromatography (ethyl acetate/Hexanes) to give compound **318** (0.15 g, 62% yield) as an off-white solid. LCMS-ESI (POS), M/Z, M+1: Found 403.0.



318 319

9-Cyclopentyl-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (319): In a 25 mL single-necked round bottom flask were placed compound **318** (94 mg, 234 μmol), palladium diacetate (21 mg, 93 μmol), and 1,1'-bis(diphenylphosphino)ferrocene (130 mg, 234 μmol). The flask was subjected to 3 cycles of evacuation and back-filling with N_2. DMF (3 mL) was added under N_2 followed by triethylamine (715 μl, 5140 μmol) and formic acid, 98 % (176 μl, 4.67 mmol). The resulting mixture was stirred in an oil bath at 65 °C for 1.5 h. The mixture was poured into ice and saturated $NaHCO_3$ aqueous solution and extracted with 10% i-PrOH/DCM (2 X). The combined organics were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/DCM with Et_3N) to give compound **319** (48 mg, 80% yield) as an reddish solid. ^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 9.08 (1 H, s), 9.01 (1 H, d, J=5.1 Hz), 8.07 (1 H, d, J=5.1 Hz), 7.28 (2 H, s), 5.42 (1 H,

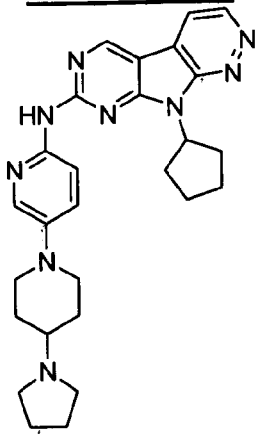
quin, J=8.6 Hz), 2.40 - 2.49 (2 H, m), 1.92 - 2.14 (4 H, m), 1.63 - 1.80 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 255.1.



319 314

9-Cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (314): In a 10 mL microwave reaction vessel were placed compound **5** (42 mg, 142 μmol), tris(dibenzylideneacetone)dipalladium (o) (13 mg, 14 μmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (20 mg, 35 μmol), and sodium tert-butoxide (41 mg, 425 μmol) followed by a solution of compound **319** (36 mg, 142 μmol) in 1,4-dioxane (3 mL). The vessel was purged with N_2 for 3 min, then capped and sujected to microwave condition (1.5 h at 110 °C). After the volatiles were removed, the residue was subjected to combi-flash column chromatography (methanol/DCM. A solution of the intermediate in DCM (15 mL) was treated with trifluoroacetic acid (0.70 mL, 9.4 mmol) at room temperature for 1.5 h. After the volatiles were removed, the residue was subjected to preparative reverse phase HPLC (acetonitrile/H_2O containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **314** (56 mg, bis-TFA salt) as a yellow solid. ^{1}H NMR (400 MHz, methanol) δ ppm 9.47 (1 H, s), 9.23 (1 H, d, J=5.5 Hz), 8.49 (1 H, d, J=5.5 Hz), 7.99 - 8.11 (2 H, m), 7.75 (1 H, d, J=9.4 Hz), 5.68 (1 H, quin, J=8.5 Hz), 3.49 - 3.58 (4 H, m), 3.41 - 3.49 (4 H, m), 2.50 - 2.71 (2 H, m), 2.12 - 2.29 (4 H, m), 1.76 - 1.94 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 416.2.

EXAMPLE 201

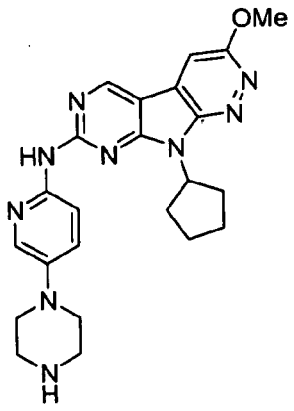


320

9-cyclopentyl-N-(5-(4-(1-pyrrolidinyl)-1-piperidinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine

Compound **320** was prepared as a TFA salt using chemistry similar to that described in example 200. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.46 (1 H, s), 9.22 (1 H, d, J=5.1 Hz), 8.45 (1 H, d, J=5.5 Hz), 8.07 (1 H, dd, J=9.6, 2.9 Hz), 8.00 (1 H, d, J=2.7 Hz), 7.67 (1 H, d, J=9.8 Hz), 5.69 (1 H, qd, J=8.5, 8.2 Hz), 3.92 (2 H, d, J=12.9 Hz), 3.66 - 3.76 (2 H, m), 3.36 - 3.38 (1 H, m), 3.21 (2 H, d, J=11.0 Hz), 2.93 (2 H, td, J=12.5, 2.0 Hz), 2.54 - 2.68 (2 H, m), 2.33 (2 H, d, J=13.3 Hz), 2.13 - 2.27 (6 H, m), 1.96 - 2.10 (2 H, m), 1.79 - 1.95 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 484.2.

EXAMPLE 202



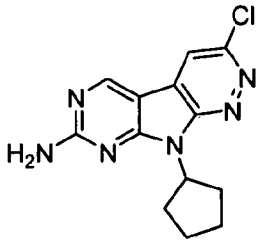
321

9-cyclopentyl-3-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine

Compound **321** was prepared as a TFA salt from **317** using chemistry similar to that described in example 1. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.22 (1 H, s), 8.02 (1 H, d, J=2.7 Hz), 7.95

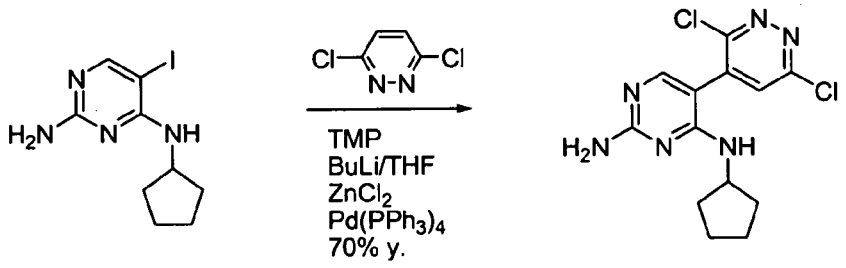
(1 H, dd, J=9.6, 2.3 Hz), 7.71 (1 H, s), 7.61 - 7.68 (3 H, m), 5.50 (1 H, quin, J=8.6 Hz), 4.15 (3 H, s), 3.45 - 3.54 (4 H, m), 3.37 - 3.45 (4 H, m), 2.48 - 2.66 (2 H, m), 2.04 - 2.22 (4 H, m), 1.73 - 1.89 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 446.0.

EXAMPLE 203



322

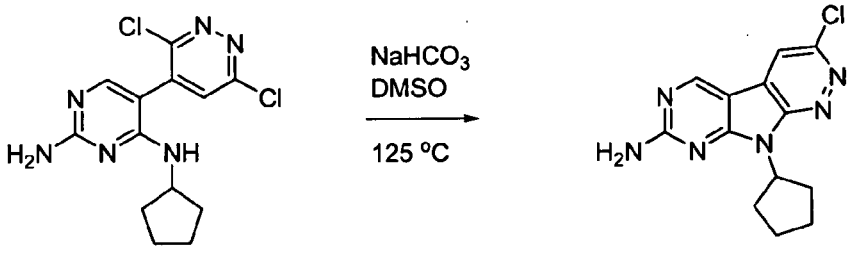
3-chloro-9-cyclopentyl-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine



243 323

N4-Cyclopentyl-5-(3,6-dichloro-4-pyridazinyl)-2,4-pyrimidinediamine (323)

Compound **323** was prepared from compound **243** and 3,6-dichloropyridazine using chemistry similar to that described in example 200. LCMS-ESI (POS), M/Z, M+1: Found 325.0.

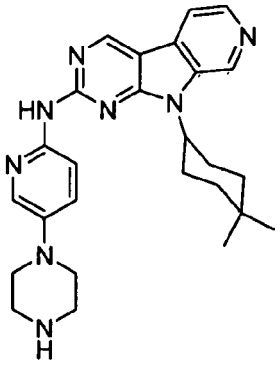


323 322

3-Chloro-9-cyclopentyl-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (322): A mixture of crude N4-cyclopentyl-5-(3,6-dichloropyridazin-4-yl)pyrimidine-2,4-diamine (**323**) (0.27 g, 0.83 mmol) and sodium bicarbonate (0.065 mL, 1.7 mmol) in DMSO (10 mL) was heated in an oil bath at 110 °C for 11 h. Then the temperature was raised to 125 °C and stirred at this temperature for 200 min at which time LC-MS showed completion. Upon workup, the mixture was poured into ice and saturated NH_4Cl aqueous solution and extracted with ethyl acetate (3 X). The combined organics were washed with saturated NH_4Cl aqueous solution (1 X), dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to combi-flash

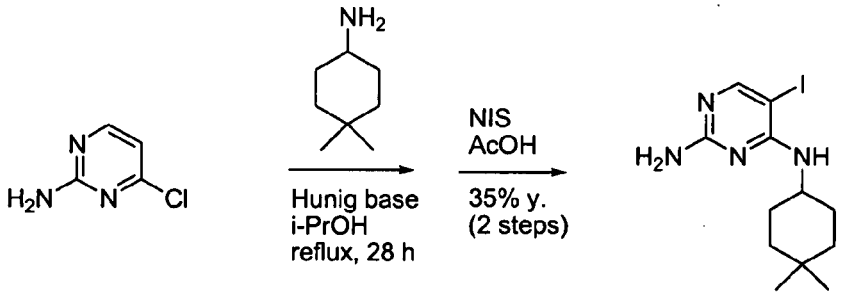
column chromatography (methanol/DCM). The impure product thus obtained was subjected to subjected to preparative reverse phase HPLC (acetonitrile/H_2O containing 0.1% TFA each). After lyophilization, 15 mg of compound **322** was obtained as a TFA salt as an off-white solid. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.06 (1 H, s), 8.21 (1 H, s), 5.50 (1 H, quin, J=8.6 Hz), 2.43 - 2.60 (2 H, m), 1.99 - 2.25 (4 H, m), 1.71 - 1.89 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 289.1.

EXAMPLE 204



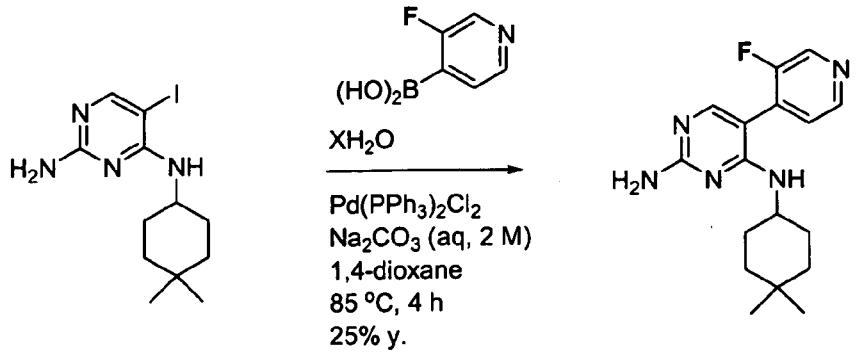
324

9-(4,4-dimethylcyclohexyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



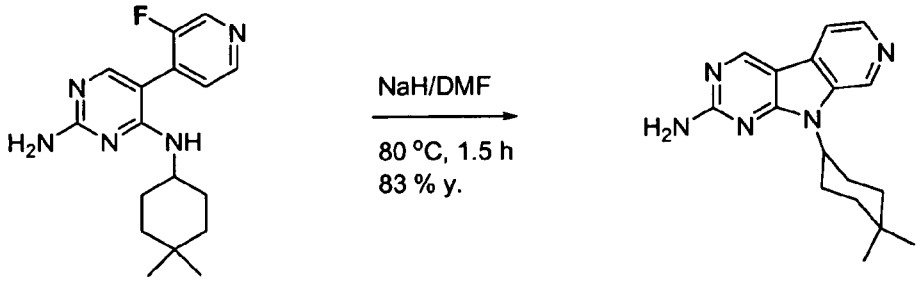
326

N4-(4,4-dimethylcyclohexyl)-5-iodo-2,4-pyrimidinediamine (326): Compound **326** was prepared as an off-white solid using chemistry similar to that described in example 200. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 7.88 (1 H, s), 6.13 (2 H, s), 5.66 (1 H, d, J=8.6 Hz), 3.78 - 3.95 (1 H, m), 1.49 - 1.66 (4 H, m), 1.30 - 1.41 (2 H, m), 1.15 - 1.28 (2 H, m), 0.94 (3 H, s), 0.91 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 347.0.



326 327

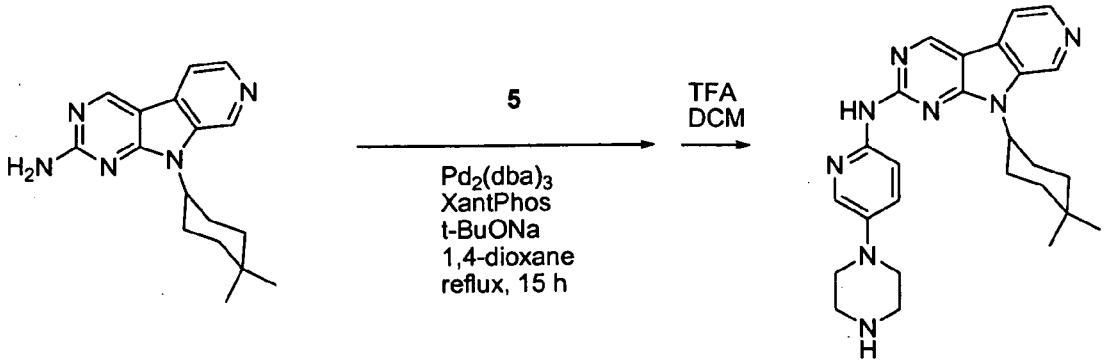
N4-(4,4-Dimethylcyclohexyl)-5-(3-fluoro-4-pyridinyl)-2,4-pyrimidinediamine (327): To a 50 mL single-necked round bottom flask were placed compound **236** (0.80 g, 2.3 mmol), 3-fluoropyridin-4-ylboronic acid (0.98 g, 6.9 mmol), *trans*-dichlorobis(triphenyl-phosphine)palladium (IIi) (0.16 g, 0.23 mmol), 1,4-dioxane (16 mL), and sodium carbonate, 2 N aqueous solution (3.5 mL, 6.9 mmol). The flask was purged with N_2 for 10 min. The resulting mixture was heated in an oil bath at 80 °C for 50 h. Upon workup, the mixture was poured into saturated Na_2CO_3 aqueous solution and extracted with ethyl acetate (2 X). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **327** (0.18 g, 25% yield) as a light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.56 (1 H, d, J=1.7 Hz), 8.48 (1 H, dd, J=4.9, 1.0 Hz), 7.78 (1 H, s), 7.27 - 7.30 (1 H, m), 4.89 (2 H, s), 4.43 (1 H, d, J=7.6 Hz), 3.88 - 4.01 (1 H, m), 1.79 - 1.88 (2 H, m), 1.26 - 1.43 (6 H, m), 0.94 (3 H, s), 0.91 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 316.1.



327 328

9-(4,4-Dimethylcyclohexyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (328): To a stirred solution of compound **327** (0.18 g, 0.57 mmol) in DMF (10 mL) was added sodium hydride, (60% in mineral oil, 0.11 g, 2.3 mmol). The resulting mixture was stirred at 80 °C for 1.5 h. Upon workup, the crude mixture was poured into ice and saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate (2 X) followed by 10% i-PrOH/DCM (2 X). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to combi-flash column chromatography (methanol/DCM with Et_3N) to give

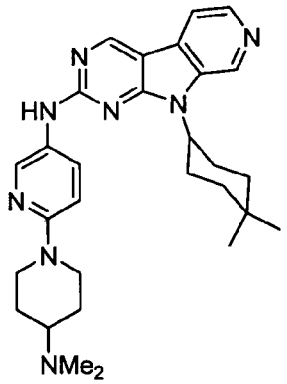
compound **328** (0.14 g, 83% yield) as a light yellow solid. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 9.04 (1 H, s), 8.92 (1 H, s), 8.35 (1 H, d, J=4.9 Hz), 7.92 (1 H, dd, J=5.1, 1.0 Hz), 6.94 (2 H, s), 4.66 - 4.76 (1 H, m, J=12.6, 12.6, 4.1, 3.9 Hz), 2.52 - 2.63 (2 H, m), 1.52 - 1.66 (4 H, m), 1.39 - 1.50 (2 H, m), 1.16 (3 H, s), 1.01 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 296.0.



328 **324**

9-(4,4-dimethylcyclohexyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (324): Compound **324** was prepared as a yellow solid (TFA salt) from compound **328** and compound **5** using chemistry similar to that described in example 200. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 10.35 (1 H, s), 9.52 (1 H, s), 9.35 (1 H, s), 8.62 (1 H, d, J=5.9 Hz), 8.49 (1 H, d, J=5.9 Hz), 8.15 (1 H, d, J=2.9 Hz), 8.04 (1 H, d, J=9.0 Hz), 7.51 (1 H, dd, J=9.0, 2.9 Hz), 4.66 - 4.79 (1 H, m), 3.34 - 3.43 (4 H, m), 3.30 (4 H, br. s.), 2.62 - 2.77 (2 H, m), 1.73 (2 H, d, J=11.3 Hz), 1.46 - 1.63 (4 H, m), 1.11 (3 H, s), 1.02 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 457.1.

EXAMPLE 205

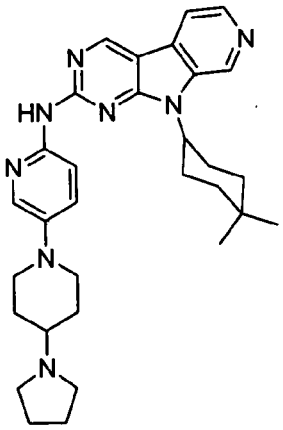


329

N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridinyl)-9-(4,4-dimethylcyclohexyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **329** was prepared as a yellow solid (TFA salt) from compound **328** and compound **91** using chemistry similar to that described in example 56. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 9.46 - 9.58 (2 H, m), 9.36 (1 H, br. s.), 8.61 (1 H, d, J=6.1 Hz), 8.44 - 8.56 (2 H, m), 7.88 (1 H, dd, J=9.0, 2.7 Hz), 6.95 (1 H, d, J=9.3 Hz), 4.67 (1 H, br. s.), 4.42 (2 H, d, J=13.4 Hz), 3.35 - 3.45 (1 H, m, J=12.0, 12.0, 4.0, 4.0, 3.8 Hz), 2.72 - 2.85 (8 H, m), 2.58 - 2.70 (2 H, m), 2.07 (2 H, d, J=10.5 Hz), 1.69 (2 H, d, J=10.5 Hz), 1.43 - 1.63 (6 H, m), 0.99 (6 H, s). LCMS-ESI (POS), M/Z, M+1: Found 499.3.

EXAMPLE 206

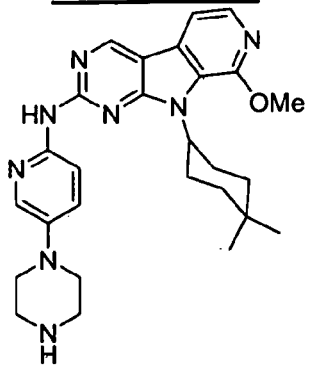


330

9-(4,4-dimethylcyclohexyl)-N-(5-(4-(1-pyrrolidinyl)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

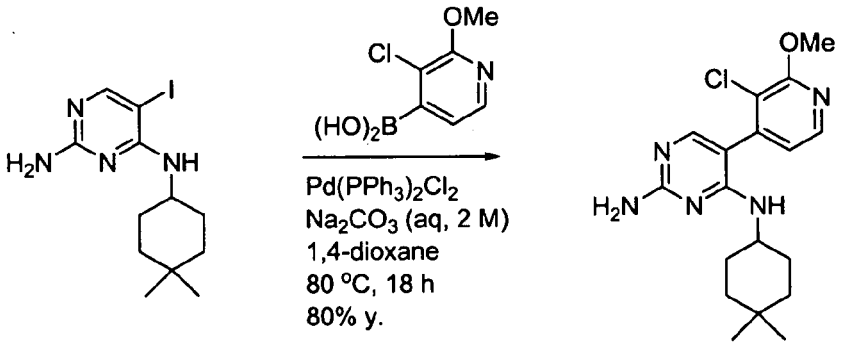
Compound **330** was prepared as yellow solid (TFA salt) from compound **328** using chemistry similar to that described in example 53. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.58 (1 H, s), 9.31 (1 H, s), 8.54 - 8.65 (2 H, m), 8.03 (1 H, d, J=2.9 Hz), 7.99 (1 H, d, J=7.3 Hz), 7.77 (1 H, d, J=9.0 Hz), 4.89 - 5.01 (1 H, m), 3.91 (2 H, d, J=12.7 Hz), 3.71 (2 H, br. s.), 3.34 - 3.42 (1 H, m), 3.15 - 3.26 (2 H, m), 2.87 - 2.99 (2 H, m), 2.72 - 2.88 (2 H, m), 2.33 (2 H, d, J=12.0 Hz), 2.20 (2 H, br. s.), 2.05 (2 H, br. s.), 1.77 - 1.94 (4 H, m), 1.54 - 1.73 (4 H, m), 1.24 (3 H, s), 1.08 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 525.3.

EXAMPLE 207



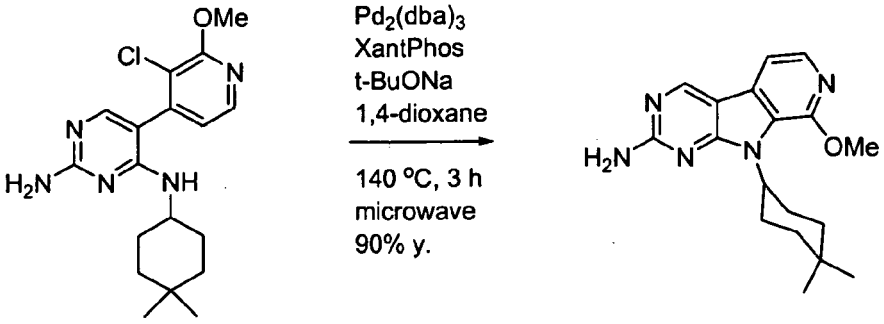
331

9-(4,4-dimethylcyclohexyl)-8-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



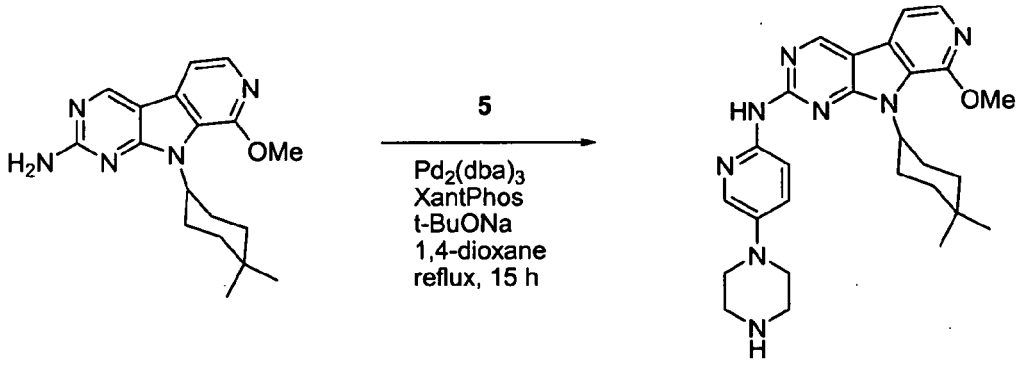
326 332

5-(3-Chloro-2-methoxy-4-pyridinyl)-N4-(4,4-dimethylcyclohexyl)-2,4-pyrimidinediamine (332): To a 50 mL single-necked round bottom flask were placed compound **326** (0.80 g, 2.3 mmol), 3-chloro-2-methoxypyridin-4-ylboronic acid (1.3 g, 6.9 mmol), and trans-dichlorobis(triphenyl-phosphine)palladium (ii) (0.16 g, 0.23 mmol). The flask was subjected to 3 cycles of evacuation and back-filling with N_2. 1,4-Dioxane (12 mL) was added followed with sodium carbonate (2 N aqueous solution) (5.8 mL, 12 mmol). The resulting mixture was heated in an oil bath at 80 °C for 18 h. Upon workup, the mixture was poured into ice and saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate (3 X). The combined organics were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **332** (0.68 g, 81% yield) as a light yellow solid. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.09 (1 H, d, J=5.1 Hz), 7.48 (1 H, s), 6.92 (1 H, d, J=5.1 Hz), 6.13 (2 H, s), 5.79 (1 H, d, J=8.3 Hz), 3.91 - 4.02 (4 H, m), 1.26 - 1.63 (6 H, m), 1.13 - 1.25 (2 H, m), 0.88 (6 H, d, J=9.8 Hz). LCMS-ESI (POS), M/Z, M+1: Found 362.0.



332 333

9-(4,4-Dimethylcyclohexyl)-8-methoxy-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (333): To a 30 mL microwave reaction vessel were placed compound **332** (0.55 g, 1.5 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.14 g, 0.15 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.22 g, 0.38 mmol), and sodium *tert*-butoxide (0.37 g, 3.8 mmol) followed by 1,4-dioxane (15 mL). The vessel was purged with N_2 for 5 min, then capped and subjected to microwave condition (3 h at 140 °C). After the volatiles were removed, the crude mixture was taken up in 4% methanol/DCM and subjected to combi-flash column chromatography (1% to 7%methanol in DCM) to give crude compound **333** as an off-white solid (0.65 g). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 9.01 (1 H, s), 7.92 (1 H, d, J=5.1 Hz), 7.59 (1 H, d, J=4.9 Hz), 6.86 (2 H, br. s.), 4.98 - 5.14 (1 H, m), 4.06 (3 H, s), 1.53 (4 H, br. s.), 1.31 - 1.44 (2 H, m), 1.16 (3 H, s), 1.00 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 326.1.

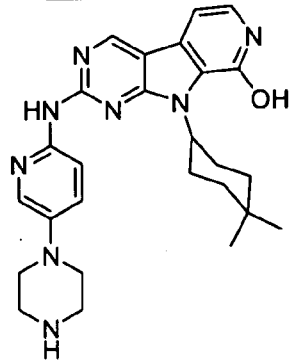


333 331

9-(4,4-Dimethylcyclohexyl)-8-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (331): In a 25 mL round bottom flask were placed compound **333** (130 mg, 399 μmol), compound **5** (119 mg, 399 μmol), tris(dibenzylideneacetone)dipalladium (0) (36.6 mg, 39.9 μmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (57.8 mg, 99.9 μmol), and sodium *tert*-butoxide (115 mg, 1198 μmol). The flask was subjected to 3 cycles of evacuation and back-filling with N_2. 1,4-Dioxane (5 mL) was added and the resulting mixture was stirred at reflux for 14 h. After the

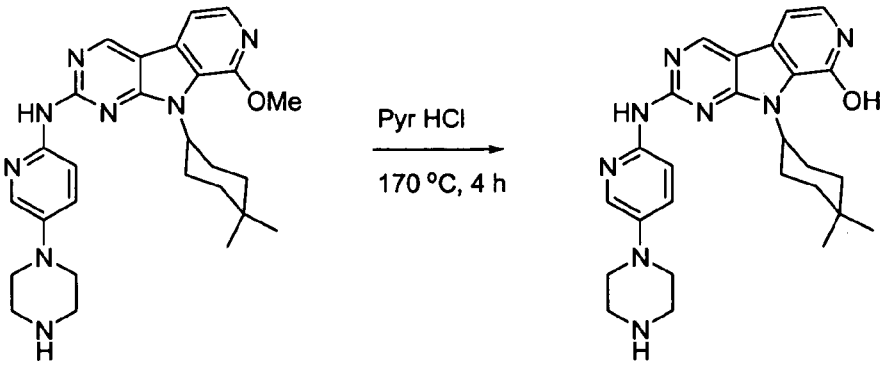
volatiles were removed, the residue, which contained both Boc protected and deprotected product, was subjected to combi-flash column chromatography (methanol/DCM) followed by reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 60%). Fractions containing the desired product were lyophilized to provided compound **331** (16 mg) as a light yellow solid (TFA salt). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 9.30 (1 H, s), 8.70 (2 H, br. s.), 8.08 (1 H, d, J=2.7 Hz), 7.96 - 8.06 (2 H, m), 7.75 (1 H, br. s.), 5.10 - 5.31 (1 H, m), 4.09 (3 H, s), 3.24 - 3.37 (8 H, m), 1.33 - 1.77 (8 H, m), 1.13 (3 H, br. s.), 1.02 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 487.1.

EXAMPLE 208



334

9-(4,4-dimethylcyclohexyl)-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol

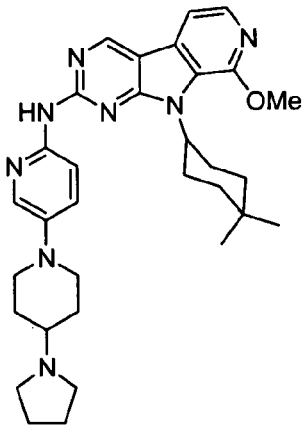


331 **334**

9-(4,4-dimethylcyclohexyl)-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol (334): A mixture of compound **331** (90 mg, 153 μmol) and pyridine hydrochloride (177 mg, 1.53 mmol) was heated at 170 °C (oil bath) for 4 h. After cooling to room temperature, the mixture was subjected to reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 50%). Lyophilization

provided compound **334** (150 mg) as a yellow solid (TFA salt). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 11.66 (1 H, br. s.), 9.30 (1 H, s), 8.80 (2 H, br. s.), 8.05 (1 H, d, J=2.7 Hz), 7.92 (1 H, d, J=8.6 Hz), 7.75 (1 H, br. s.), 7.28 (1 H, t, J=5.7 Hz), 7.06 (1 H, d, J=6.3 Hz), 3.33 - 3.43 (4 H, m), 3.29 (5 H, d, J=1.6 Hz), 2.71 - 2.94 (2 H, m), 1.47 - 1.70 (4 H, m), 1.31 - 1.45 (2 H, m), 1.16 (3 H, s), 0.99 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 473.2.

EXAMPLE 209

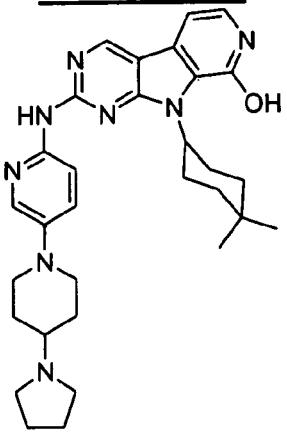


335

9-(4,4-dimethylcyclohexyl)-8-methoxy-N-(5-(4-(1-pyrrolidinyl)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **335** was prepared from compound **333** using chemistry similar to that described in example 56. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.33 (1 H, s), 8.02 - 8.16 (2 H, m), 7.96 (1 H, d, J=2.7 Hz), 7.75 (1 H, d, J=5.1 Hz), 7.49 (0 H, br. s.), 5.27 - 5.41 (1 H, m), 4.19 (3 H, s), 3.89 (2 H, d, J=12.9 Hz), 3.71 (2 H, br. s.), 3.35 - 3.42 (1 H, m), 3.15 - 3.26 (2 H, m), 2.91 (2 H, td, J=12.5, 2.0 Hz), 2.33 (2 H, d, J=13.3 Hz), 2.13 - 2.25 (2 H, m), 1.97 - 2.09 (2 H, m), 1.81 - 1.94 (2 H, m), 1.60 - 1.70 (2 H, m), 1.44 - 1.57 (2 H, m), 1.26 (3 H, s), 1.05 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 555.2.

EXAMPLE 210

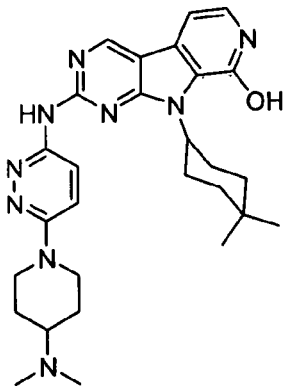


336

9-(4,4-dimethylcyclohexyl)-2-((5-(4-(1-pyrrolidinyl)-1-piperidinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol

Compound **336** was prepared as a yellow solid (TFA salt) from compound **333** using chemistry similar to that described in example 208. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.33 (1 H, s), 8.10 (1 H, dd, J=9.6, 2.9 Hz), 7.93 (1 H, d, J=2.7 Hz), 7.54 (1 H, d, J=9.8 Hz), 7.35 (1 H, d, J=7.0 Hz), 7.15 (1 H, d, J=6.7 Hz), 3.89 (2 H, d, J=12.9 Hz), 3.71 (2 H, br. s.), 3.35 - 3.41 (1 H, m), 3.15 - 3.27 (2 H, m), 2.86 - 3.03 (4 H, m), 2.33 (2 H, d, J=12.5 Hz), 2.20 (2 H, br. s.), 1.96 - 2.11 (2 H, m), 1.81 - 1.95 (2 H, m), 1.56 - 1.76 (4 H, m), 1.42 - 1.55 (2 H, m), 1.26 (3 H, s), 1.03 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 541.3.

EXAMPLE 211



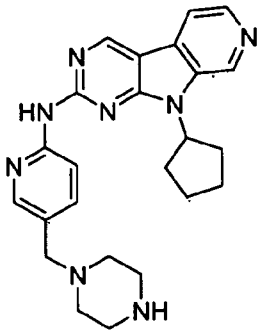
337

2-((6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)amino)-9-(4,4-dimethylcyclohexyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol

Compound **337** was prepared as a yellow solid (TFA salt) from compound **333** using chemistry similar to that described in example 208. ^{1}H NMR (500 MHz, *$DMSO\text{-}d_6$*) δ ppm 11.63 (1 H, br. s.), 9.49 (1 H, br. s.), 9.29 (1 H, s), 8.06 (1 H, d, J=9.8 Hz), 7.27 (1 H, t, J=5.9 Hz), 7.03 (1

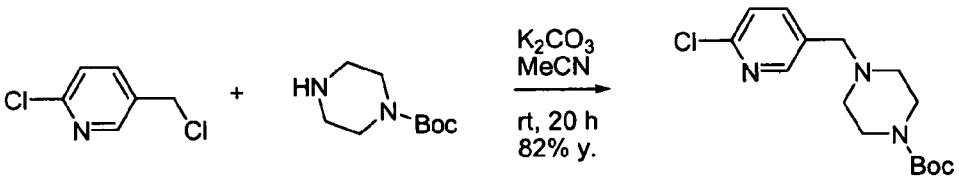
H, d, J=6.1 Hz), 4.42 (2 H, d, J=13.2 Hz), 2.96 (2 H, t, J=12.6 Hz), 2.79 (9 H, d, J=5.1 Hz), 2.03 - 2.16 (2 H, m), 1.48 - 1.71 (6 H, m), 1.29 - 1.42 (2 H, m), 1.10 (3 H, br. s.), 0.98 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 516.3.

EXAMPLE 212



338

9-cyclopentyl-N-(5-(1-piperazinylmethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



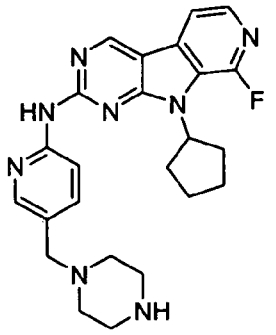
339

tert-Butyl 4-((6-chloro-3-pyridinyl)methyl)-1-piperazinecarboxylate (339): To a stirred suspension of 2-chloro-5-(chloromethyl)pyridine (2.0 g, 12 mmol) in acetonitrile (40 mL) was added potassium carbonate (1.5 mL, 25 mmol) followed by *tert*-butyl 1-piperazinecarboxylate (2.3 g, 12 mmol). The resulting mixture was stirred at room temperature for 20 h. Upon workup, the mixture was poured into ice and 2 N NaOH aqueous solution and extracted with ethyl acetate (2 X). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **339** (3.17 g, 82% yield) as a thick colorless liquid. ^{1}H NMR 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.32 (1 H, d, J=2.0 Hz), 7.66 (1 H, d, J=7.4 Hz), 7.30 (1 H, d, J=8.2 Hz), 3.50 (2 H, s), 3.37 - 3.47 (4 H, m), 2.38 (4 H, br. s.), 1.46 (9 H, s). LCMS-ESI (POS), M/Z, M+1: Found 312.1.

9-cyclopentyl-N-(5-(1-piperazinylmethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (338): Compound **338** was prepared as an off-white solid (TFA salt)

from compound **4** and compound **339** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.68 (1 H, s), 9.35 (1 H, s), 8.68 (2 H, q, J=6.3 Hz), 8.43 (1 H, d, J=1.5 Hz), 8.26 (1 H, dd, J=8.9, 2.1 Hz), 7.88 (1 H, d, J=8.8 Hz), 5.48 (1 H, quin, J=8.7 Hz), 3.78 (2 H, s), 3.27 - 3.30 (4 H, m), 2.83 (4 H, br. s.), 2.48 - 2.59 (2 H, m), 2.15 - 2.31 (4 H, m), 1.83 - 1.97 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 429.2.

EXAMPLE 213

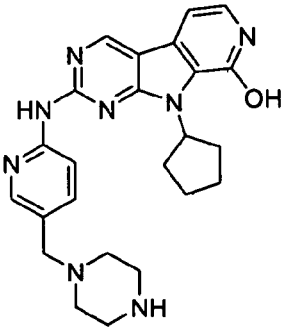


340

9-cyclopentyl-8-fluoro-N-(5-(1-piperazinylmethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

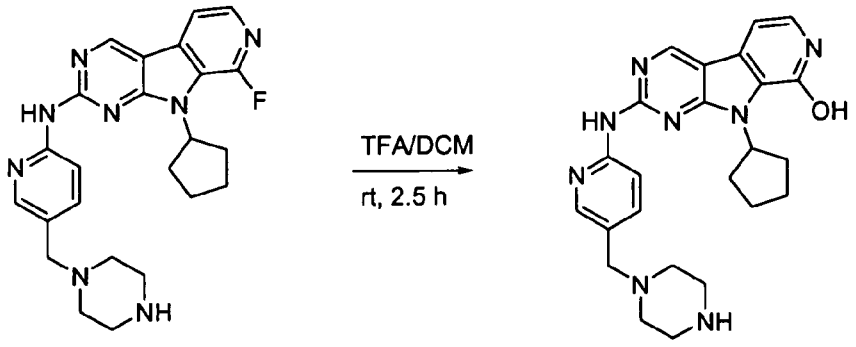
Compound **340** was prepared as an off-white solid (TFA salt) from compound **245** and compound **339** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.49 (1 H, s), 8.40 (1 H, d, J=1.5 Hz), 8.30 (1 H, dd, J=8.9, 2.1 Hz), 8.10 - 8.17 (2 H, m), 7.63 (1 H, d, J=9.0 Hz), 5.66 (1 H, quin, J=9.0 Hz), 3.75 (2 H, s), 3.26 - 3.30 (4 H, m), 2.80 (4 H, br. s.), 2.36 - 2.49 (2 H, m), 2.10 - 2.26 (4 H, m), 1.79 - 1.92 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 447.3.

EXAMPLE 214



341

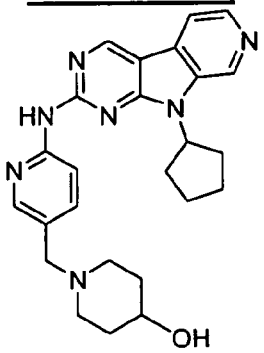
9-cyclopentyl-2-((5-(1-piperazinylmethyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol



340 341

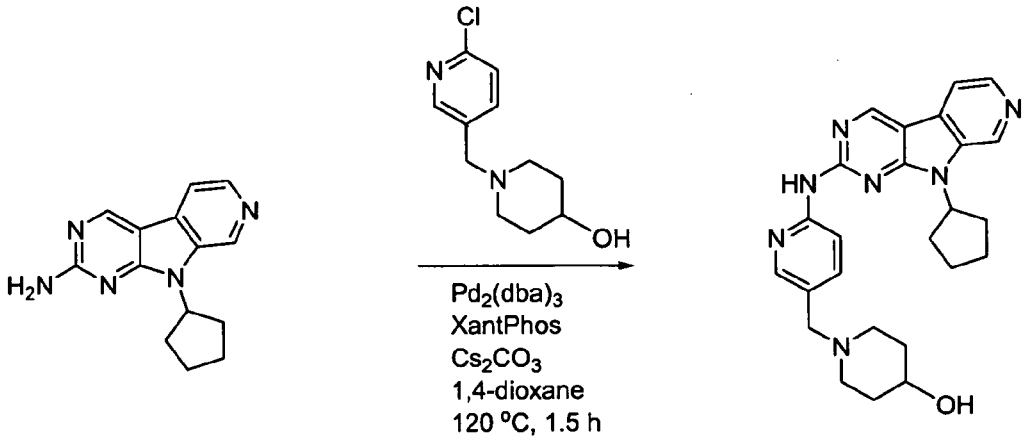
Compound **341** formed as a side product in example 213 and was isolated after reverse phase HPLC as a light yellow solid (TFA salt). LCMS-ESI (POS), M/Z, M+1: Found 445.1.

EXAMPLE 215



342

1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-4-piperidinol

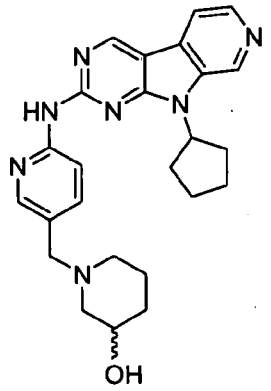


4 342

1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-4-piperidinol (342): In a 10 mL microwave reaction vessel were placed compound **4** (40 mg, 158 μmol), 1-(6-chloro-pyridin-3-ylmethyl)piperidin-4-ol (36 mg, 158 μmol), tris(dibenzylideneacetone)dipalladium (o) (7.2 mg, 7.9 μmol), 9,9-dimethyl-4,5-

bis(diphenylphosphino)xanthene (11 mg, 20 μmol), and cesium carbonate (25 μl, 316 μmol) followed by 1,4-dioxane (3 mL). The vessel was purged with N_2 for 5 min, then capped and subjected to microwave condition (1.5 h at 120 °C). After the volatiles were removed, the residue was purified by combi-flash column chromatography followed by reverse phase preparative HPLC (acetonitrile/H_2O containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **342** (10 mg) as an off-white solid (TFA salt). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 10.00 (1 H, s), 9.32 (1 H, s), 9.03 (1 H, s), 8.46 (1 H, d, J=5.1 Hz), 8.32 (1 H, d, J=8.3 Hz), 8.19 (1 H, d, J=1.7 Hz), 8.04 - 8.10 (1 H, m), 7.72 (1 H, dd, J=8.6, 2.0 Hz), 5.39 (1 H, quin, J=8.8 Hz), 4.54 (1 H, d, J=3.9 Hz), 3.43 (3 H, s), 2.64 - 2.72 (2 H, m), 2.37 - 2.45 (2 H, m), 2.00 - 2.17 (6 H, m), 1.65 - 1.84 (4 H, m), 1.39 (2 H, t, J=9.9 Hz). LCMS-ESI (POS), M/Z, M+1: Found 444.2.

EXAMPLE 216

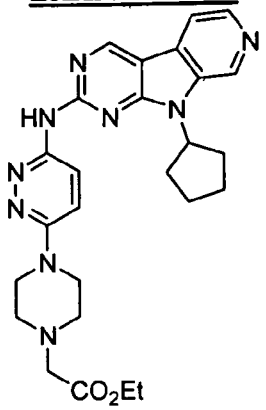


343

1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-3-piperidinol

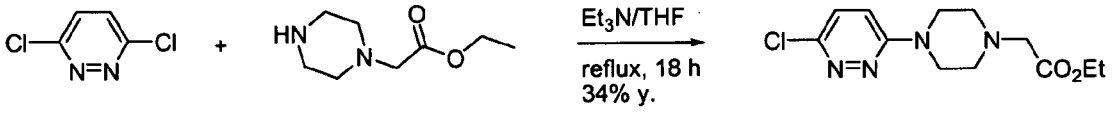
Compound **343** was prepared as a light yellow solid (TFA salt) from compound **4** using chemistry similar to that described in example 215. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.60 (1 H, s), 9.31 (1 H, s), 8.64 - 8.67 (1 H, m), 8.59 - 8.64 (1 H, m), 8.53 (1 H, d, J=2.0 Hz), 8.41 (1 H, d, J=8.6 Hz), 8.11 (1 H, dd, J=8.8, 2.2 Hz), 5.46 (1 H, quin, J=8.9 Hz), 4.05 - 4.53 (2 H, m), 3.53 (1 H, br. s.), 3.10 (1 H, br. s.), 2.50 - 2.64 (2 H, m), 2.14 - 2.36 (5 H, m), 1.75 - 2.00 (3 H, m). LCMS-ESI (POS), M/Z, M+1: Found 444.2.

EXAMPLE 217



344

ethyl (4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinyl)acetate



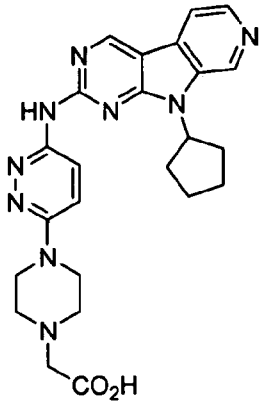
345

Ethyl 2-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)acetate (345): Triethylamine (2.2 mL, 16 mmol) followed by 1-(ethoxycarbonylmethyl)piperazine (2.6 mL, 16 mmol) were added to a stirred suspension of 1-(ethoxycarbonylmethyl)piperazine (2.6 mL, 16 mmol) in THF (40 mL). The resulting mixture was stirred at reflux for 18 h. After cooling, the precipitate was removed by vacuum filtration through a layer of celite. The cake was washed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was subjected to combi-flash column chromatography (methanol/DCM with Et_3N) to give compound **345** (1.5 g, 34% yield) as an off-white solid. ^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 7.53 (1 H, d), 7.38 (1 H, d, J=9.4 Hz), 4.09 (2 H, q, J=7.0 Hz), 3.54 - 3.63 (4 H, m), 3.29 (2 H, s), 2.57 - 2.65 (4 H, m), 1.19 (3 H, t, J=7.0 Hz). LCMS-ESI (POS), M/Z, M+1: Found 285.1.

ethyl (4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinyl)acetate (344): Compound **344** was prepared as a light yellow solid (TFA salt) from compound **4** and compound **345** using chemistry similar to that described in example 200. ^1H NMR (500 MHz, *CD_3OD*) δ ppm 9.65 (1 H, s), 9.33 (1 H, s), 8.63 - 8.68 (2 H, m), 8.15 (1 H, d, J=9.8 Hz), 7.94 (1 H, d, J=9.8 Hz), 5.46 (1 H, qt), 4.33 (2 H, q, J=7.1 Hz), 4.11 (2 H, s), 3.98 (4 H, br. s.), 3.46 (4 H, t, J=5.1 Hz), 2.45 - 2.59 (2 H, m), 2.13 - 2.31 (4

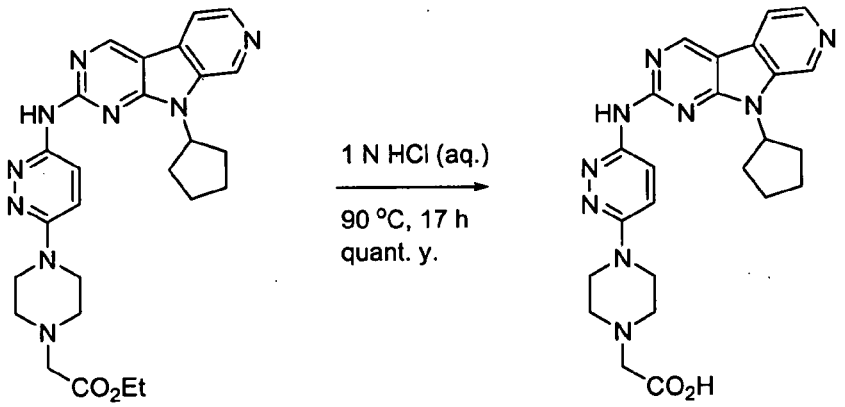
H, m), 1.84 - 1.96 (2 H, m), 1.34 (3 H, t, J=7.2 Hz). LCMS-ESI (POS), M/Z, M+1: Found 502.3.

EXAMPLE 218



346

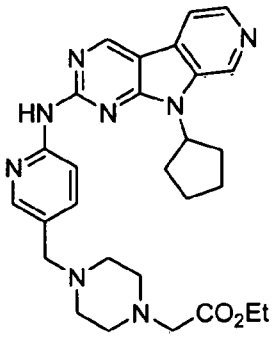
(4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinyl)acetic acid



344 346

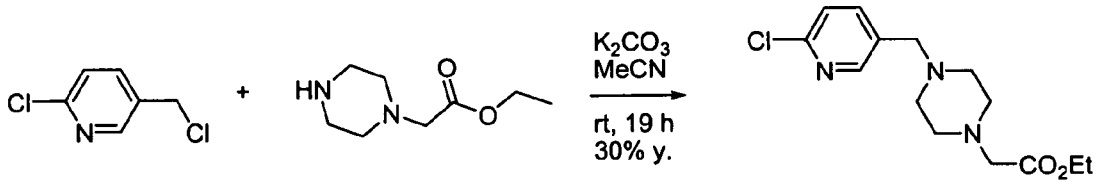
(4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinyl)acetic acid (346): A mixture of compound **344** and hydrochloric acid (1 N aqueous solution) (7 mL) was stirred at 90 °C for 17 h. After concentration, the residue was subjected to reverse phase preparative HPLC (acetonitrile/H_2O containing 0.1% TFA each, 40 min from 10 to 30%). Lyophilization provided compound **346** (50 mg) as a yellow solid (TFA salt). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 10.94 (1 H, br. s.), 9.55 (1 H, s), 9.33 (1 H, s), 8.65 (1 H, d, J=6.1 Hz), 8.53 (1 H, d, J=5.9 Hz), 8.23 (1 H, d, J=9.5 Hz), 7.60 (1 H, d, J=9.8 Hz), 5.34 (1 H, dq, J=8.9, 8.8 Hz), 4.16 (2 H, br. s.), 3.40 (8 H, br. s.), 2.33 - 2.44 (2 H, m), 1.92 - 2.18 (4 H, m), 1.62 - 1.81 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 474.2.

EXAMPLE 219



347

Ethyl (4-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-1-piperazinyl)acetate



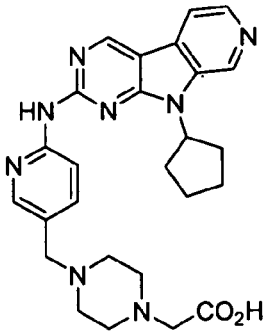
348

Ethyl 2-(4-((6-chloropyridin-3-yl)methyl)piperazin-1-yl)acetate (348): To a stirred suspension of 2-chloro-5-(chloromethyl)pyridine (2.0 g, 12 mmol) in acetonitrile (60 mL) was added potassium carbonate (1.5 mL, 25 mmol) followed by 1-(ethoxycarbonylmethyl)piperazine (2.0 mL, 12 mmol). The resulting mixture was stirred at room temperature for 19 h. The mixture was filtered through celite and the filter cake was washed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was subjected to combi-flash column chromatography (methanol/DCM with Et_3N) to give compound **348** (1.1 g, 30% yield) as a colorless liquid. ^1H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.31 (1 H, d, J=2.0 Hz), 7.66 (1 H, d, J=6.1 Hz), 7.28 (1 H, d, J=8.1 Hz), 4.18 (2 H, q, J=7.1 Hz), 3.50 (2 H, br. s.), 3.21 (2 H, s), 2.36 - 2.77 (8 H, m), 1.27 (3 H, t, J=7.2 Hz). LCMS-ESI (POS), M/Z, M+1: Found 298.1.

Ethyl (4-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-1-piperazinyl)acetate (347): Compound **347** was prepared as an off-white solid (TFA salt) from compound **4** and compound **348** using chemistry similar to that described in example 200. ^1H NMR (500 MHz, *CD_3OD*) δ ppm 9.57 (1 H, s), 9.27 (1 H, s), 8.60 (2 H, s), 8.47 (1 H, d, J=2.0 Hz), 8.32 - 8.43 (1 H, m), 8.07 (1 H, dd, J=8.8, 2.2 Hz), 5.46 (1 H, dq,

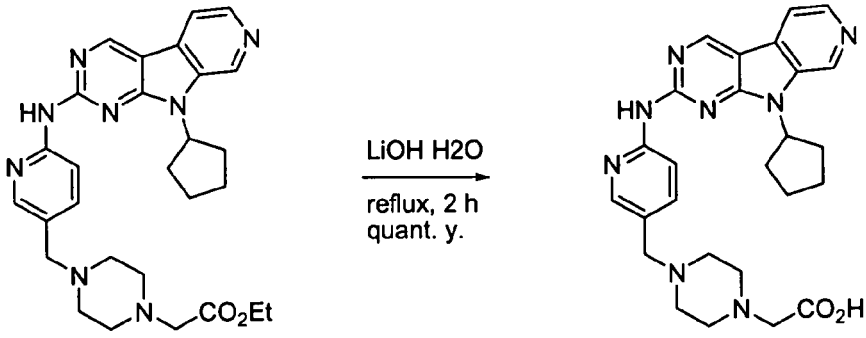
J=9.0, 8.9 Hz), 4.12 - 4.28 (4 H, m), 3.65 (2 H, br. s.), 2.96 - 3.21 (8 H, m), 2.48 - 2.61 (2 H, m), 2.15 - 2.31 (4 H, m), 1.85 - 1.99 (2 H, m), 1.28 (3 H, t, J=7.2 Hz). LCMS-ESI (POS), M/Z, M+1: Found 515.2.

EXAMPLE 220



349

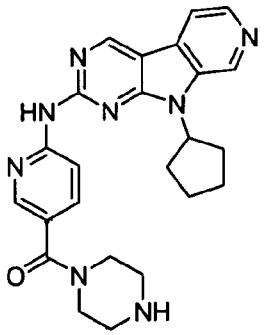
(4-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-1-piperazinyl)acetic acid



347 **349**

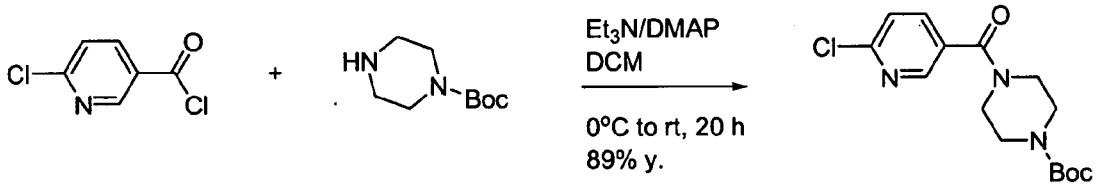
(4-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-1-piperazinyl)acetic acid (349): A mixture of compound **347** (50 mg, 97 μmol) and lithium hydroxide, monohydrate (14 μl, 486 μmol) in methanol (9 mL) and water (3 mL) was heated at reflux for 2 h. After cooling, the crude mixture was subjected to reverse phase preparative HPLC (acetonitrile/H_2O containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **349** (40 mg) as a light yellow solid (TFA salt). ^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 10.84 (1 H, s), 9.62 (1 H, s), 9.38 (1 H, s), 8.68 (1 H, d, J=5.9 Hz), 8.58 (1 H, d, J=6.3 Hz), 8.26 - 8.48 (2 H, m), 7.89 - 8.01 (1 H, m), 5.40 (1 H, quin, J=8.9 Hz), 2.75 - 4.63 (12 H, m), 2.39 - 2.47 (2 H, m), 2.01 - 2.23 (4 H, m), 1.70 - 1.87 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 487.3.

EXAMPLE 221



350

9-cyclopentyl-N-(5-(1-piperazinylcarbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

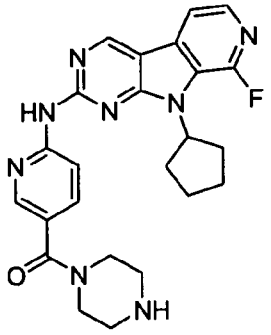


351

***tert*-Butyl 4-(2-chloronicotinoyl)piperazine-1-carboxylate (351):** To a stirred ice-cooled solution of tert-butyl 1-piperazinecarboxylate (2.2 g, 12 mmol), triethylamine (3.2 mL, 23 mmol), and 4-dimethylaminopyridine (0.014 g, 0.11 mmol) in DCM (15 mL) was added 6-chloropyridine-3-carbonyl chloride (2.0 g, 11 mmol) in one portion. The resulting mixture was stirred at 0 °C and gradually warmed up to ambient temperature for 20 h. Upon workup, the mixture was subjected to combi-flash column chromatography (methanol/DCM) to give compound **351** (3.3 g, 89% yield) as a white solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.46 (1 H, d, J=2.0 Hz), 7.74 (1 H, dd, J=8.2, 2.3 Hz), 7.42 (1 H, dd, J=8.2, 0.8 Hz), 3.20 - 4.02 (8 H, m), 1.48 (9 H, s). LCMS-ESI (POS), M/Z, M+1: Found 326.0.

9-cyclopentyl-N-(5-(1-piperazinylcarbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (350): Compound **350** was prepared as a light yellow solid (HCl salt) from compound **4** and compound **351** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 11.06 (1 H, br. s.), 9.70 (1 H, s), 9.47 (1 H, s), 9.39 (2 H, br. s.), 8.67 - 8.75 (2 H, m), 8.51 (1 H, d, J=1.7 Hz), 8.37 (1 H, d, J=8.6 Hz), 8.02 (1 H, dd, J=8.7, 2.3 Hz), 5.43 (1 H, dq, J=8.9, 8.8 Hz), 3.77 (4 H, br. s.), 3.18 (4 H, br. s.), 2.42 - 2.48 (2 H, m), 2.02 - 2.20 (4 H, m), 1.70 - 1.83 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 443.2.

EXAMPLE 222

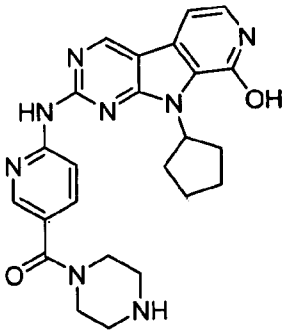


352

9-cyclopentyl-8-fluoro-N-(5-(1-piperazinylcarbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

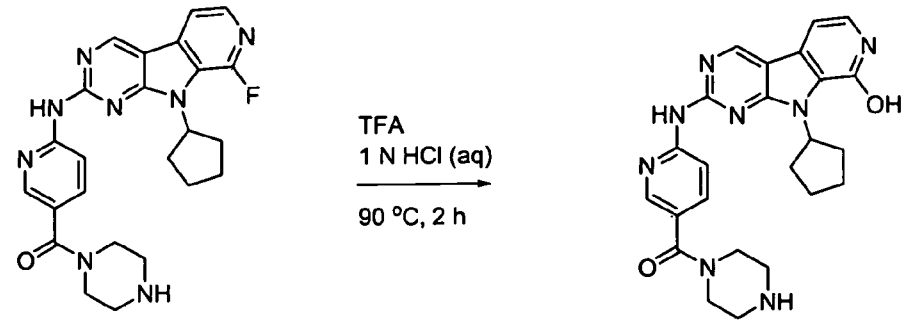
Compound **352** was prepared as an off-white solid (TFA salt) from compound **245** using chemistry similar to that described in example 200. ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 10.60 (1 H, s), 9.45 (1 H, s), 8.83 (2 H, br. s.), 8.47 (1 H, d, J=1.6 Hz), 8.41 (1 H, d, J=8.6 Hz), 8.12 (1 H, dd, J=5.3, 2.9 Hz), 8.05 - 8.09 (1 H, m), 7.97 (1 H, dd, J=9.0, 2.3 Hz), 5.51 (1 H, quin, J=8.9 Hz), 3.74 (4 H, br. s.), 3.20 (4 H, br. s.), 2.33 - 2.41 (2 H, m), 1.98 - 2.22 (4 H, m), 1.69 - 1.85 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 460.9.

EXAMPLE 223



353

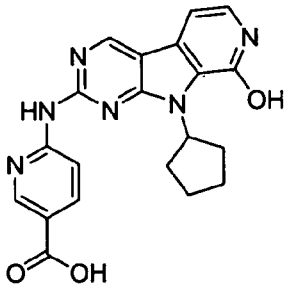
9-cyclopentyl-2-((5-(1-piperazinylcarbonyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol



352 353

9-cyclopentyl-2-((5-(1-piperazinylcarbonyl)-2-pyridinyl)amino)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol (353): Compound **352** was treated with trifluoroacetic acid (4 mL, 54 mmol) in 1 N hydrochloric acid, aqueous solution (8 mL) for 2 h at 90 °C. After the volatiles were partially removed, the residue was subjected to reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **353** (8 mg) as a light yellow solid (TFA salt). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.30 (1 H, s), 8.54 (1 H, s), 7.95 - 8.20 (2 H, m), 7.34 (1 H, d, J=6.7 Hz), 7.14 (1 H, d, J=6.7 Hz), 6.26 (1 H, dq, J=9.4, 9.1 Hz), 3.93 (4 H, br. s.), 3.33 - 3.38 (4 H, m), 2.53 - 2.70 (2 H, m), 2.04 - 2.28 (4 H, m), 1.68 - 1.91 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 459.2.

EXAMPLE 224

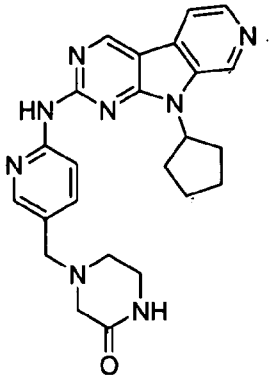


354

6-((9-cyclopentyl-8-hydroxy-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinecarboxylic acid

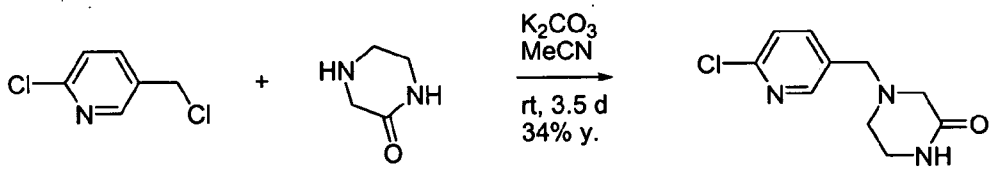
Compound **354** was obtained in the hydrolysis of compound **352** (example 223) as a light yellow solid (HCl salt). ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.42 (1 H, s), 9.04 (1 H, d, J=1.5 Hz), 8.58 (1 H, dd, J=8.9, 2.1 Hz), 7.57 (1 H, d, J=9.0 Hz), 7.40 (1 H, d, J=6.8 Hz), 7.19 (1 H, d, J=6.6 Hz), 6.25 (1 H, dq, J=9.2, 9.0 Hz), 2.52 - 2.65 (2 H, m), 2.07 - 2.25 (4 H, m), 1.73 - 1.87 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 391.1.

EXAMPLE 225



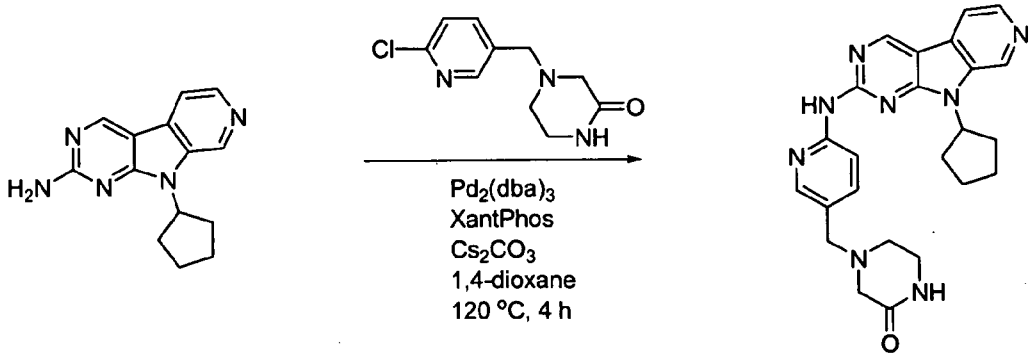
355

4-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-2-piperazinone



356

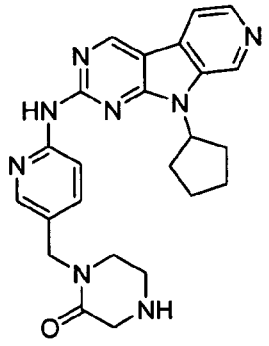
4-((6-Chloropyridin-3-yl)methyl)piperazin-2-one (356): A mixture of 2-chloro-5-(chloromethyl)pyridine (1.4 g, 8.4 mmol), piperazinone (0.84 g, 8.4 mmol), and potassium carbonate (1.0 mL, 17 mmol) in a mixed solvent consisting of acetonitrile (40 mL) and THF (20 mL) was stirred at room temperature for 3.5 days. Upon workup, the mixture was filtered through a layer of celite and the cake was washed with ethyl acetate. The filtrate was concentrated in vacuo and the residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **356** (0.65 g, 34% yield) as an off-white solid. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.35 (1 H, d, J=2.0 Hz), 7.81 (1 H, dd, J=8.1, 2.4 Hz), 7.76 (1 H, br. s.), 7.49 (1 H, d, J=8.3 Hz), 3.57 (2 H, s), 3.10 - 3.16 (2 H, m), 2.93 (2 H, s), 2.52 - 2.56 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 226.0.



4 356 355

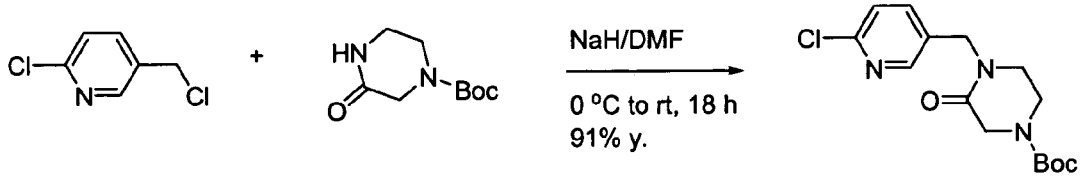
4-((6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-2-piperazinone (355): In a 10 mL microwave reaction vessel were placed compound **4** (93 mg, 367 μmol), compound **356** (83 mg, 367 μmol), tris(dibenzylideneacetone)dipalladium (o) (17 mg, 18 μmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 46 μmol), and cesium carbonate (359 mg, 1101 μmol) followed by 1,4-dioxane (3 mL). The vessel was purged with N_2 for 5 min, then capped and subjected to microwave irradiation for 4 h at 120 °C. The crude mixture was taken up in 4% methanol/DCM and subjected to combi-flash column chromatography (methanol/DCM) followed by preparative reverse phase HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **355** (100 mg) as an off-white solid (TFA salt). ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.67 (1 H, s), 9.34 (1 H, s), 8.69 (1 H, d), 8.66 (1 H, d), 8.48 (1 H, d, J=1.7 Hz), 8.24 (1 H, dd, J=8.8, 2.2 Hz), 8.04 (1 H, d, J=8.6 Hz), 5.48 (1 H, quin, J=8.7 Hz), 4.03 (2 H, s), 3.40 - 3.49 (4 H, m), 3.09 (2 H, t, J=5.3 Hz), 2.48 - 2.60 (2 H, m), 2.14 - 2.32 (4 H, m), 1.85 - 1.98 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 443.2.

EXAMPLE 226



357

1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-2-piperazinone



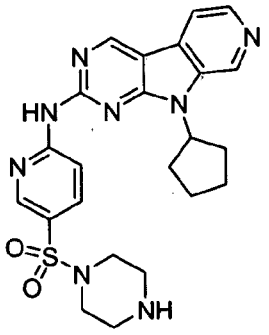
358

***tert*-Butyl 4-((6-chloropyridin-3-yl)methyl)-3-oxopiperazine-1-carboxylate (358):** To a stirred ice-cooled suspension of sodium hydride, (60% dispersion in mineral oil, 0.83 g, 21 mmol) in DMF (15 mL) was added a suspension of *tert*-butyl 3-oxopiperazine-1-carboxylate

(2.5 g, 12 mmol) in DMF (45 mL) through a syringe. The ice-H_2O bath was removed and the resulting mixture, which was a suspension, was stirred at ambient temperature for 30 min. Complete dissolution was observed. 2-chloro-5-(chloromethyl)pyridine (2.0 g, 12 mmol) was added in one portion as a solid. The resulting mixture was stirred at ambient temperature for 18 h then poured into ice and saturated $NaHCO_3$ aqueous solution. It was extracted with ethyl acetate (2 X). The combined organics were washed with saturated $NaHCO_3$ aqueous solution (3 X), dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **358** (3.65 g, 91% yield) as a white solid. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 8.31 (1 H, d, J=2.2 Hz), 7.65 (1 H, dd, J=8.3, 2.4 Hz), 7.33 (1 H, d, J=8.1 Hz), 4.59 (2 H, s), 4.15 (2 H, s), 3.62 (2 H, t, J=5.4 Hz), 3.29 (2 H, t, J=5.1 Hz), 1.46 (9 H, s). LCMS-ESI (POS), M/Z, M+1: Found 326.0.

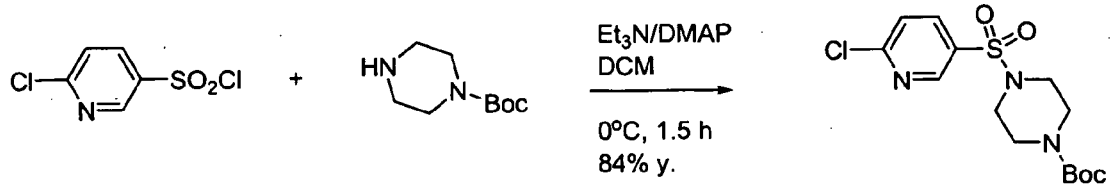
1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-2-piperazinone (357): Compound **357** was prepared as a off-white solid (TFA salt) from compound **4** and compound **358** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.67 (1 H, s), 9.35 (1 H, s), 8.70 (1 H, d), 8.66 (1 H, d), 8.48 (1 H, d, J=1.7 Hz), 8.20 (1 H, dd, J=8.8, 2.2 Hz), 7.91 (1 H, d, J=8.8 Hz), 5.48 (1 H, quin, J=8.7 Hz), 4.76 (2 H, s), 3.96 (2 H, s), 3.71 (2 H, t, J=5.7 Hz), 3.53 - 3.62 (2 H, m), 2.46 - 2.61 (2 H, m), 2.14 - 2.33 (4 H, m), 1.82 - 1.98 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 442.9.

EXAMPLE 227



359

9-Cyclopentyl-N-(5-(1-piperazinylsulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

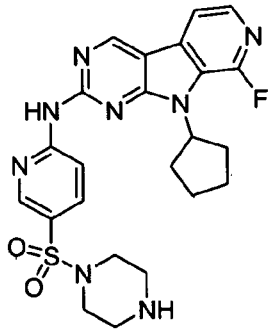


360

***tert*-Butyl 4-((6-chloro-3-pyridinyl)sulfonyl)-1-piperazinecarboxylate (360):** To a stirred ice-cooled solution of *tert*-butyl 1-piperazinecarboxylate (0.88 g, 4.7 mmol), triethylamine (1.3 mL, 9.4 mmol), and 4-dimethylaminopyridine (0.0058 g, 0.047 mmol) in DCM (10 mL) was added 6-chloropyridine-3-sulfonyl chloride (1.0 g, 4.7 mmol) in one portion. The resulting mxiture was stirred at 0 °C and gradually warmed up to ambient temperature for 1.5 h. Upon workup, the mixture was directly subjected to combi-flash column chromatography (methanol/DCM) to give compound **360** (1.44 g, 84% yield) as a white solid. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.75 (1 H, d, J=2.0 Hz), 8.17 (1 H, dd, J=8.4, 2.6 Hz), 7.80 (1 H, d, J=9.0 Hz), 3.40 (4 H, t, J=4.8 Hz), 2.97 (4 H, t, J=5.0 Hz), 1.35 (9 H, s). LCMS-ESI (POS), M/Z, M+1: Found 306 (minus tBu) and 384 (plus Na^+).

9-Cyclopentyl-N-(5-(1-piperazinylsulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (359): Compound **359** was prepared as a white solid (TFA salt) from compound **4** and compound **360** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.59 (1 H, s), 9.29 (1 H, s), 8.72 - 8.78 (2 H, m), 8.63 - 8.66 (1 H, m), 8.61 (1 H, d), 8.22 (1 H, dd, J=8.8, 2.4 Hz), 5.51 (1 H, quin, J=8.9 Hz), 3.37 (8 H, s), 2.46 - 2.60 (2 H, m), 2.13 - 2.34 (4 H, m), 1.87 - 2.01 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 478.9.

EXAMPLE 228

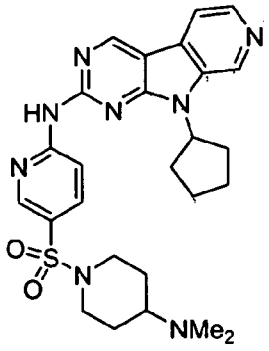


361

9-cyclopentyl-8-fluoro-N-(5-(1-piperazinylsulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

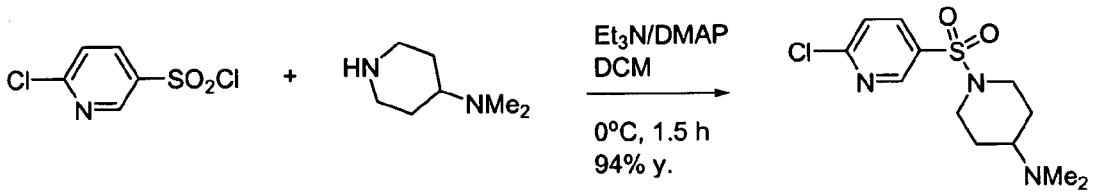
Compound **361** was prepared as a white solid (TFA salt) from compound **245** and compound **360** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.37 (1 H, s), 8.73 (1 H, d, J=2.0 Hz), 8.68 (1 H, d, J=8.8 Hz), 8.21 (1 H, dd, J=9.0, 2.4 Hz), 8.01 - 8.08 (2 H, m), 5.67 (1 H, quin, J=9.2 Hz), 3.36 (8 H, s), 2.35 - 2.49 (2 H, m), 2.09 - 2.28 (4 H, m), 1.81 - 1.95 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 497.2.

EXAMPLE 229



362

9-cyclopentyl-N-(5-((4-(dimethylamino)-1-piperidinyl)sulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

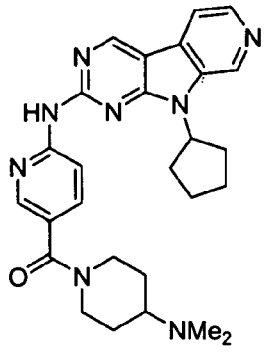


363

1-(6-Chloropyridin-3-ylsulfonyl)-N,N-dimethylpiperidin-4-amine (363): To a stirred ice-cooled solution of 4-(dimethylamino)piperidine (1.2 mL, 9.4 mmol), triethylamine (2.6 mL, 19 mmol), and 4-dimethylaminopyridine (0.012 g, 0.094 mmol) in DCM (18 mL) was added 6-chloropyridine-3-sulfonyl chloride (2.0 g, 9.4 mmol) in one portion. The resulting mxiture was stirred at 0 °C for 1.5 h. Upon workup, the mixture was directly subjected to combi-flash column chromatography (methanol/DCM) to give compound **363** (2.7 g, 94% yield) as a white solid. LCMS-ESI (POS), M/Z, M+1: Found 304.0.

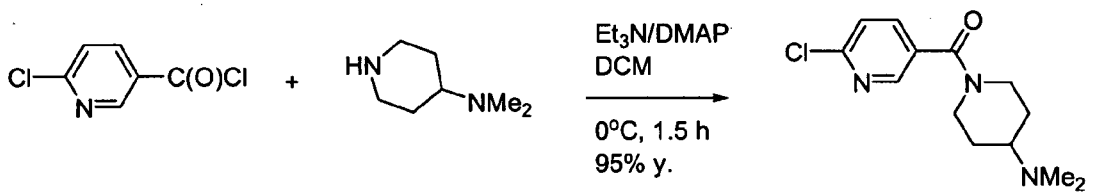
9-cyclopentyl-N-(5-((4-(dimethylamino)-1-piperidinyl)sulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (362): Compound **362** was prepared as an off-white solid (TFA salt) from compound **4** and compound **363** using chemistry similar to that described in example 200. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.56 (1 H, s), 9.25 (1 H, s), 8.66 - 8.75 (2 H, m), 8.58 (2 H, s), 8.18 (1 H, dd, J=8.8, 2.5 Hz), 5.50 (1 H, quin, J=8.8 Hz), 4.01 (2 H, d, J=12.5 Hz), 3.22 (1 H, tt, J=12.1, 3.8 Hz), 2.86 (6 H, s), 2.44 - 2.60 (4 H, m), 2.12 - 2.35 (6 H, m), 1.74 - 2.01 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 521.2.

EXAMPLE 230



364

9-Cyclopentyl-N-(5-((4-(dimethylamino)-1-piperidinyl)carbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

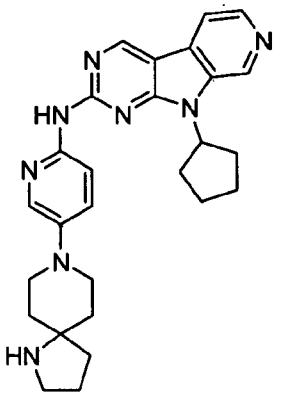


365

(6-Chloropyridin-3-yl)(4-(dimethylamino)piperidin-1-yl)methanone (365): Compound **365** was prepared from 6-chloropyridine-3-carbonyl chloride using chemistry similar to that described in example 226. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.47 (1 H, d, J=2.3 Hz), 7.92 (1 H, dd, J=8.2, 2.3 Hz), 7.61 (1 H, d, J=8.2 Hz), 4.35 - 4.60 (1 H, m), 3.57 (1 H, br. s.), 3.09 (1 H, br. s.), 2.81 (2 H, br. s.), 2.39 (6 H, s), 1.67 - 1.98 (2 H, m), 1.48 (2 H, qd, J=12.0, 4.3 Hz). LCMS-ESI (POS), M/Z, M+1: Found 268.1.

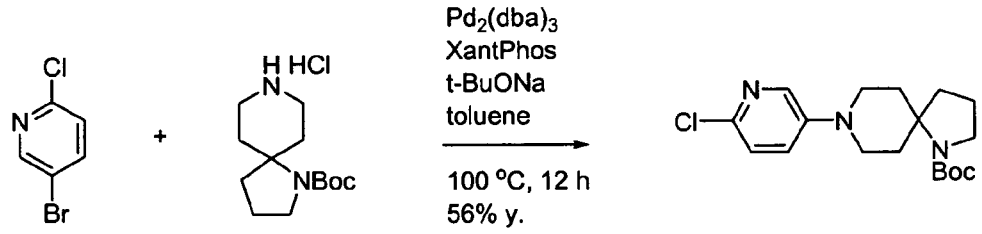
9-Cyclopentyl-N-(5-((4-(dimethylamino)-1-piperidinyl)carbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (364): Compound **364** was prepared as a light yellow solid (TFA salt) from compound **4** and compound **365** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.57 (1 H, s), 9.27 (1 H, s), 8.56 - 8.64 (2 H, m), 8.51 (1 H, d, J=1.7 Hz), 8.44 (1 H, d, J=8.8 Hz), 8.02 (1 H, dd, J=8.7, 2.3 Hz), 5.47 (1 H, quin, J=8.9 Hz), 3.49 - 3.60 (1 H, m, J=12.0, 12.0, 3.8, 3.7 Hz), 2.91 (6 H, s), 2.48 - 2.61 (2 H, m), 2.02 - 2.34 (6 H, m), 1.85 - 1.98 (2 H, m), 1.70 - 1.85 (2 H, m, J=12.3, 12.3, 12.2, 4.4 Hz). LCMS-ESI (POS), M/Z, M+1: Found 485.2.

EXAMPLE 231



366

9-cyclopentyl-N-(5-(1,8-diazaspiro[45]dec-8-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

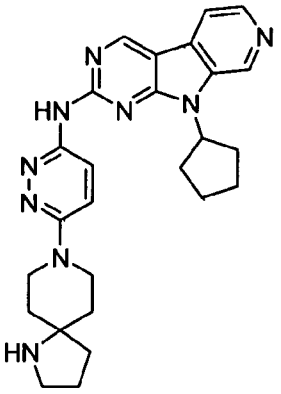


367

***tert*-Butyl 8-(6-chloro-3-pyridinyl)-1,8-diazaspiro[45]decane-1-carboxylate (367):** Compound **367** was prepared as an off-white solid using chemistry similar to that described in Example 1. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.99 (1 H, br. s.), 7.14 (2 H, br. s.), 3.55 - 3.83 (2 H, m), 3.47 (2 H, d, J=15.1 Hz), 2.49 - 3.08 (4 H, m), 1.86 - 2.07 (2 H, m), 1.72 - 1.84 (2 H, m), 1.29 - 1.55 (11 H, m). LCMS-ESI (POS), M/Z, M+1: Found 352.1.

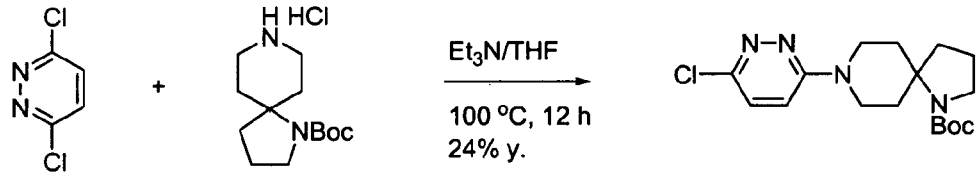
9-cyclopentyl-N-(5-(1,8-diazaspiro[45]dec-8-yl)-2-pyridinyl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (366): Compound **366** was prepared as a yellow solid (TFA salt) from compound **4** and compound **367** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 9.55 (1 H, s), 9.32 (1 H, s), 8.70 (2 H, br. s.), 8.65 (1 H, d, J=6.1 Hz), 8.54 (1 H, d, J=5.9 Hz), 8.10 (1 H, d, J=2.9 Hz), 8.02 (1 H, d, J=8.3 Hz), 7.65 (1 H, d, J=8.3 Hz), 5.36 (1 H, quin, J=8.7 Hz), 3.57 (2 H, ddd, J=12.7, 4.6, 4.4 Hz), 3.28 (3 H, quin, J=6.4 Hz), 3.06 (2 H, ddd, J=12.8, 9.7, 3.2 Hz), 2.38 - 2.47 (2 H, m), 1.84 - 2.17 (12 H, m), 1.68 - 1.81 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 469.3.

EXAMPLE 232



368

9-cyclopentyl-N-(6-(1,8-diazaspiro[45]dec-8-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

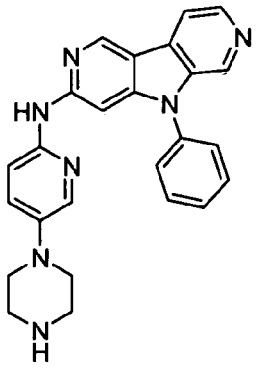


369

***tert*-Butyl 8-(6-chloro-3-pyridazinyl)-1,8-diazaspiro[45]decane-1-carboxylate (369):** Compound **369** was prepared using chemistry similar to that described in example 4. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.24 (1 H, d, J=10.0 Hz), 6.96 (1 H, d, J=9.8 Hz), 4.35 (2 H, d, J=12.7 Hz), 3.39 - 3.55 (2 H, m), 3.03 (2 H, t, J=12.8 Hz), 2.80 - 2.92 (1 H, m), 2.60 (1 H, t, J=13.1 Hz), 1.94 - 2.11 (2 H, m), 1.81 (2 H, quin, J=6.8 Hz), 1.21 - 1.53 (11 H, m). LCMS-ESI (POS), M/Z, M+1: Found 353.0.

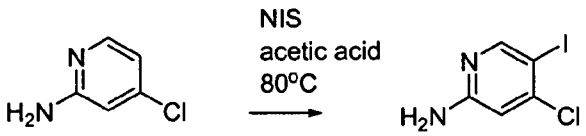
9-cyclopentyl-N-(6-(1,8-diazaspiro[45]dec-8-yl)-3-pyridazinyl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (368): Compound **368** was prepared as a yellow solid (TFA salt) from compound **4** and compound **369** using chemistry similar to that described in example 200. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 10.98 (1 H, br. s.), 9.55 (1 H, s), 9.31 (1 H, s), 8.68 - 8.76 (1 H, m), 8.65 (1 H, d, J=5.9 Hz), 8.52 (1 H, d, J=5.6 Hz), 8.14 (1 H, d, J=9.8 Hz), 7.66 (1 H, d, J=9.3 Hz), 5.34 (1 H, quin, J=8.7 Hz), 4.04 (1 H, dt, J=13.9, 4.4 Hz), 3.34 - 3.40 (2 H, m), 3.29 (2 H, ddd, J=12.5, 6.6, 6.4 Hz), 2.32 - 2.42 (2 H, m), 1.94 - 2.17 (8 H, m), 1.83 - 1.94 (4 H, m), 1.65 - 1.79 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 470.2.

EXAMPLE 233

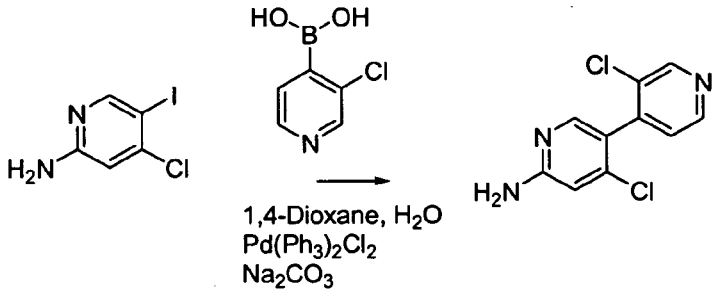


370

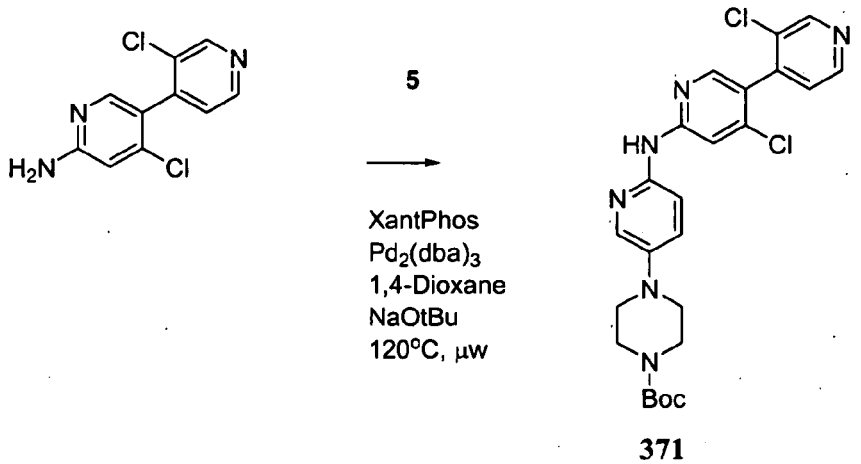
5-phenyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine



4-chloro-5-iodopyridin-2-amine. 4-Chloropyridin-2-amine (0.142 g, 1.10 mmol) and N-iodosuccinimide (0.273 g, 1.22 mmol) were combined in 1.5mL of acetic acid. The solution was sonicated briefly and then heated to 80°C. After 1hour the solution was cooled to room temperature and then concentrated under vacuum. After adjusting the pH to ~8/9 with aqueous ammonia, a light brown solid was collected by filtration. The solid was purified on a 12g Combiflash column eluting with a gradient of DCM to 5%methanol/0.25%NH4OH (~28% in water)/DCM. The fractions containing the product were combined and concentrated under vacuum to give 4-chloro-5-iodopyridin-2-amine (187mg, 67%) as an off-white solid. 1H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.20 (1 H, s), 6.69 (1 H, s), 6.40 (2 H, s); LCMS-ESI (POS), M/Z, M+1: Found 254.9.



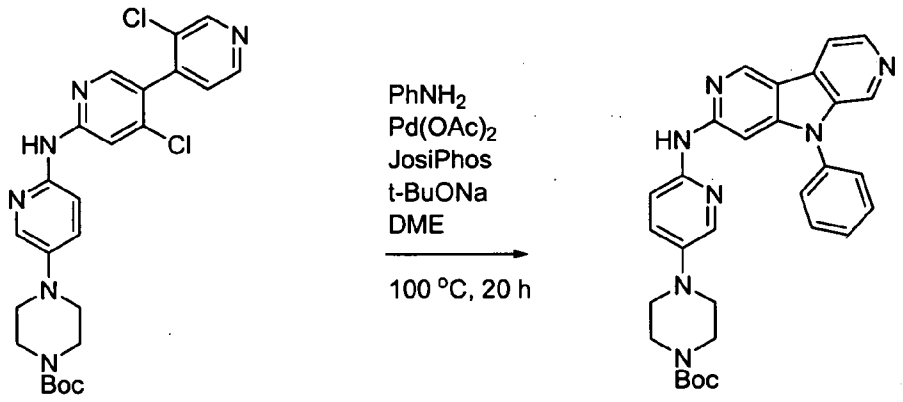
4-chloro-5-(3-chloropyridin-4-yl)pyridin-2-amine. 4-Chloro-5-iodopyridin-2-amine (8.100 g, 31.8 mmol), sodium carbonate (5.00g, 47.7 mmol), and 3-chloropyridin-4-ylboronic acid hydrate (11.2g, 63.7mmol) were combined in 100mL of 1,4-Dioxane and 25mL of water. Nitrogen was bubbled through the solution for ~2min before adding trans-dichlorobis(triphenyl-phosphine)palladium (II) (2.05 g, 2.92 mmol). The solution was heated to 60°C overnight. Additional trans-dichlorobis(triphenyl-phosphine)palladium (II) (0.2g, 0.285mmol), 3-chloropyridin-4-ylboronic acid hydrate (4.00g, 22.8mmol), 15mL of water (degassed) and sodium carbonate (1.75g, 16.6mmol) were added. The solution was heated to 100°C for 5 hours. Additional 3-chloropyridin-4-ylboronic acid hydrate (4.00g, 22.8mmol) was added and the reaction continued for 2 h at 100°C. The solution was concentrated under vacuum to 1/5th the volume and extracted between DCM and water. The aqueous layer was extracted with 10%isopropanol/DCM. The combined organics were dried over $MgSO_4$ and then concentrated under vacuum to give an orange solid. The solid was slurried with DCM and then filtered through a fritted funnel. The solids were washed with additional DCM. The combined filtrate was purified on a 80g Combiflash column (dry loaded), eluting with 2%methanol/0.1%NH4OH (~28% in water) /DCM to 8% methanol /0.4% NH4OH (~28% in water)/ DCM. The fractions containing the product were concentrated under vacuum to give a yellowish solid. The solids were triturated with DCM to give 4-chloro-5-(3-chloropyridin-4-yl)pyridin-2-amine (3.93g, 51%) as an off white solid. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.73 (1 H, s), 8.58 (1 H, d, J=4.9 Hz), 7.87 (1 H, s), 7.44 (1 H, d, J=4.9 Hz), 6.64 (1 H, s), 6.55 (2 H, br. s.); LCMS-ESI (POS), M/Z, M+1: Found 239.9.



371

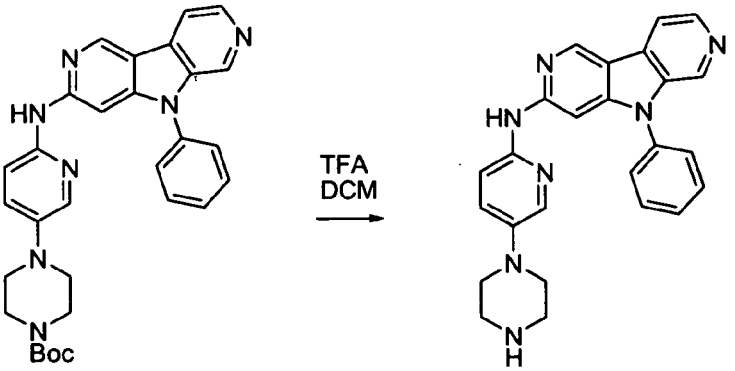
***tert*-Butyl 4-(6-(4-chloro-5-(3-chloropyridin-4-yl)pyridin-2-ylamino)pyridin-3-yl)piperazine-1-carboxylate (371).** 4-Chloro-5-(3-chloropyridin-4-yl)pyridin-2-amine (0.263

g, 1.10 mmol), sodium 2-methylpropan-2-olate (0.316 g, 3.29 mmol), and compound **5** (0.424 g, 1.42 mmol) were combined in anhydrous 1,4-dioxane (5 mL). Nitrogen was bubbled through the solution for ~1min before adding 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0634 g, 0.110 mmol) and $Pd_2(dba)_3$ (0.0502 g, 0.0548 mmol). The solution was then heated to 120°C with microwave irradiation for 1hour. The solution was purified on a 40g CombiFlash column (dry loaded) eluting with a gradient of hexane to ethyl acetate. The fractions containing the product were combined and concentrated under vacuum to give compound **371** (0.492g, 90%) as a yellow solid. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 9.95 (1 H, s), 8.78 (1 H, br. s.), 8.63 (1 H, d, J=4.9 Hz), 8.17 (1 H, s), 8.04 (1 H, s), 8.01 (1 H, d, J=2.9 Hz), 7.55 (1 H, d, J=9.0 Hz), 7.52 (1 H, d, J=4.9 Hz), 7.46 (1 H, dd, J=9.0, 2.9 Hz), 3.41 - 3.54 (4 H, m), 2.99 - 3.10 (4 H, m), 1.42 (9 H, s); LCMS-ESI (POS), M/Z, M+1: Found 501.1.



371 **372**

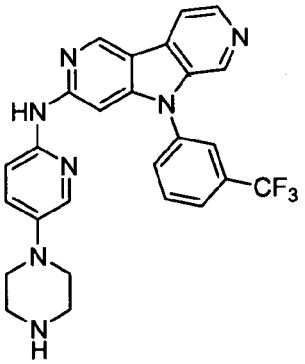
tert-Butyl 4-(6-((5-phenyl-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (372): In a 10 mL single-necked round bottom flask were placed *tert*-butyl 4-(6-(4-chloro-5-(3-chloropyridin-4-yl)pyridin-2-ylamino)pyridin-3-yl)piperazine-1-carboxylate (**371**) (50 mg, 100 μmol), palladium diacetate (11 mg, 50 μmol), Josiphos (28 mg, 50 μmol), and sodium *tert*-butoxide (29 mg, 299 μmol). The flask was subjected to 3 cycles of evacuation and back-filling with N_2. Aniline (36 μl, 399 μmol) was added under N_2 followed by 1,2-dimethoxyethane (3 mL). The resulting mixture was stirred at 100 °C for 20 h. After the volatiles were removed, the residue was subjected to combi-flash column chromatography (methanol/DCM). The product containing compound **372** after concentration was used without further purification. LCMS-ESI (POS), M/Z, M+1: Found 522.2.



372 370

5-phenyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine (370): A solution of crude compound **372** in DCM (8 mL) was treated with trifluoroacetic acid (2.0 mL, 27 mmol) at room temperature for 2 h. After the volatiles were removed, the residue was subjected to reverse phase preparative HPLC (acetonitrile/H_2O containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **370** (12 mg) as a yellow solid (TFA salt). ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.46 (1 H, s), 8.80 (1 H, d, J=0.7 Hz), 8.65 (1 H, d, J=5.6 Hz), 8.53 (1 H, d, J=5.6 Hz), 8.05 (1 H, d, J=2.9 Hz), 7.90 (1 H, dd, J=9.3, 2.9 Hz), 7.77 - 7.83 (2 H, m), 7.68 - 7.76 (3 H, m), 7.24 (1 H, d, J=9.3 Hz), 7.14 (1 H, s), 3.46 - 3.53 (4 H, m), 3.40 - 3.46 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 422.2.

EXAMPLE 234



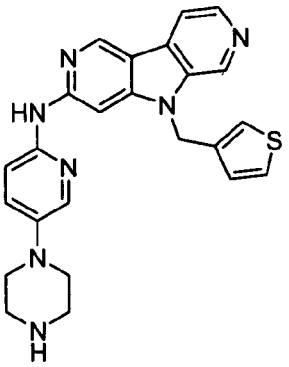
373

N-(5-(1-piperazinyl)-2-pyridinyl)-5-(3-(trifluoromethyl)phenyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine

Compound **373** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.62 (1 H, d, J=1.0 Hz), 9.01 (1 H, s), 8.81 (1 H, d, J=5.4 Hz), 8.74 (1 H, d, J=5.9 Hz), 8.18 (1 H, s), 7.97 - 8.11 (5 H, m),

7.34 (1 H, d, J=9.5 Hz), 7.10 (1 H, s), 3.48 - 3.56 (4 H, m), 3.40 - 3.48 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 490.1.

EXAMPLE 235

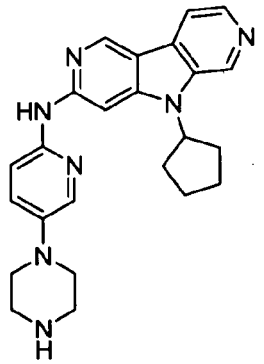


374

N-(5-(1-piperazinyl)-2-pyridinyl)-5-(3-thiophenylmethyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine

Compound **374** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.44 (1 H, s), 9.21 (1 H, s), 8.63 (1 H, d, J=5.9 Hz), 8.56 (1 H, d, J=5.6 Hz), 8.05 (1 H, d, J=2.9 Hz), 7.95 (1 H, dd, J=9.5, 2.9 Hz), 7.45 (1 H, dd, J=5.1, 2.9 Hz), 7.40 - 7.43 (1 H, m), 7.37 (1 H, s), 7.30 (1 H, d, J=9.3 Hz), 7.05 (1 H, dd, J=5.1, 1.5 Hz), 5.77 (2 H, s), 3.47 - 3.52 (4 H, m), 3.41 - 3.47 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 441.9.

EXAMPLE 236

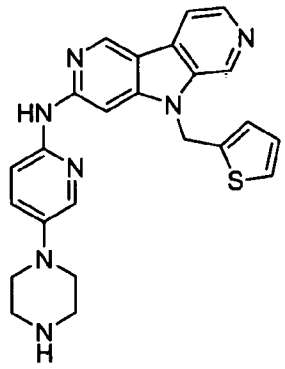


375

5-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine

Compound **375** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. LCMS-ESI (POS), M/Z, M+1: Found 414.1.

EXAMPLE 237

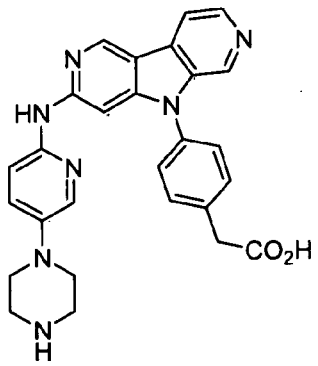


376

N-(5-(1-piperazinyl)-2-pyridinyl)-5-(2-thiophenylmethyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine

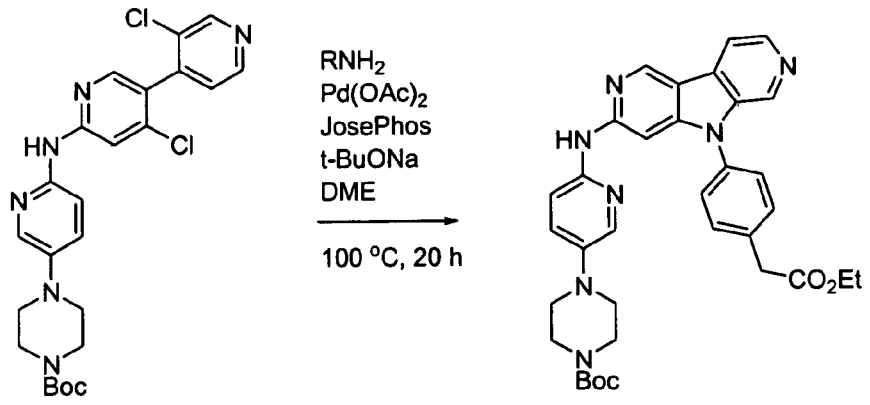
Compound **376** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.40 (1 H, d, J=0.7 Hz), 9.25 (1 H, d, J=0.7 Hz), 8.62 (1 H, d, J=5.6 Hz), 8.50 (1 H, d, J=5.6 Hz), 8.06 (1 H, d, J=2.7 Hz), 7.93 (1 H, dd, J=9.3, 2.9 Hz), 7.44 (1 H, s), 7.37 (1 H, dd, J=5.1, 1.2 Hz), 7.31 (1 H, d, J=9.3 Hz), 7.27 (1 H, dd, J=3.7, 1.0 Hz), 7.01 (1 H, dd, J=5.1, 3.4 Hz), 5.96 (2 H, s), 3.47 - 3.53 (4 H, m), 3.42 - 3.47 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 442.1.

EXAMPLE 238



377

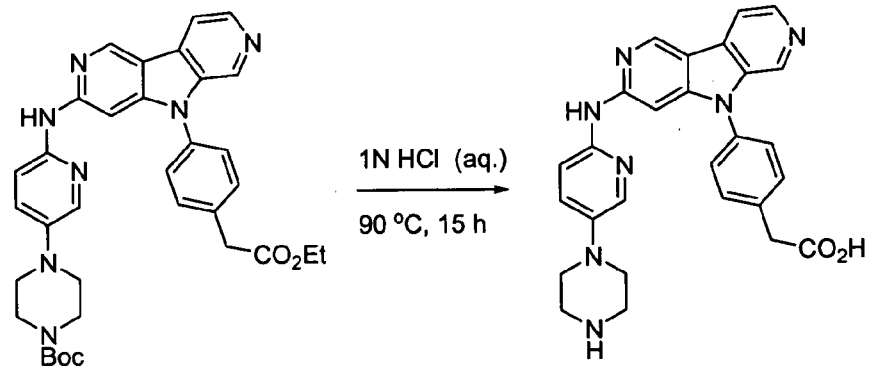
(4-(3-((5-(1-piperazinyl)-2-pyridinyl)amino)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-5-yl)phenyl)acetic acid



371 378

tert-Butyl 4-(6-((5-(4-(2-ethoxy-2-oxoethyl)phenyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (378)

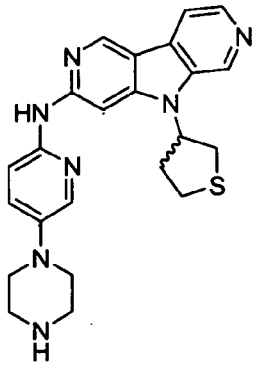
Compound **378** was prepared using chemistry similar to that described in example 233. LCMS-ESI (POS), M/Z, M+1: Found 608.3.



378 377

(4-(3-((5-(1-Piperazinyl)-2-pyridinyl)amino)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-5-yl)phenyl)acetic acid (377): A mixture of crude compound **378** and 1N hydrochloric acid (aqueous solution) (10 mL, 10.0 mmol) was stirred at 90 °C for 15 h. After concentration, the residue was taken up with 1 N HCl aqueous solution and subjected to reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **377** (6 mg) as a yellow solid (TFA salt). ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.48 (1 H, s), 8.85 (1 H, s), 8.66 (1 H, d, J=5.6 Hz), 8.57 (1 H, d, J=5.6 Hz), 8.04 (1 H, d, J=2.7 Hz), 7.93 (1 H, dd, J=9.3, 2.9 Hz), 7.67 - 7.74 (4 H, m), 7.25 (1 H, d, J=9.3 Hz), 7.13 (1 H, s), 3.85 (2 H, s), 3.46 - 3.51 (4 H, m), 3.41 - 3.46 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 480.2.

EXAMPLE 239

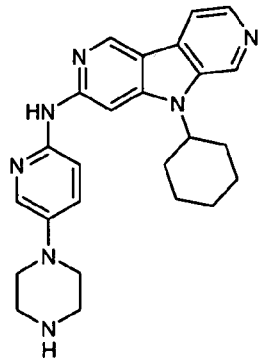


379

N-(5-(1-piperazinyl)-2-pyridinyl)-5-(tetrahydro-3-thiophenyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine

Compound **379** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.54 (1 H, s), 9.44 (1 H, s), 8.72 (1 H, d), 8.67 (1 H, d, J=5.9 Hz), 8.08 (1 H, dd, J=9.5, 2.9 Hz), 8.01 (1 H, d, J=2.7 Hz), 7.61 (1 H, s), 7.41 (1 H, d, J=9.3 Hz), 5.64 - 5.74 (1 H, m), 3.48 - 3.56 (6 H, m), 3.42 - 3.47 (4 H, m), 3.12 - 3.20 (2 H, m), 2.59 - 2.81 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 432.1.

EXAMPLE 240

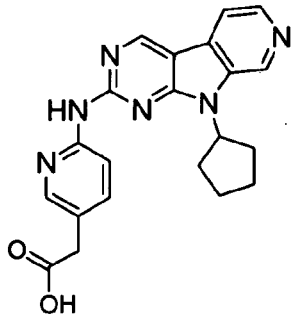


380

5-cyclohexyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine

Compound **380** was prepared using chemistry similar to that described in example 233. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 9.56 (1 H, s), 9.47 (1 H, s), 8.77 (1 H, d, J=6.1 Hz), 8.65 (1 H, d, J=6.1 Hz), 8.10 (1 H, dd, J=9.5, 2.9 Hz), 8.00 (1 H, d, J=2.7 Hz), 7.54 (1 H, s), 7.42 (1 H, d, J=9.5 Hz), 4.77 - 4.84 (1 H, m), 3.50 - 3.54 (4 H, m), 3.43 - 3.48 (4 H, m), 2.31 - 2.44 (2 H, m), 2.04 - 2.16 (4 H, m), 1.86 - 1.95 (1 H, m), 1.65 - 1.77 (2 H, m), 1.46 - 1.59 (1 H, m); LCMS-ESI (POS), M/Z, M+1: Found 428.2.

EXAMPLE 241

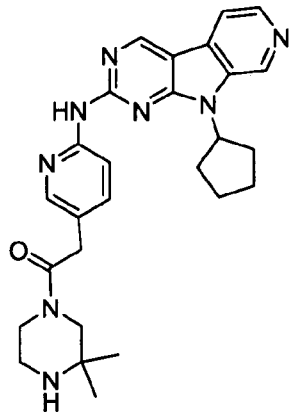


381

(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)acetic acid

Sodium 2-methylpropan-2-olate (97 mg, 1007 μmol) was added to a dioxane (3 mL) solution containing methyl 2-(6-chloropyridin-3-yl)acetate (69 mg, 369 μmol), tris(dibenzylideneacetone)dipalladium(23 mg, 25 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (29 mg, 50 μmol), and compound **4** (85 mg, 336 μmol) . The resulting mixture was stirred in the microwave at 120 °C for 3 h. The mixture was then purified on silica eluting with a DCM/methanol gradient (0-10%). Desired fractions containing the ester were pooled and concentrated. The ester was then dissolved in a 3 N NaOH / methanol (1:1) solution and stirred for 3 h at 50 °C. Next, the solution was acidified to pH 2 and concentrated to dryness. The resulting residue was then purified by prep HPLC. Desired fractions were pooled and lyophilized to give compound **381** (86 mg, 66% yield). ^{1}H NMR (400 MHz, *CD_3OD*, TFA salt) δ ppm 1.82 - 2.05 (m, 2 H) 2.11 - 2.38 (m, 4 H) 2.45 - 2.64 (m, 2 H) 3.83 (s, 2 H) 5.50 (qn, J=8.61 Hz, 1 H) 7.84 (d, J=8.80 Hz, 1 H) 8.20 (dd, J=9.00, 2.15 Hz, 1 H) 8.41 (d, J=1.57 Hz, 1 H) 8.56 - 8.73 (m, 2 H) 9.23 - 9.40 (m, 1 H) 9.55 - 9.72 (m, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 389, Calculated 389.

EXAMPLE 242

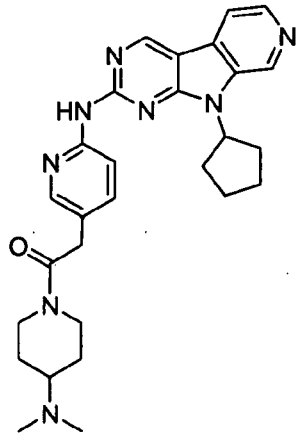


382

9-cyclopentyl-N-(5-(2-(3,3-dimethyl-1-piperazinyl)-2-oxoethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Triethylamine (4 eq.) was added to a DMF solution containing 2,2-dimethylpiperazine (1.2 eq.), compound **381** (1 eq.), and PyBOP (1.1 eq.). The resulting solution was stirred for 3 h at room temperature. The product was purified via reverse phase HPLC (10-70% acetonitrile/water). Desired fractions were pooled and lyophilized to give compound **382**. ^{1}H NMR (400 MHz, *CD_3OD*, TFA salt) δ ppm 1.43 (s, 3 H) 1.50 (s, 3 H) 1.93 (d, *J*=6.06 Hz, 2 H) 2.15 - 2.34 (m, 4 H) 2.47 - 2.62 (m, 1 H) 3.43 (dd, *J*=3.33, 1.56 Hz, 1 H) 3.71 (s, 1 H) 3.77 (s, 1 H) 3.83 - 4.00 (m, 2 H) 4.06 (s, 1 H) 5.39 - 5.58 (m, 1 H) 7.94 (br. s., 1 H) 8.09 (dd, *J*=8.71, 2.05 Hz, 1 H) 8.35 (d, *J*=1.76 Hz, 1 H) 8.55 - 8.67 (m, 1 H) 9.29 (s, 1 H) 9.55 - 9.69 (m, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 577.2, Calculated 577.

EXAMPLE 243

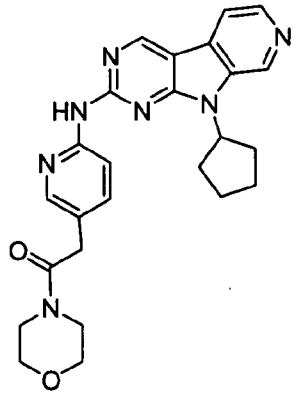


383

9-cyclopentyl-N-(5-(2-(4-(dimethylamino)-1-piperidinyl)-2-oxoethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **383** was prepared using chemistry similar to that described in example 242. ^{1}H NMR (500 MHz, *CD_3OD*, TFA salt) δ ppm 1.65 (dd, *J*=12.35, 4.52 Hz, 1 H) 1.81 (dd, *J*=12.35, 4.28 Hz, 1 H) 1.89 - 2.00 (m, 2 H) 2.11 - 2.35 (m, 6 H) 2.48 - 2.63 (m, 2 H) 2.70 - 2.84 (m, 1 H) 2.93 (s, 6 H) 3.23 - 3.29 (m, 1 H) 3.48 - 3.58 (m, 1 H) 4.01 (s, 2 H) 4.27 - 4.37 (m, 1 H) 4.72 - 4.82 (m, 1 H) 5.50 (qn, *J*=8.80 Hz, 1 H) 7.85 (d, *J*=8.80 Hz, 1 H) 8.14 (dd, *J*=8.80, 1.96 Hz, 1 H) 8.36 (d, *J*=1.71 Hz, 1 H) 8.63 - 8.70 (m, 2 H) 9.34 (s, 1 H) 9.64 - 9.71 (m, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 499, Calculated 499.

EXAMPLE 244

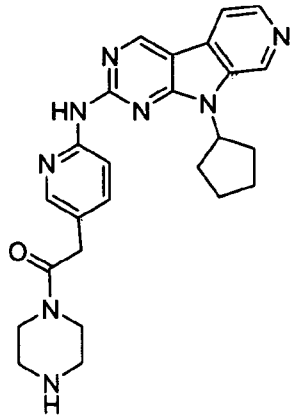


384

9-cyclopentyl-N-(5-(2-(4-morpholinyl)-2-oxoethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Title compound **384** was prepared using chemistry similar to that described in example 242. ^{1}H NMR (500 MHz, *CD_3OD*, TFA salt) δ ppm 1.86 - 2.00 (m, 2 H) 2.16 - 2.35 (m, 4 H) 2.47 - 2.63 (m, 2 H) 3.63 - 3.67 (m, 2 H) 3.70 (ddd, *J*=14.37, 4.71, 4.40 Hz, 4 H) 3.74 - 3.78 (m, 2 H) 3.98 (s, 2 H) 5.50 (qn, *J*=8.80 Hz, 1 H) 7.81 (d, *J*=8.80 Hz, 1 H) 8.16 (dd, *J*=8.80, 2.20 Hz, 1 H) 8.36 (d, *J*=1.96 Hz, 1 H) 8.62 - 8.71 (m, 2 H) 9.33 (s, 1 H) 9.62 - 9.71 (m, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 458, Calculated 458

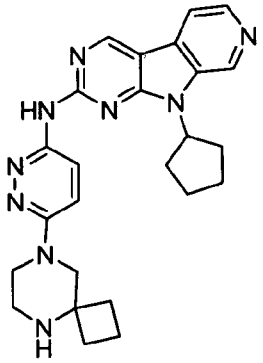
EXAMPLE 245



385
9-cyclopentyl-N-(5-(2-oxo-2-(1-piperazinyl)ethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **385** was prepared using chemistry similar to that described in example 242. ^{1}H NMR (500 MHz, *CD$_3$OD*, TFA salt) δ ppm 1.94 (ddd, *J*=11.49, 5.62, 5.38 Hz, 2 H) 2.17 - 2.35 (m, 4 H) 2.48 - 2.64 (m, 2 H) 3.30 (ddd, 2 H) 3.36 - 3.40 (m, 2 H) 3.83 - 3.99 (m, 4 H) 4.01 (s, 2 H) 5.50 (qn, *J*=8.80 Hz, 1 H) 7.89 (d, *J*=8.80 Hz, 1 H) 8.11 (dd, *J*=8.80, 1.96 Hz, 1 H) 8.35 (d, *J*=1.71 Hz, 1 H) 8.59 - 8.70 (m, 2 H) 9.30 (s, 1 H) 9.64 (s, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 457, Calculated 457.

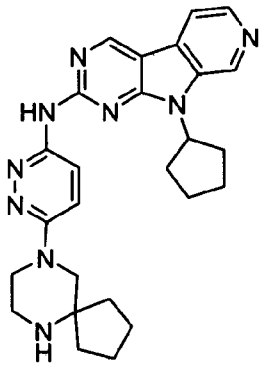
EXAMPLE 246



386
9-cyclopentyl-N-(6-(5,8-diazaspiro[3.5]non-8-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **386** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (400 MHz, *CD$_3$OD*) δ ppm 1.80 (m, 2 H) 1.93 - 2.22 (m, 6 H) 2.22 - 2.44 (m, 4 H) 3.24 - 3.30 (m, 2 H) 3.69 - 3.82 (m, 2 H) 3.86 (s, 2 H) 5.35 (qn, *J*=8.71 Hz, 1 H) 7.65 (d, *J*=9.78 Hz, 1 H) 8.18 - 8.30 (m, 2 H) 8.41 (d, *J*=5.67 Hz, 1 H) 8.98 (s, 1 H) 9.30 (s, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 456, Calculated 456.

EXAMPLE 247

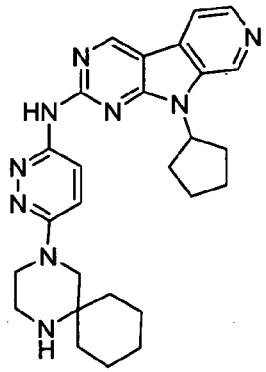


387

9-cyclopentyl-N-(6-(6,9-diazaspiro[4.5]dec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **387** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (500 MHz, *CD_3OD*, TFA salt) δ ppm 1.70 - 1.86 (m, 8 H) 1.88 - 1.99 (m, 2 H) 1.99 - 2.06 (m, 2 H) 2.06 - 2.15 (m, 2 H) 2.26 - 2.40 (m, 2 H) 3.29 - 3.38 (m, 2 H) 3.65 (s, 2 H) 3.73 - 3.84 (m, 2 H) 5.33 (qn, *J*=8.93 Hz, 1 H) 7.48 (d, *J*=10.03 Hz, 1 H) 8.04 (d, *J*=5.38 Hz, 1 H) 8.29 - 8.41 (m, 2 H) 8.85 (s, 1 H) 9.16 (s, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 470, Calculated 470.

EXAMPLE 248

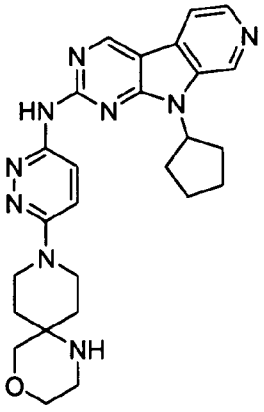


388

9-cyclopentyl-N-(6-(1,4-diazaspiro[5.5]undec-4-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

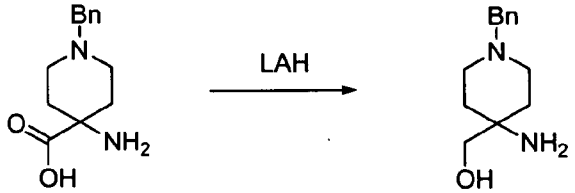
Compound **388** was prepared using chemistry similar to that described in example 1. ^{1}H NMR (400 MHz, *CD_3OD*, TFA salt) δ ppm 1.56 - 1.82 (m, 7 H) 1.82 - 1.97 (m, 2 H) 1.97 - 2.12 (m, 2 H) 2.12 - 2.34 (m, 4 H) 2.42 - 2.61 (m, 2 H) 3.40 - 3.56 (m, 2 H) 3.89 - 4.06 (m, 4 H) 5.47 (qn, *J*=8.80 Hz, 1 H) 7.96 (d, *J*=10.17 Hz, 1 H) 8.12 (d, *J*=9.78 Hz, 1 H) 8.66 (s, 2 H) 9.33 (s, 1 H) 9.66 (s, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 470, Calculated 470.

EXAMPLE 249



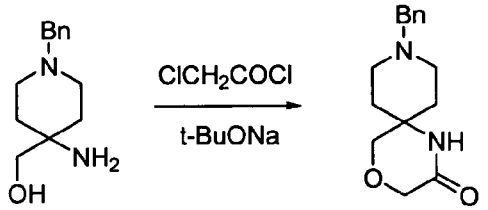
389

9-cyclopentyl-N-(6-(4-oxa-1,9-diazaspiro[5.5]undec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



390 391

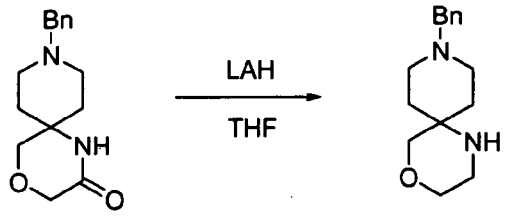
(4-Amino-1-benzylpiperidin-4-yl)methanol (391): Lithium aluminum hydride (1.94 g, 51.2 mmol) was added to a THF (100 mL) solution of 4-amino-1-benzylpiperidine-4-carboxylic acid [Albert, J. S. et al. *J. Med. Chem.* **2002,** 45, (18), 3972-3983] (**390**) (3.00 g, 12.8 mmol). The resulting mixture was stirred for 1.5 h at reflux. The reaction was cooled to room temperature and the following additions were made slowly: 2 mL of water followed by 2 mL of 1 N NaOH, and finally 4 mL of water. The mixture was then filtered and concentrated to give compound **391** as a thick clear oil (2.22 g, 79% yield). The material was used in the next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 221, Calculated 221.



391 392

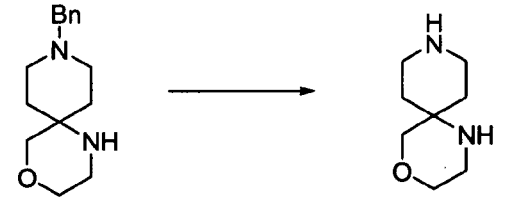
9-(phenylmethyl)-4-oxa-1,9-diazaspiro[5.5]undecan-2-one (392): Triethylamine (2 mL 14 mmol) was added to a DCM (50 mL) solution containing chloroacetyl chloride (1 mL, 14 mmol) and compound **391** (3 g, 14 mmol) . The resulting mixture was stirred 2h at 23 °C. The solvent was stripped and THF was added followed by potassium tert-butoxide (5 g, 41 mmol). The resulting solution was stirred overnight at room temperature. The reaction was

then concentrated to dryness and the resulting residue was washed with 200 mL of absolute ethanol. The ethanolic solution was then concentrated to give 3.16 g of 9-(phenylmethyl)-4-oxa-1,9-diazaspiro[5.5]undecan-2-one. The material was used in the next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 261, Calculated 261.



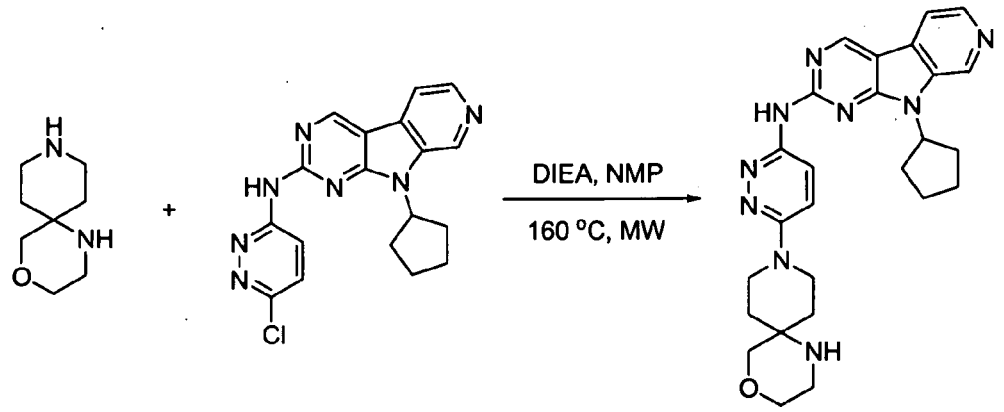
392 393

9-(phenylmethyl)-4-oxa-1,9-diazaspiro[5.5]undecane (393): LAH (2.00 g, 52.7 mmol) was added to a THF (100 mL) solution containing 9-(phenylmethyl)-4-oxa-1,9-diazaspiro[5.5]undecan-2-one (3.1893 g, 12.3 mmol). The resulting mixture was stirred 1 h at reflux. The reaction was then cooled to room temperature and the following additions were made slowly: 2 mL of water followed by 2mL of 1 N NaOH, and finally 4 mL of water. The mixture was then filtered and concentrated to give a thick clear oil (2.66g, 88% yield). The material was used in the next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 247, Calculated 247.



393 394

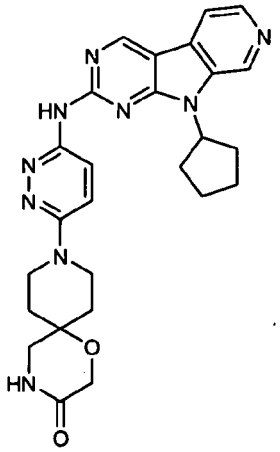
4-oxa-1,9-diazaspiro[5.5]undecane (395): Pearlman'sCatalyst (28.5 mg, 203 μmol) was added to an ethanolic (40 mL) solution containing compound **393** (500 mg, 2030 μmol). The resulting mixture was placed under an atmosphere of hydrogen and stirred overnight at 100 °C (bath temperature). Next, the reaction was cooled to room temperature, filtered, and concentrated to give compound **394** (301 mg, 95% yield). The material was used without further purification. LCMS-ESI (POS), M/Z, M+1: Found 157, Calculated 157.



394 140 389

9-cyclopentyl-N-(6-(4-oxa-1,9-diazaspiro[5.5]undec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (389): Compound **394** (30 mg, 191 μmol) was added to an NMP (4 mL) solution containing compound **140** (70 mg, 191 μmol) and N,N-diisopropyl-ethylamine (74 mg, 574 μmol). The resulting mixture was heated in a microwave for 12 h at 165 °C. After cooling, the mixture was purified on the reverse phase HPLC (10-50% acetonitrile Method). Desired fractions were pooled and lyophilized to give compoumd **389** (10 mg,11% yield). ^{1}H NMR (400 MHz, *CD$_3$OD*, TFA salt) δ ppm 1.81 - 2.07 (m, 4 H) 2.10 - 2.38 (m, 6 H) 2.52 (m, 2 H) 3.37 - 3.42 (m, 3 H) 3.42 - 3.54 (m, 2 H) 3.91 - 4.03 (m, 3 H) 4.11 - 4.28 (m, 2 H) 5.49 (qn, *J*=8.80 Hz, 1 H) 7.97 (d, *J*=9.98 Hz, 1 H) 8.09 (d, *J*=9.98 Hz, 1 H) 8.58 - 8.63 (m, 1 H) 8.62 - 8.68 (m, 1 H) 9.30 (s, 1 H) 9.63 (s, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 486, Calculated 486.

EXAMPLE 250



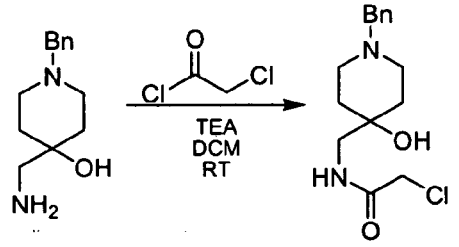
396

9-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-oxa-4,9-diazaspiro[5.5]undecan-3-one



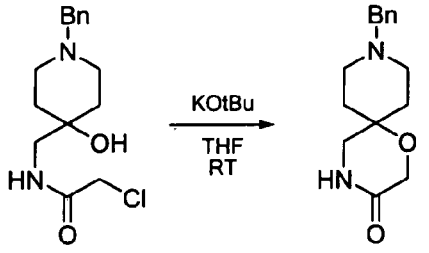
397

4-(aminomethyl)-1-benzylpiperidin-4-ol (397): To a pre-cooled solution (20 °C) of 1-benzyl-4-piperidone (35.0 mL, 196 mmol) and triethylamine (5.5 mL, 40 mmol) was added trimethylsilylcyanide (32.0 mL, 240 mmol), portionwise over 10 minutes. Once the addition was complete, the reaction mixture was stirred at room temperature for 3 hours. This reaction mixture was then cautiously added (10 mL portions over 12 minutes) to a stirring mixture of lithium aluminum hydride (8.5 g, 224 mmol) in tetrahydrofuran (420 mL). Once the addition was complete the reaction mixture was refluxed for 1.5 hours. After cooling to room temperature, the reaction was quenched with water (8.5 mL), followed by 1N NaOH (8.5 mL), and then water (2 x 8.5 mL). The resulting mixture was allowed to stir at room temperature overnight. The solids were filtered off and rinsed with DCM and ethanol. The filtrate was concentrated down to a solid and then purified by flash chromatography (0-20% methanol in DCM with 1% NH_4OH) to give compound **397** as a yellow solid (39.7 g, 92%). LCMS-ESI (POS), M/Z, M+1: Found 221.2, Calculated 221.2.



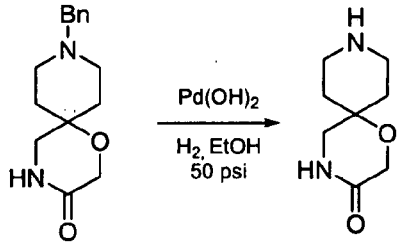
397 398

N-((1-benzyl-4-hydroxypiperidin-4-yl)methyl)-2-chloroacetamide (398): To a solution of compound **397** (39.7 g, 180 mmol) in dichloromethane (350 mL) was added triethylamine (50.0 mL, 359 mmol), followed by dropwise addition of chloroacetyl chloride (16.5 mL, 207 mmol) over 15 minutes. The resulting solution was stirred at room temperature for 1.25 hours. The crude mixture was diluted with DCM and water, and extracted with DCM twice. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give compound **398** (41.9 g, 78%). LCMS-ESI (POS), M/Z, M+1: Found 297.1, Calculated 297.1.



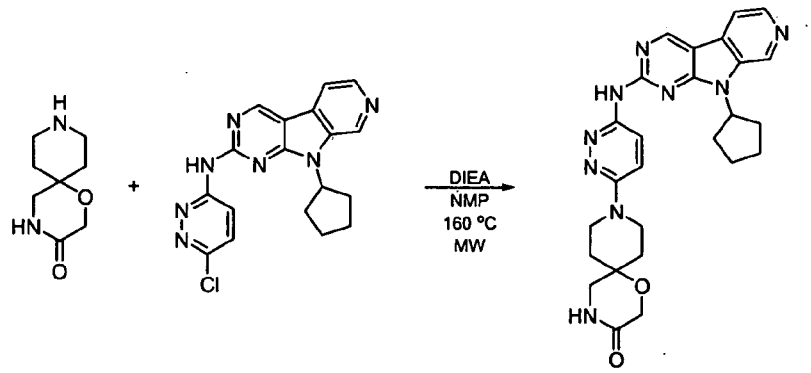
398 399

9-benzyl-1-oxa-4,9-diazaspiro[5.5]undecan-3-one (399): To a mixture of compound **398** (41.9 g, 141 mmol) in tetrahydrofuran (300 mL) was added potassium tert-butoxide (31.8 g, 283 mmol), portionwise over 40 minutes. After 3.5 hours of stirring at room temperature, the reaction was concentrated in vacuo. The residue was diluted with DCM and water, and then neutralized with 3N HCl. The remaining solids were filtered off and the filtrate was concentrated to an oil. The residue was taken up in hot ethanol (100 mL). After allowing the solution to cool to ~45 °C, the salts were filtered off, and the filtrate was concentrated to a brown solid. The crude material was purified by flash chromatography (0-20% methanol in DCM with 1% NH_4OH) to give compound **399** as an orange solid (22.8 g, 62%). LCMS-ESI (POS), M/Z, M+1: Found 261.1, Calculated 261.1.



399 400

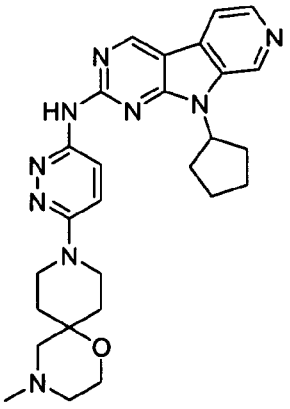
1-oxa-4,9-diazaspiro[5.5]undecan-3-one (400): To a solution of compound **399** (316.1 mg, 1214 μmol) in ethanol (15 mL) was added palladium hydroxide, 20 wt % pd (dry basis) on carbon, wet (300 mg, 427 μmol). After hydrogenating the reaction mixture at 50 psi for 6 days, the mixture was filtered thru a plug of celite and concentrated in vacuo to give compound **400** (287.0 mg). LCMS-ESI (POS), M/Z, M+1: Found 171.1, Calculated 171.1.



400 140 396

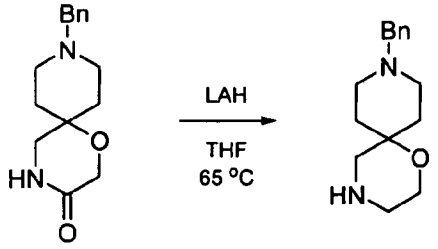
9-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-oxa-4,9-diazaspiro[5.5]undecan-3-one (396): To a mixture of compound **400** (110.0 mg, 646 μmol) and compound **140** (40.0 mg, 109 μmol) in N-methylpyrrolidinone (1.50 mL) was added N,N-diisopropylethylamine (DIEA) (0.100 mL, 575 μmol). The resulting mixture was heated at 160 ^{o}C under microwave irradiation for 6 h. The crude material was purified by reverse phase HPLC (acetonitrile/H_2O containing 0.1% TFA each, 25 min from 10 to 40%). The isolated material was further purified by prep-TLC (10% methanol in DCM with 1% NH_4OH) to give compound **396** as a yellow solid (2.5 mg, 5%). ^{1}H NMR (500 MHz, *CD_3OD*) δ 9.21 (s, 1 H) 8.91 (s, 1 H) 8.37 - 8.46 (m, 2 H) 8.08 (d, *J*=5.38 Hz, 1 H) 7.46 (d, *J*=10.03 Hz, 1 H) 5.43 (quin, 1 H) 4.21 (s, 2 H) 4.06 (ddd, *J*=13.27, 3.48, 3.30 Hz, 2 H) 3.37 - 3.42 (m, 4 H) 2.44 (dd, *J*=12.96, 8.31 Hz, 2 H) 2.08 - 2.24 (m, 4 H) 2.03 (d, *J*=13.45 Hz, 2 H) 1.84 - 1.93 (m, 2 H) 1.74 - 1.83 (m, 2 H) ppm; LCMS-ESI (POS), M/Z, M+1: Found 500.2, Calculated 500.2.

EXAMPLE 251



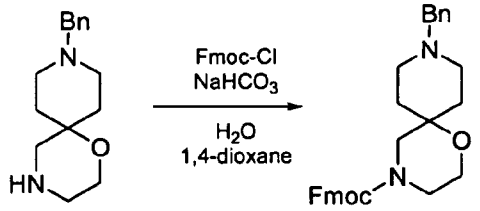
401

9-cyclopentyl-N-(6-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



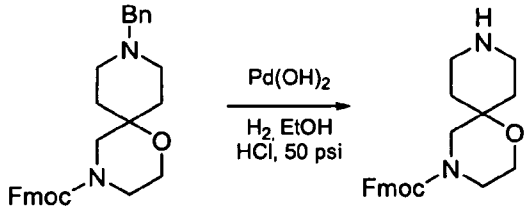
399 402

9-benzyl-1-oxa-4,9-diazaspiro[5.5]undecane (402): To a stirring mixture of lithium aluminum hydride (2.22 g, 58.5 mmol) in tetrahydrofuran (70 mL) was added compound **399** (3.60 g, 13.8 mmol), portionwise over three minutes. After 1.25 hours of reflux the reaction was cooled to room temperature and quenched with water (2.22 mL), then 1N NaOH (2.22 mL), then water (2 x 2.22 mL). The remaining solids were filtered off, and the filtrate was concentrated to give compound **402** (2.81 g, 82%). LCMS-ESI (POS), M/Z, M+1: Found 247.1, Calculated 247.2.



402 403

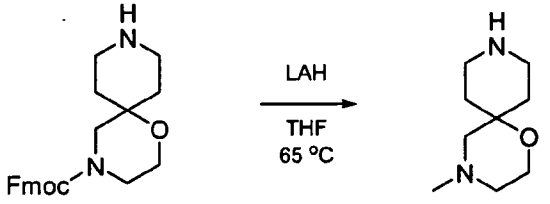
9H-fluoren-9-ylmethyl-9-(phenylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (403): To a solution of compound **402** (2.81 g, 11.4 mmol) in 1,4-dioxane (53 mL) was added 10% sodium bicarbonate in water (21.5 mL) followed by 9-fluorenylmethyl chloroformate (2.96 g, 11.4 mmol). The resulting mixture was stirred at room temperature for four hours, and then neutralized with 3N HCl. The solution was concentrated to a solid and then purified by flash chromatography (0-10% methanol in DCM with 1% NH_4OH) to give compound **403** as a white solid (1.2 g, 22.5%). LCMS-ESI (POS), M/Z, M+1: Found 469.1, Calculated 469.2.



403 404

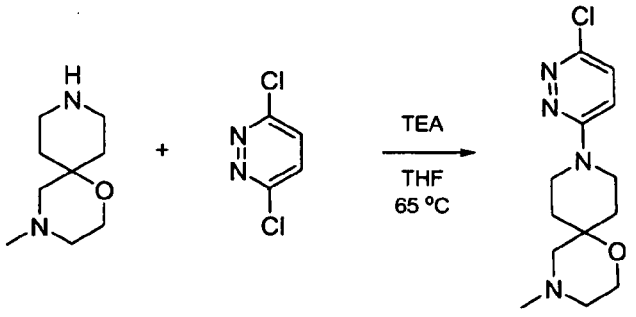
9H-fluoren-9-ylmethyl-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate(404): To a solution of compound **403** (1.43 g, 3.05 mmol) in ethanol (27 mL) was added palladium

hydroxide, 20 wt % pd (dry basis) on carbon, wet (1.51 g, 2.15 mmol), followed by hydrochloric acid (0.10 mL). The sealed glass tube was then evacuated and purged with hydrogen three times. The sealed tube was then charged with hydrogen (50 psi), and allowed to stir at room temperature for three days. HPLC showed ~85% conversion to the desired product. After filtering the mixture through a plug of celite, the filtrate was concentrated to a solid and purified by flash chromatography (0-20% methanol in DCM with 1% NH_4OH) to give compound **404** (709 mg, 61%) as a white solid. LCMS-ESI (POS), M/Z, M+1: Found 379.1, Calculated 379.2.



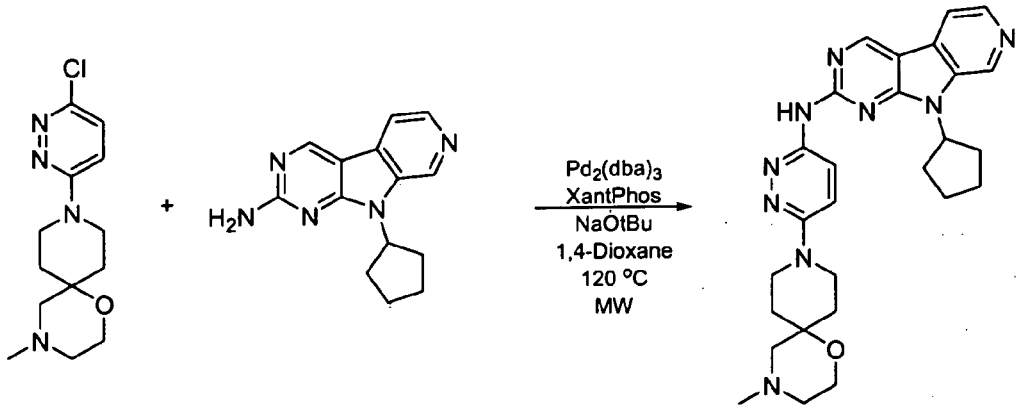
404 **405**

4-methyl-1-oxa-4,9-diazaspiro[5.5]undecane (405): To a mixture of compound **404** (586.4 mg, 1.545mmol) in tetrahydrofuran (20 mL) was added lithium aluminum hydride (240.5 mg, 6.34 mmol). After 1.5 hours at reflux the reaction was cooled to room temperature and quenched with water (240.5 µL), followed by 1N NaOH (240.5 µL), and then water (2 x 240.5 µL). The remaining solids were filtered off, and the filtrate was concentrated to give compound **405** (406 mg), as a sticky white solid. LCMS-ESI (POS), M/Z, M+1: Found 171.1, Calculated 171.1.



405 **406**

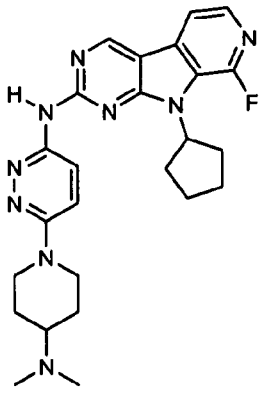
9-(6-chloro-3-pyridazinyl)-4-methyl-1-oxa-4,9-diazaspiro[5.5]undecane (406): To a solution of compound **405** (406.0 mg, 2.39 mmol) in tetrahydrofuran (17 mL) was added 3,6-dichloropyridazine (361.7 mg, 2.43 mmol), followed by triethylamine (0.680 mL, 4.89 mmol). The resulting solution was stirred at reflux for 38 hours. The reaction mixture was then concentrated and the residue was purified by reverse phase HPLC (acetonitrile/H_2O containing 0.1% TFA each, 25 min from 10 to 40%) to give compound **406** as a sticky yellow solid (303 mg, 45%). LCMS-ESI (POS), M/Z, M+1: Found 283.1, Calculated 283.1.



406 4 401

9-cyclopentyl-N-(6-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (401): To a solution of compound **4** (53.2 mg, 0.210 mmol) in 1,4-dioxane (3 mL) were added compound **406** (61.3 mg, 0.22 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (32.0 mg, 55.3 μmol), tris(dibenzylideneacetone)dipalladium (o) (30.9 mg, 33.7 μmol), and sodium *tert*-butoxide (103.9 mg, 1.08 mmol). After purging with argon for 3 minutes, the reaction mixture was heated at 120 °C under microwave irradiation for 1.5 h. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC (acetonitrile/H_2O containing 0.1% TFA each, 25 min from 10 to 30%) to give compound **401** as a TFA salt (26.7 mg, 15%). ^{1}H NMR (500 MHz, *CD_3OD*) δ 9.67 (s, 1 H) 9.35 (s, 1 H) 8.67 (br. s., 2 H) 7.99 - 8.14 (m, 2 H) 5.48 (quin, 1 H) 4.09 - 4.21 (m, 2 H) 3.94 - 4.07 (m, 2 H) 3.34 - 3.63 (m, 2 H) 2.93 (s, 3 H) 2.42 - 2.62 (m, 4 H) 2.11 - 2.33 (m, 6 H) 1.59 - 1.99 (m, 6 H) ppm; LCMS-ESI (POS), M/Z, M+1: Found 500.4, Calculated 500.3.

EXAMPLE 252

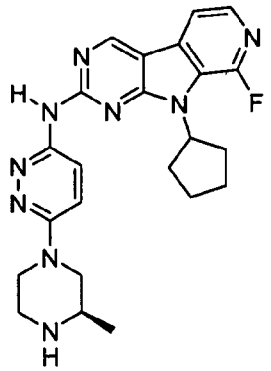


407

9-Cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

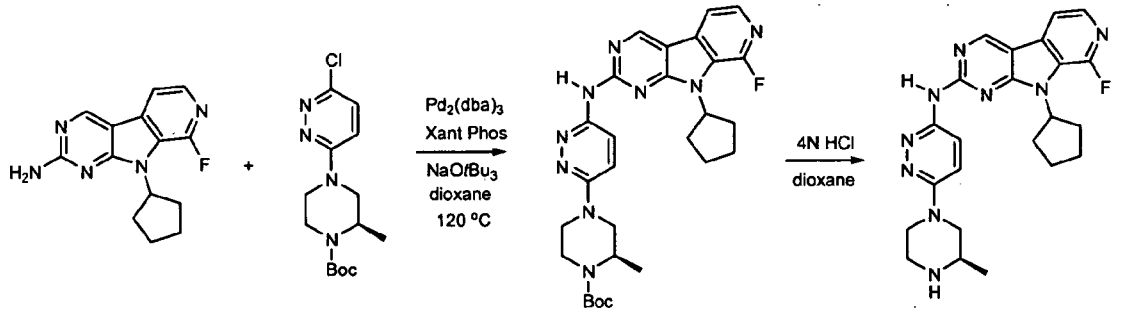
Compound **407** was prepared from compound **245** using chemistry similar to that described in example 4. The yield is 45%. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.47 (1 H, s), 8.11 (2 H, s), 8.08 (1 H, d, *J*=10.0 Hz) 7.88 (1 H, d, *J*=10.0 Hz), 5.65 (1 H, t, *J*=9.0 Hz), 4.54 - 4.58 (2 H, m), 3.60 (1 H, m), 3.17 (2 H, ddd, *J*=14.5, 12.5, 1.8 Hz), 2.44 (2 H, m), 2.10 - 2.33 (6 H, m), 1.71 - 1.95 (4 H, m); LCMS-ESI (POS), M/Z, M+1: Found 476.2, Calculated 476.3

EXAMPLE 253



408

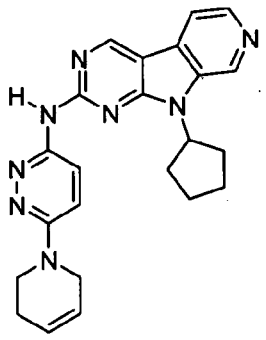
9-Cyclopentyl-8-fluoro-N-(6-((3R)-3-methyl-1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



245 **11** **408**

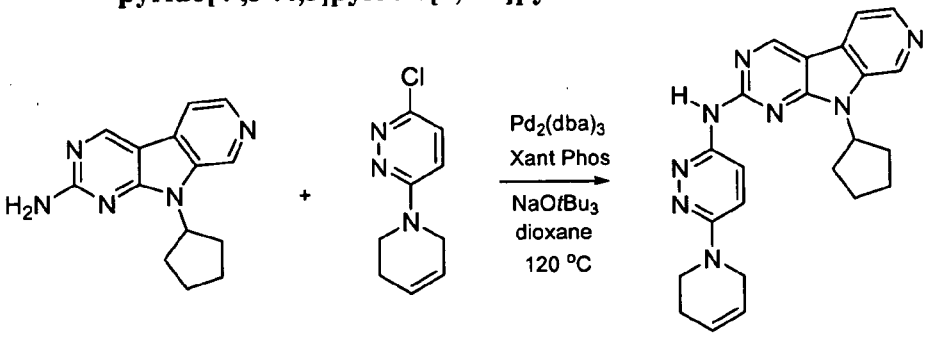
9-Cyclopentyl-8-fluoro-N-(6-((3R)-3-methyl-1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (408): Compound **408** was prepared from compound **245** and compound **11** using chemistry similar to that described in example 4. The two step yield is 12%. 1H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.48 (1 H, s), 8.10 - 8.14 (2 H, m), 8.00 (1 H, d, *J*=10 Hz), 8.05 (1 H, d, *J*=10 Hz), 5.66 (1 H, t, *J*=9.0 Hz), 4.43 - 4.49 (2 H, m), 3.52 - 3.62 (2 H, m), 3.29 - 3.48 (2 H, m), 3.20 (1 H, dd, *J*=14.4, 10.8 Hz), 2.45 (2 H, ddd, *J*=9.2, 7.0, 4.5 Hz), 2.13 - 2.27 (4 H, m), 1.87-1.88 (2 H, m), 1.46 (3 H, d, *J*=6.6 Hz); LCMS-ESI (POS), M/Z, M+1: Found 448.1, Calculated 448.2

EXAMPLE 254



409

9-Cyclopentyl-N-(6-(3,6-dihydro-1(2H)-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

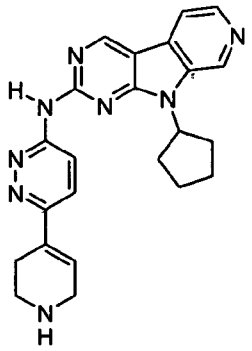


4 410 409

3-Chloro-6-(3,6-dihydro-1(2H)-pyridinyl)pyridazine (410) was prepared using chemistry similar to that described for compound **11**. The yield is 86%. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 7.44 (1 H, d, J=9.5 Hz), 7.29 (1 H, d, J=9.5 Hz), 5.96 (1 H, m, J=10.1, 4.1, 4.1, 2.3, 2.1 Hz), 5.85 (1 H, m, J=10.1, 3.3, 3.3, 2.0, 1.7 Hz), 4.05 (2 H, dq, J=2.9, 2.8 Hz), 3.80 (2 H, t, J=5.6 Hz), 2.30 (2 H, d, J=2.7 Hz); LCMS-ESI (POS), M/Z, M+1: Found 196.0, Calculated 196.1.

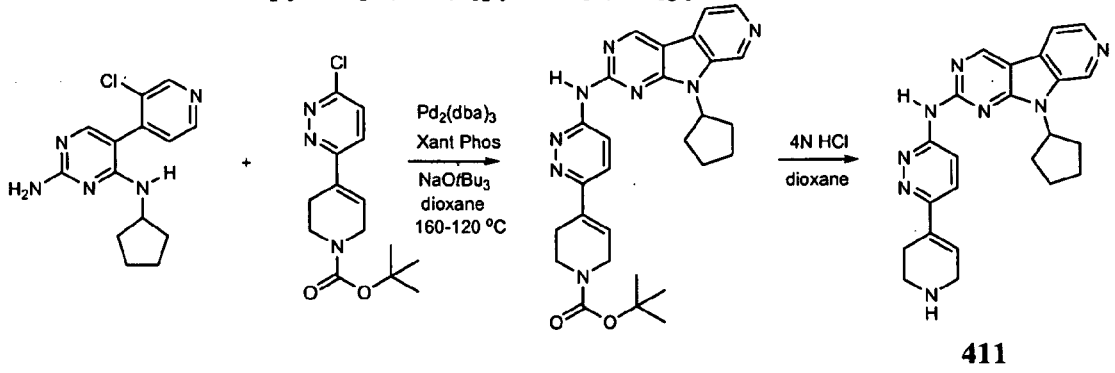
9-Cyclopentyl-N-(6-(3,6-dihydro-1(2H)-pyridinyl)-3-pyridazinyl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (409): Compound **409** was prepared from compound **4** and compound **410** using chemistry similar to that described in example 1. The yield is 20%. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.68 (1 H, d, *J*=1.5 Hz), 9.36 (1 H, s), 9.36 (1 H, d, *J*=0.5 Hz), 8.69 (3 H, t, *J*=2.2 Hz), 8.60 - 8.72 (1 H, m), 8.22 (1 H, d, *J*=10.5 Hz), 8.08 (1 H, dd, *J*=10.0, 1.0 Hz), 6.02 - 6.09 (1 H, m, *J*=8.1, 4.1, 4.1, 2.0 Hz), 5.89 (1 H, dddd, *J*=8.4, 3.4, 3.3, 1.5 Hz), 5.50 (2 H, t, *J*=8.8 Hz), 4.17 (3 H, qd, *J*=2.7, 2.6 Hz), 3.87 (3 H, t, *J*=5.7 Hz), 2.47 - 2.60 (3 H, m), 2.37 - 2.43 (2 H, m, *J*=6.1, 6.1, 3.5, 2.2 Hz), 2.15 - 2.35 (7 H, m), 1.87 - 1.99 (3 H, m); LCMS-ESI (POS), M/Z, M+1: Found 413.2, Calculated 413.2.

EXAMPLE 255



411

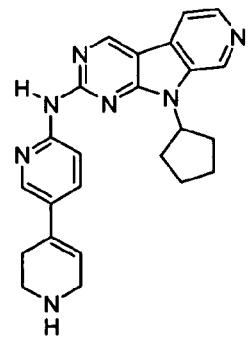
9-Cyclopentyl-N-(6-(1,2,3,6-tetrahydro-4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



411

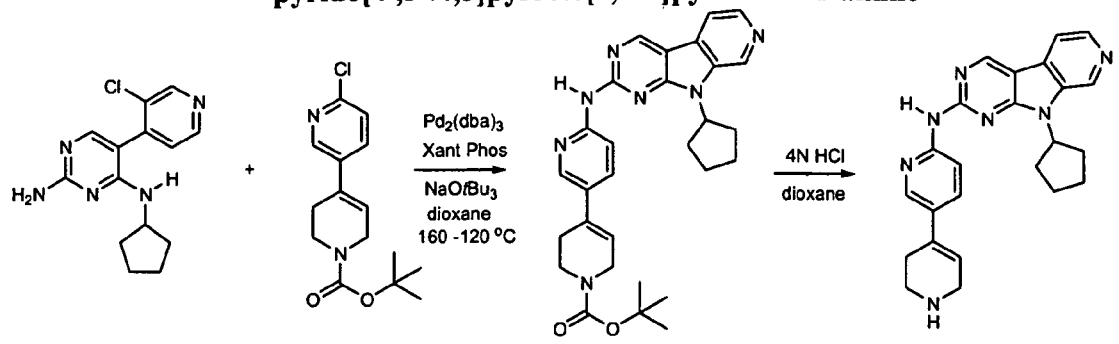
9-Cyclopentyl-N-(6-(1,2,3,6-tetrahydro-4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (411): Compound **411** was prepared using chemistry similar to that described in example 20. The two step yield is 29%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.62 (1 H, s), 9.30 (1 H, s), 8.61 - 8.73 (3 H, m), 8.15 (1 H, d, *J*=9.5 Hz), 6.77 (1 H, tt, *J*=3.5, 1.7 Hz), 5.50 (1 H, t, *J*=8.8 Hz), 4.01 (1 H, q, *J*=2.8 Hz), 3.07 - 3.12 (1 H, m, *J*=6.2, 4.1, 2.0, 2.0 Hz), 2.49 - 2.60 (2 H, m), 2.13 - 2.33 (4 H, m), 1.93 (1 H, dt, *J*=8.8, 2.3 Hz), 1.88 - 1.98 (1 H, m); LCMS-ESI (POS), M/Z, M+1: Found 413.2, Calculated 413.2.

EXAMPLE 256



412

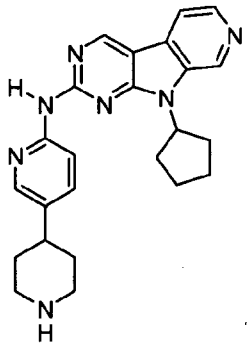
9-Cyclopentyl-N-(1',2',3',6'-tetrahydro-3,4'-bipyridin-6-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



412

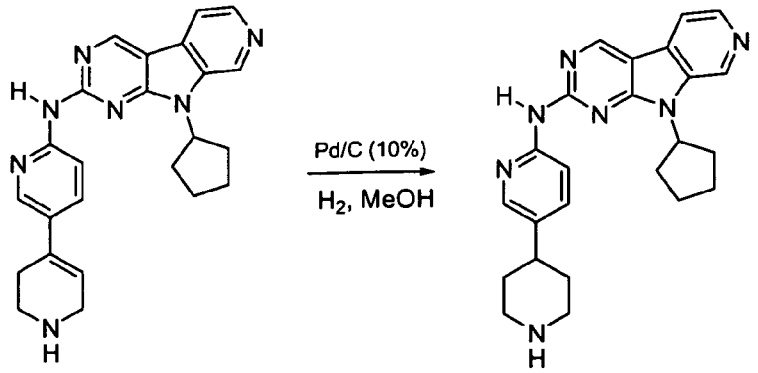
9-Cyclopentyl-N-(1',2',3',6'-tetrahydro-3,4'-bipyridin-6-yl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (412): Compound **412** was prepared using chemistry similar to that described in example 20. The two step yield is 70%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.90 (1 H, s), 9.50 (1 H, s), 8.92 (1 H, d, *J*=6.1 Hz), 8.75 - 8.83 (1 H, m), 8.57 - 8.65 (2 H, m), 7.73 - 7.78 (1 H, m), 6.52 (1 H, tt, *J*=3.5, 1.7 Hz), 5.54 (1 H, quin, *J*=8.7 Hz), 3.96 - 4.01 (2 H, m), 3.68 (6 H, s), 3.58 (2 H, t, *J*=6.1 Hz), 2.88 - 2.95 (2 H, m, *J*=6.3, 6.3, 2.2, 2.1, 2.1 Hz), 2.57 (2 H, dq, *J*=12.8, 8.5 Hz), 2.21 - 2.37 (4 H, m), 1.89 - 2.00 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 412.1, Calculated 412.2.

EXAMPLE 257



413

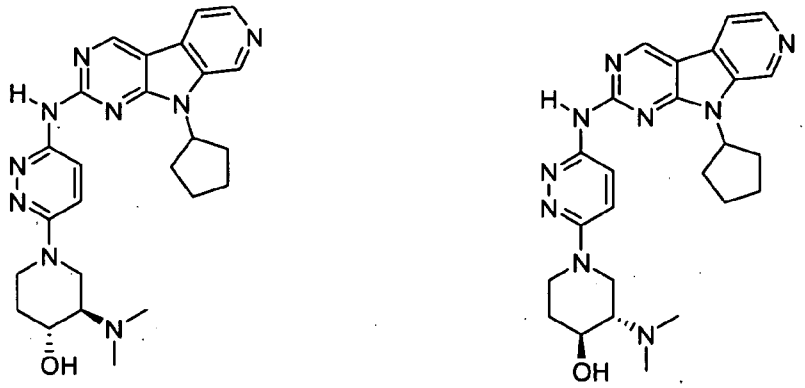
9-cyclopentyl-N-(5-(4-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



412 **413**

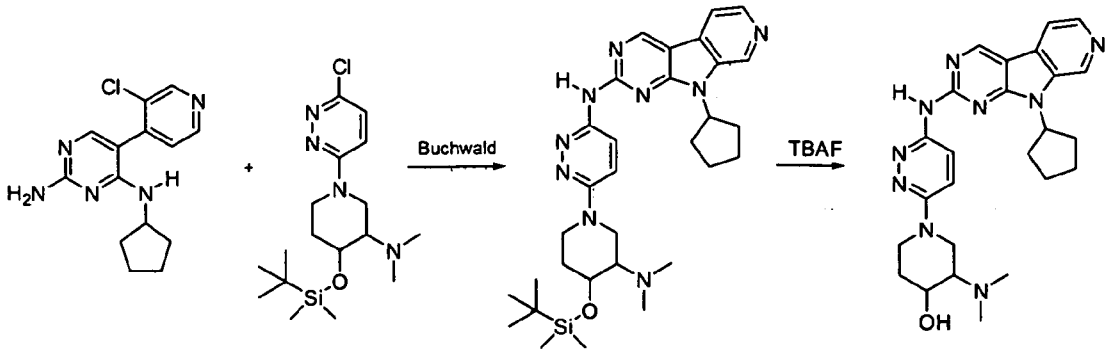
9-Cyclopentyl-N-(5-(4-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (413): To a solution of compound **412** (90mg, 0.22 mmol) in methanol (5mL) was added Pd/C (10% wt, dry basis) (50mg). The reaction was stirred at room temperature with H_2 ballon for 3 hours. Insolubles were removed by filtration. The filtrate was purified using prep-HPLC to give compound **413** as a yellow solid (30mg, 33%). 1H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 10.98 (1 H, br. s.), 9.64 (1 H, s), 9.42 (1 H, s), 8.83 (1 H, dd, *J*=3.5, 1.1 Hz), 8.71 (1 H, d, *J*=6.1 Hz), 8.55 - 8.68 (2 H, m), 8.30 (1 H, d, *J*=2.7 Hz), 8.17 (1 H, d, *J*=8.6 Hz), 7.85 (1 H, dd, *J*=8.8, 2.4 Hz), 5.41 (1 H, dq, *J*=8.9, 8.8 Hz), 3.43 (2 H, dd, *J*=10.4, 2.3 Hz), 2.96 (3 H, tt, *J*=12.1, 3.7 Hz), 2.42 (2 H, m), 2.00-2.08 (4H, m), 1.68 - 1.92 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 414.2, Calculated 414.2.

EXAMPLE 258



414A (chirality arbitrarily assigned) **414B**

1-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-3-(dimethylamino)-4-piperidinol



414

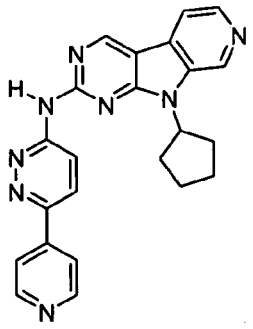
(3R*,4R*)-1-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-3-(dimethylamino)-4-piperidinol (414): Compound **414** was prepared using chemistry similar to that described in example 20. The crude coupling product (50mg, 0.085mmol) was treated with 5 mL of 1M TBAF (in THF) at room temperature for 3 hours. After removal of solvent, the residue was dissolved in DMSO and purified by prep-HPLC to give the racemic alcohol **414** (33mg, 82%). This compound was dissolved in 2 mL of MeOH and to this solution was added 4 drops of 4 N HCl in dioxane. The solution was concentrated to give a yellow solid as an HCl salt.

^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.77 (1 H, s), 9.44 (1 H, s), 8.78 (1 H, d, *J*=6.1 Hz), 8.72 (1 H, d, *J*=6.1 Hz), 8.14 (1 H, m), 8.05 (1 H, m, *J*=10.0 Hz), 5.50 (1 , quin, *J*=8.7 Hz), 4.80 (1 H, m), 4.33 (1 H, m), 4.15 (1 H, ddd, *J*=10.3, 8.0, 4.9 Hz), 3.26 (1 H, m), 2.66 (2 H, m), 2.15 - 2.34 (4 H, m), 1.85 - 1.98 (2 H, m), 1.61 - 1.80 (1 H, m); LCMS-ESI (POS), M/Z, M+1: Found 474.2, Calculated 474.3.

The two enantiomers were resolved by SFC (Resolution conditions: 250x30 mm AS-H SFC column with 50g/min methanol (0.2% DEA)+ 75g/min CO2 on Thar 350 SFC. Outlet pressure = 140 bar; Temp. = 24 C; Wavelength = 264 nm. Multiple 0.5 mL injections of 22 mg/8 mL sample in methanol solution (2.75mg/mL). Cycle time = 5.0 min; run time = 6.0 min) to give yellow solids. Compound **414A** has a retention time 4.13 minute and compound **414B** has a retention time 4.43 minute. NMR as the free base (each enantiomer). ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.09 (1 H, s), 8.77 (1 H, s), 8.23 - 8.33 (2 H, m), 7.94 (1 H, d, *J*=5.1 Hz), 7.28 (1 H, d, *J*=10.0 Hz), 5.29 (2 H, t, *J*=8.8 Hz), 4.27 (1 H, ddd, *J*=13.1, 4.2, 2.1 Hz), 4.07 (1 H, dd, *J*=11.2, 2.4 Hz), 3.77 (1 H, td, *J*=9.9, 4.6 Hz), 2.82 - 2.94 (2 H, m), 2.38 (6 H, s), 2.30 (2 M, m), 1.94 - 2.13 (6 H, m), 1.77 (2 H, dt, *J*=12.0, 6.8 Hz), 1.51 (1 H, ddd, *J*=10.4, 2.2, 2.1 Hz); LCMS-ESI (POS), M/Z, M+1: Found 474.2, Calculated 474.3; each ee 99%.

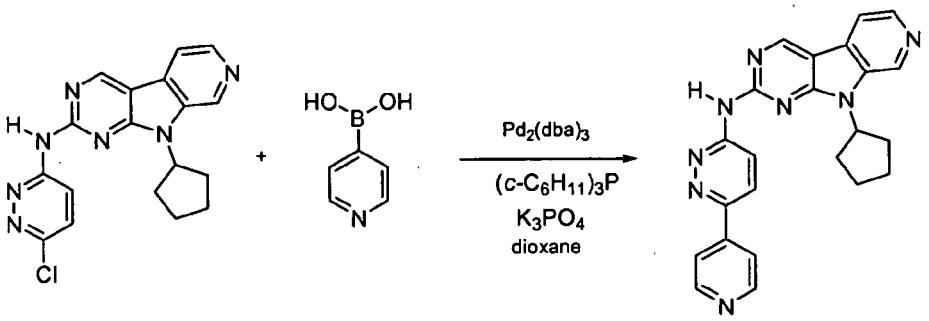
For convenience, they are arbitrarily assigned the structures as drawn, with absolute configuration remaining uncertain. Biological data reported in table 9 for compound **414A** as example 258A and for compound **414B** as example 258B.

EXAMPLE 259



415

9-cyclopentyl-N-(6-(4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

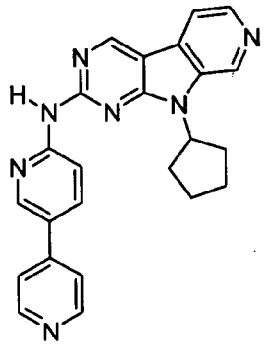


140 **415**

9-cyclopentyl-N-(6-(4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (415): To a solution of compound **140** (199mg, 544 μmol) in dioxane (3mL) were added pyridin-4-ylboronic acid (66.9 mg, 544 μmol), $Pd_2(dba)_3$ (24.9 mg, 27.2 μmol), tricyclohexylphosphine (15.3 mg, 54.4 μmol), and potassium phosphate (231 mg, 1.09 mmol) (in 1mL of water). The reaction mixture was purged with N_2 for 20 minutes and the reaction was heated at 100 °Cdegree for 18 hours. DCM was added to the reaction and the mixture was washed with water and brine. The organic layer was dried with sodium sulfate. The product was purified using Combiflash (DCM/methanol) followed by trituration with ethyl acetate to give compound **415** as a yellow solid (63mg, 28%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 9.25 (1 H, s), 8.97 - 9.05 (2 H, m), 8.92 (1 H, s), 8.79 (2 H, d, *J*=6.1 Hz), 8.57 (1 H, d, *J*=5.1 Hz), 8.00 - 8.08 (3 H, m), 7.96 (1 H, dd, *J*=5.1, 1.2 Hz), 5.48 (1 H, quin, *J*=8.9 Hz),

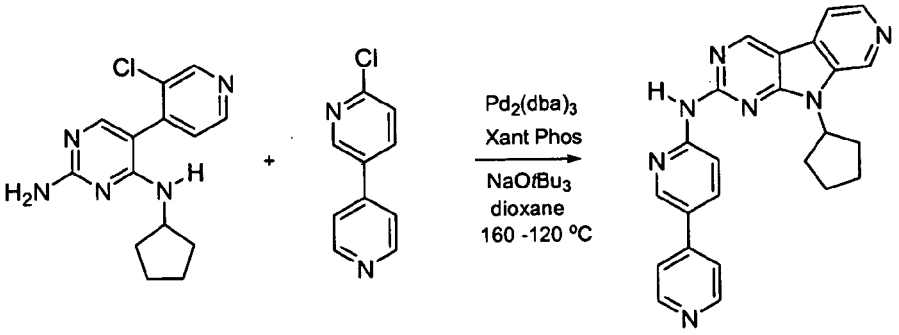
2.48(2 H, m), 2.20-2.28 (4 H, m), 1.95 (2 H, dddd, *J*=8.2, 4.5, 4.3, 4.2 Hz), 1.63 (2 H, br. s.); LCMS-ESI (POS), M/Z, M+1: Found 409.1, Calculated 409.2.

EXAMPLE 260



416

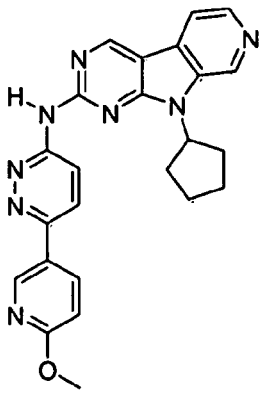
N-3,4'-bipyridin-6-yl-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



416

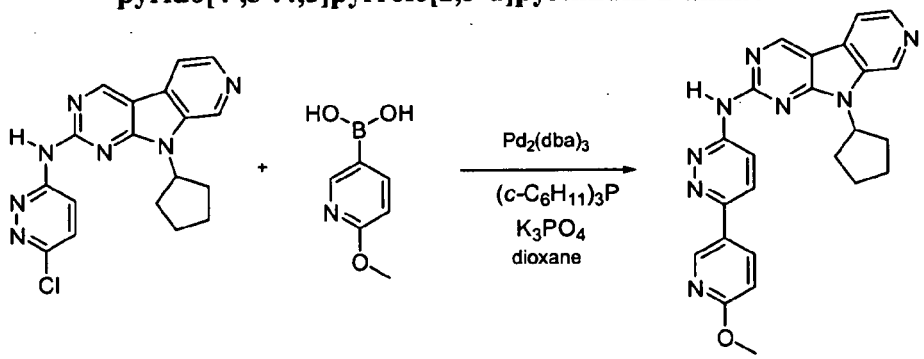
N-3,4'-bipyridin-6-yl-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (416): Compound **416** was prepared using chemistry similar to that described in example 20. The yield is 65%. ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 9.23 (1 H, s), 8.99 (1 H, d, *J*=1.2 Hz), 8.65 - 8.81 (4 H, m), 8.54 (1 H, d, *J*=5.1 Hz), 8.12 (1 H, dd, *J*=8.7, 2.6 Hz), 7.94 (1 H, dd, *J*=5.1, 1.2 Hz), 7.54 - 7.63 (2 H, m), 5.48 (1 H, quin, *J*=9.0 Hz), 2.46 - 2.57 (2 H, m), 2.13 - 2.31 (4 H, m), 1.89 - 2.00 (2 H, m, *J*=11.4, 7.8, 7.7, 7.7, 3.8 Hz), 1.63 (1 H, br. s.); LCMS-ESI (POS), M/Z, M+1: Found 408.2, Calculated 408.2.

EXAMPLE 261



417

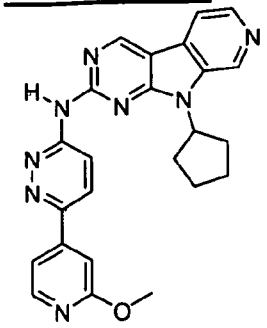
9-Cyclopentyl-N-(6-(6-methoxy-3-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



140 417

9-Cyclopentyl-N-(6-(6-methoxy-3-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (417): Compound **417** was prepared using chemistry similar to that described in example 259. The yield is 26%. ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 9.31 (1 H, d, *J*=1.7 Hz), 8.99 (1 H, d, *J*=0.7 Hz), 8.92 (1 H, d, *J*=9.3 Hz), 8.85 (1 H, d, *J*=2.4 Hz), 8.56 (1 H, d, *J*=5.6 Hz), 8.40 (1 H, dd, *J*=8.7, 2.6 Hz), 8.10 - 8.15 (1 H, m), 7.97 (1 H, d, *J*=9.5 Hz), 6.94 (1 H, d, *J*=8.6 Hz), 5.45 (1 H, qd, *J*=9.0, 8.8 Hz), 4.05 (3 H, s), 2.43 - 2.52 (2 H, m), 2.16 - 2.33 (4 H, m), 1.91 - 2.00 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 439.0, Calculated 439.2.

EXAMPLE 262

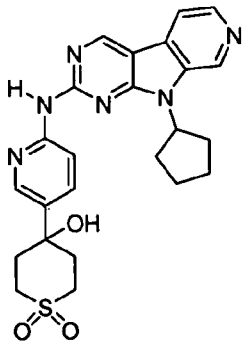


418

9-Cyclopentyl-N-(6-(2-methoxy-4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

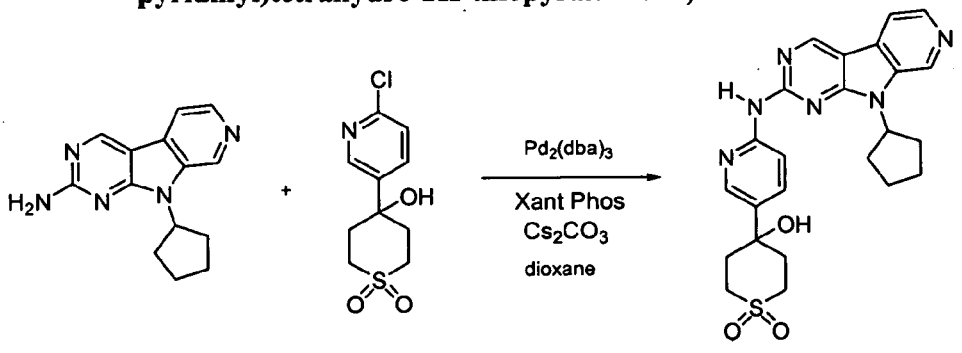
Compound **418** was prepared using chemistry similar to that described in example 259. The yield is 52%. ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 9.23 (1 H, s), 8.97 - 9.02 (2 H, m), 8.75 (1 H, s), 8.56 (1 H, d, *J*=5.1 Hz), 8.34 (1 H, d, *J*=5.4 Hz), 7.96 - 8.03 (2 H, m), 7.65 (1 H, dd, *J*=5.4, 1.7 Hz), 7.44 (1 H, dd, *J*=1.5, 0.7 Hz), 5.47 (1 H, quin, *J*=9.0 Hz), 5.36 (25 H, d, *J*=1.2 Hz), 2.44 - 2.53 (2 H, m, *J*=13.0, 9.0, 8.7, 8.7 Hz), 2.16 - 2.31 (4 H, m), 1.90 - 1.99 (2 H, m, *J*=8.2, 4.5, 4.2, 4.2 Hz), 1.59 (1 H, d, *J*=8.1 Hz); LCMS-ESI (POS), M/Z, M+1: Found 439.1, Calculated 439.2.

EXAMPLE 263



419

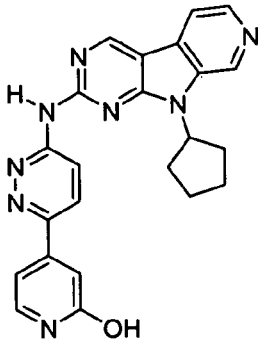
4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)tetrahydro-2H-thiopyran-4-ol 1,1-dioxide



4 **420** **419**

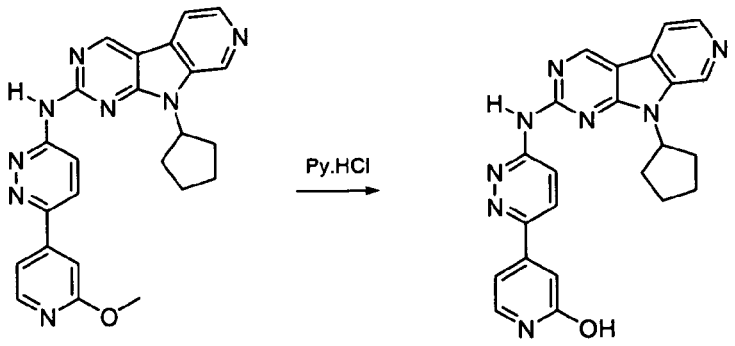
4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)tetrahydro-2H-thiopyran-4-ol 1,1-dioxide (419): To a mixture of compound **4** (120mg, 474 μmol), $Pd_2(dba)_3$ (21.7 mg, 23.7 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (27.4 mg, 47.4 μmol) and cesium carbonate (309 mg, 947 μmol) was added a solution of compound **420** (124 mg, 474 μmol) in dioxane (3mL). The reaction was purged with N_2 for 20 minutes and then heated at 120 degree in microwave for 2 hours. DCM was added to the reaction and the mixture was washed with H2O and brine. The organic layer was dried with sodium sulfate. The crude product was purified using Combiflash (DCM/methanol) and suspended in methanol. A saturated solution of HCl in methanol (10 drops) was added. The solution was concentrated to give compound **419** as a light yellow solid (HCl salt) (18mg, 8%). ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.90 (1 H, s), 9.51 (1 H, s), 8.92 (1 H, d, *J*=6.1 Hz), 8.77 (1 H, d, *J*=5.9 Hz), 8.66 - 8.74 (1 H, m), 8.58 (1 H, dt, *J*=9.0, 1.0 Hz), 7.76 (1 H, d, *J*=9.3 Hz), 5.55 (1 H, qd, *J*=8.4, 8.2 Hz), 3.62 (2 H, tt, *J*=13.6, 1.7 Hz), 3.37 (2 H, s), 3.09 (2 H, dd, *J*=12.5, 1.0 Hz), 2.64 - 2.77 (2 H, m, *J*=13.7, 13.7, 1.8, 1.6 Hz), 2.57 (2 H, dd, *J*=12.6, 8.2 Hz), 2.19 - 2.41 (6 H, m), 1.87 - 2.01 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 479.2, Calculated 479.2

EXAMPLE 264



421

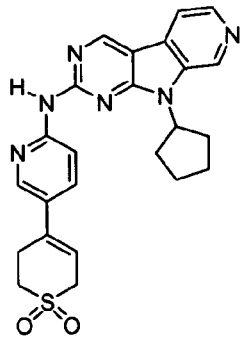
4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-2-pyridinol



418 421

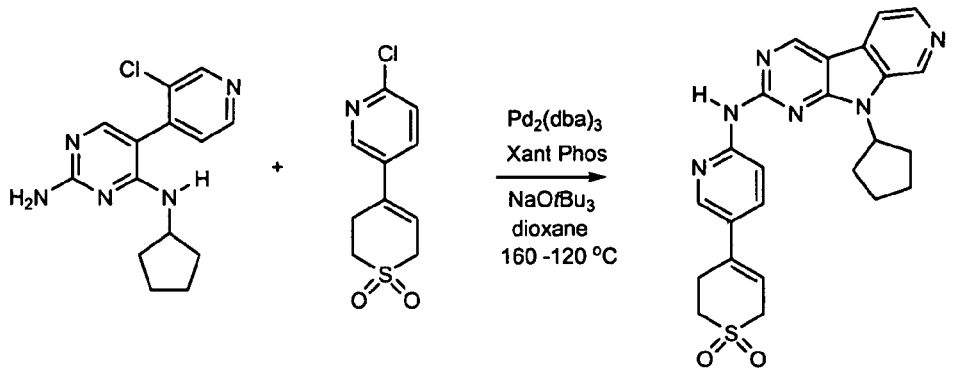
4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-2-pyridinol (421): Compound **418** (25mg, 57 μmol) and pyridine hydrochloride (500mg) in a small vial were heated at 150 degree (oil bath) for 1 hour. DCM was added to the reaction and sat. $NaHCO_3$ was added to wash. The crude product was collected by filtration and was further washed with DCM and a small amount of methanol. The pure product was then suspended in methanol and to this mixture was added 3 drops of saturated HCl methanol solution. Concentration of the solution gave compound **421** as a yellow solid (HCl salt). The yield is 96%. ^1H NMR (500 MHz, *CD_3OD*) δ ppm 9.87 (1 H, s), 9.50 (1 H, s), 8.88 (1 H, d, *J*=6.1 Hz), 8.76 (1 H, d, *J*=6.1 Hz), 8.68 (1 H, d, *J*=9.5 Hz), 8.49 (1 H, d, *J*=9.5 Hz), 7.77 (1 H, d, *J*=6.8 Hz), 7.37 (1 H, d, *J*=0.7 Hz), 7.29 (1 H, dd, *J*=6.2, 1.1 Hz), 5.55 (1 H, quin, *J*=8.7 Hz), 2.54 - 2.63 (2 H, m), 2.22 - 2.38 (4 H, m), 1.91 - 2.01 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 425.2, Calculated 425.2.

EXAMPLE 265



422

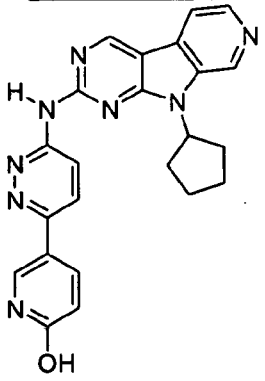
9-Cyclopentyl-N-(5-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



422

9-Cyclopentyl-N-(5-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (422): Compound **422** was prepared using chemistry similar to that described in example 20. The two step yield is 75%. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.87 (1 H, s), 9.49 (1 H, s), 8.91 (1 H, d, *J*=6.1 Hz), 8.77 (1 H, d, *J*=6.1 Hz), 8.54 - 8.58 (2 H, m), 7.72 (1 H, d, *J*=9.8 Hz), 6.31 (1 H, t, *J*=1.5 Hz), 5.53 (1 H, dq, *J*=8.8, 8.6 Hz), 4.92 (1 H, br. s.), 3.98 (2 H, td, *J*=3.1, 1.5 Hz), 3.43 - 3.48 (2 H, m), 3.23 (2 H, td, *J*=6.4, 2.0 Hz), 2.57 (2 H, ddd, *J*=8.8, 6.5, 6.2 Hz), 2.21 - 2.35 (4 H, m), 1.90 - 1.99 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 461.2, Calculated 461.2

EXAMPLE 266

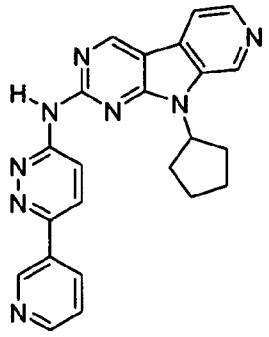


423

5-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-2-pyridinol

Compound **423** was prepared from compound **417** using chemistry similar to that described in example 264. The yield is 99%. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.87 (1 H, s), 9.50 (1 H, s), 8.88 (1 H, d, *J*=5.0 Hz), 8.76 (1 H, d, *J*=5.0 Hz), 8.61 (1 H, d, *J*=10 Hz), 8.38 - 8.42 (1 H, m), 6.74 (1 H, d, *J*=10.0 Hz), 5.54 (1 H, t, *J*=8.7 Hz), 2.54 - 2.63 (2 H, m), 2.23 - 2.37 (4 H, m), 1.97 (2 H, dd, *J*=7.1, 1.2 Hz); LCMS-ESI (POS), M/Z, M+1: Found 425.2, Calculated 425.2

EXAMPLE 267

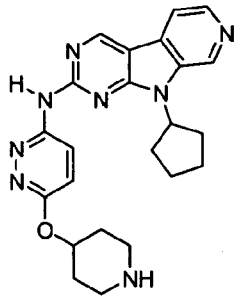


424

9-Cyclopentyl-N-(6-(3-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

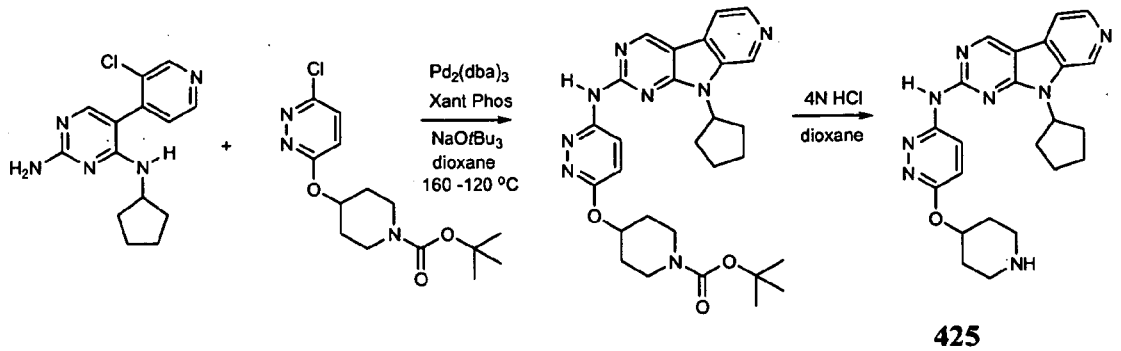
Compound **424** was prepared from compound **140** using chemistry similar to that described in example 259. The yield is 9%. 1H NMR (500 MHz, *CD_3OD*) δ ppm ppm 9.75 (1 H, s), 9.59 (1 H, d, *J*=1.0 Hz), 9.59 (1 H, s), 9.37 (1 H, s), 9.27 (1 H, dt, *J*=8.3, 1.7 Hz), 8.95 (1 H, d, *J*=0.7 Hz), 8.75 (1 H, d, *J*=6.1 Hz), 8.61 - 8.70 (1 H, m), 8.53 (1 H, d, *J*=9.5 Hz), 8.22 (1 H, dd, *J*=8.2, 5.7 Hz), 5.44 (1 H, quin, *J*=8.7 Hz), 2.42 - 2.52 (2 H, m), 2.08 - 2.26 (4 H, m), 1.79 - 1.90 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 409.1, Calculated 409.2.

EXAMPLE 268



425

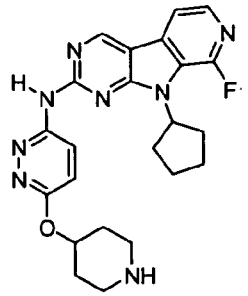
9-Cyclopentyl-N-(6-(4-piperidinyloxy)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



425

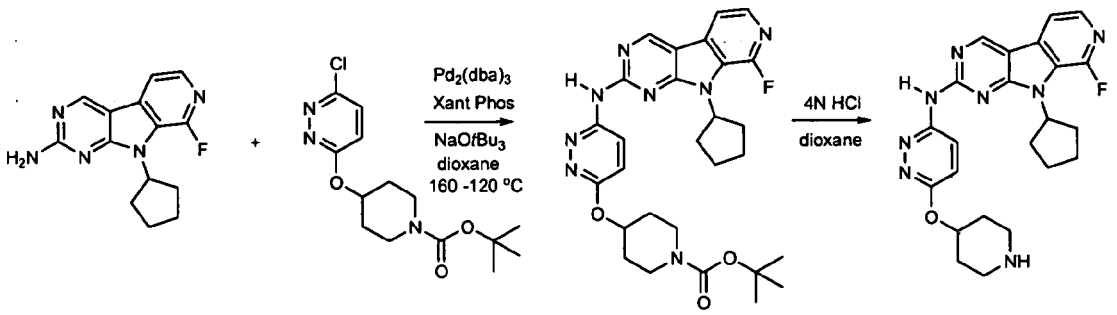
9-Cyclopentyl-N-(6-(4-piperidinyloxy)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (425): Compomd **425** was prepared using chemistry similar to that described in example 20. The two step yield is 84%. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.86 (1 H, s), 9.50 (1 H, s), 8.88 (1 H, d, *J*=6.1 Hz), 8.76 (1 H, d, *J*=6.1 Hz), 8.17 (1 H, d, *J*=9.5 Hz), 7.87 (1 H, d, *J*=9.5 Hz), 5.48 (1 H, tt, *J*=6.6, 3.3 Hz), 3.45 - 3.53 (3 H, m), 3.31 - 3.38 (6 H, m), 2.52 - 2.61 (2 H, m), 2.19 - 2.42 (4 H, m), 1.89 - 1.99 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 431.2, Calculated 431.2

EXAMPLE 269



426

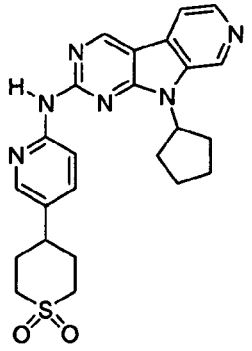
9-Cyclopentyl-8-fluoro-N-(6-(4-piperidinyloxy)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



245 **426**

9-Cyclopentyl-8-fluoro-N-(6-(4-piperidinyloxy)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (426): Compound **426** was prepared from compound **245** using chemistry similar to that described in example 4. The two step yield is 11%. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.59 (1 H, s), 8.18 (2 H, s), 8.02 (1 H, d, *J*=9.8 Hz), 7.84 (1 H, d, *J*=9.8 Hz), 5.69 (1 H, t, *J*=9.0 Hz), 5.46 (1 H, dt, *J*=6.5, 3.2 Hz), 3.45 - 3.53 (2 H, m), 2.47 - 2.51 (2 H, m), 2.46 (1 H, dd, *J*=5.4, 2.9 Hz), 2.31 - 2.42 (2 H, m), 2.11 - 2.31 (4 H, m), 1.81 - 1.93 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 449.2, Calculated 449.2.

EXAMPLE 270

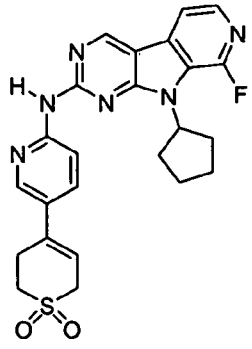


427

9-Cyclopentyl-N-(5-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

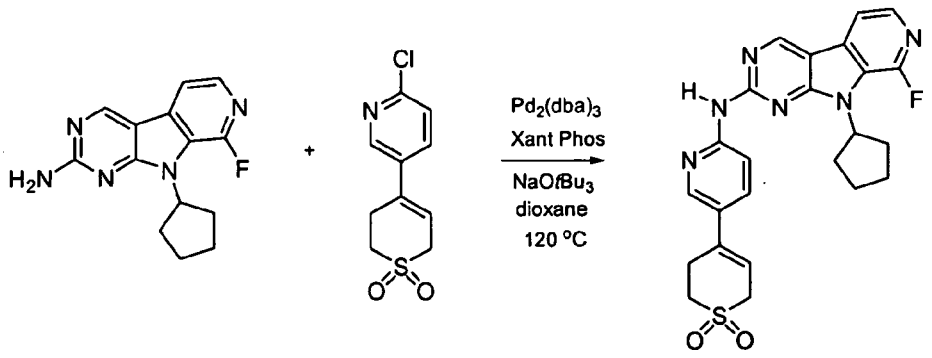
Compound **427** was prepared from compound **422** using chemistry similar to that described in example 257. The yield is 20%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.88 (1 H, s), 9.50 (1 H, s), 8.92 (1 H, d, *J*=6.1 Hz), 8.77 (1 H, d, *J*=6.1 Hz), 8.41 - 8.52 (2 H, m), 7.73 (1 H, d, *J*=9.0 Hz), 5.54 (1 H, quin, *J*=8.7 Hz), 3.31 - 3.49 (2 H, m), 3.17 - 3.31 (3 H, m), 3.07 (2 H, q, *J*=7.3 Hz), 2.50 - 2.63 (2 H, m), 2.21 - 2.44 (8 H, m), 1.88 - 2.01 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 463.1, Calculated 463.2

EXAMPLE 271



428

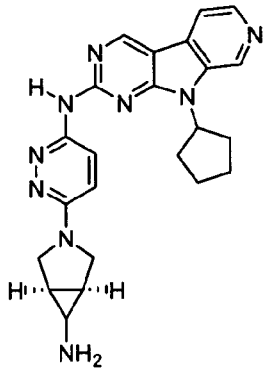
9-Cyclopentyl-N-(5-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



245 428

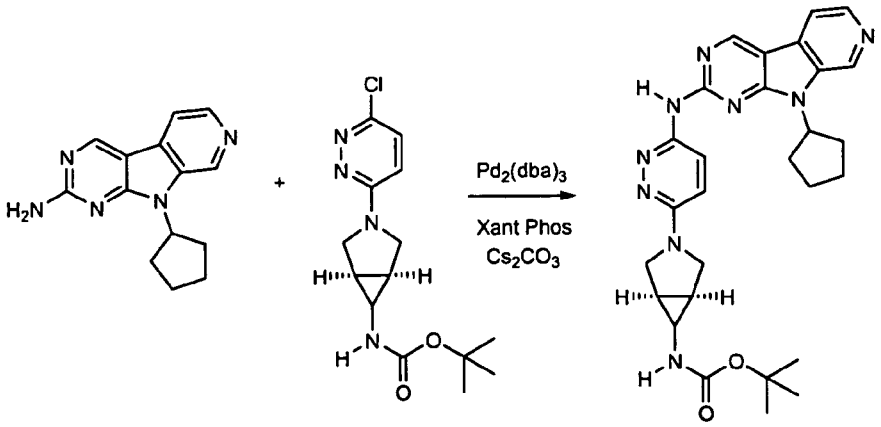
9-Cyclopentyl-N-(5-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (428): Compound **428** was prepared from compound **245** using chemistry similar to that described in example 1. The yield is 8%. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 9.06 (1 H, s), 8.46 (1 H, d, *J*=8.8 Hz), 8.30 (1 H, d, *J*=2.2 Hz), 8.19 (1 H, s), 7.63 - 7.70 (2 H, m), 5.84 - 5.88 (1 H, m), 5.48 (1 H, qd, *J*=9.1, 8.9 Hz), 3.78 (2 H, dd, *J*=4.5, 1.3 Hz), 3.19 - 3.24 (2 H, m), 3.14 (2 H, dd, *J*=6.1, 1.5 Hz), 2.34 - 2.44 (2 H, m, *J*=7.3, 5.1, 2.7, 2.7 Hz), 2.34 - 2.44 (4 H, m), 1.97 - 2.15 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 478.9, Calculated 479.2.

EXAMPLE 272



429

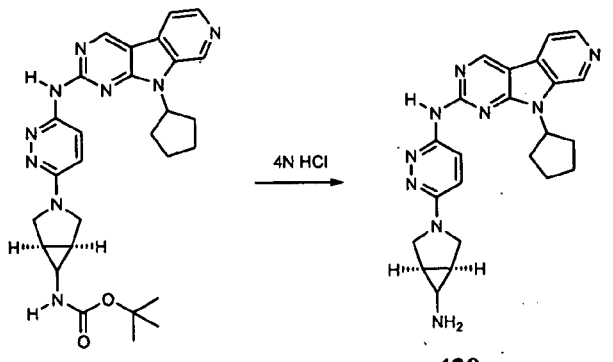
N-(6-((1R,5S)-6-amino-3-azabicyclo[310]hex-3-yl)-3-pyridazinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



4 430 431

(1R,5S)-3-{6-[(9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino]-3-pyridazinyl-3-azabicyclo[310]hex-6-yl}carbamate (431):

In analogy to example 1, starting materials and reagents in dioxane (4mL) were purged with N_2 for 20 minutes. (Compound **430** was prepared by the method used for compound **11** in example 4.) The reaction was then heated at 100 °C in a microwave reactor for 3.5 hours. DCM was added to the reaction and the mixture was washed with water and brine. The organic layer was dried with sodium sulfate. The product was purified using Combiflash (DCM/methanol) and further purified by HPLC to give compound **431** as a yellow solid (60 mg, 39%). ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.62 (1 H, s), 9.33 (1 H, s), 8.64 - 8.70 (2 H, m), 8.38 - 8.49 (1 H, m), 7.72 - 7.78 (1 H, m), 5.48 (1 H, quin, *J*=8.8 Hz), 3.89 - 4.01 (2 H, m), 3.80 (2 H, dt, *J*=11.1, 2.4 Hz), 2.51 (2 H, dd, *J*=7.8, 1.2 Hz), 2.15 - 2.37 (4 H, m), 2.05 (2 H, t, *J*=3.4 Hz), 1.87 - 1.97 (2 H, m), 1.48 (9 H, s); LCMS-ESI (POS), M/Z, M+1: Found 528.3, Calculated 528.3.

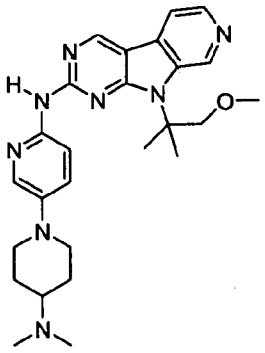


431 429

N-(6-((1R,5S)-6-amino-3-azabicyclo[310]hex-3-yl)-3-pyridazinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (429): Compound **429** was prepared from compound **431** using chemistry similar to that described in example 20. The yield is 73%. ^{1}H

NMR (500 MHz, *CD_3OD*) δ ppm 9.62 (1 H, s), 9.33 (1 H, s), 8.64 - 8.70 (2 H, m), 8.38 - 8.49 (1 H, m), 7.72 - 7.78 (1 H, m), 5.48 (1 H, quin, *J*=8.8 Hz), 3.89 - 4.01 (2 H, m), 3.80 (2 H, dt, *J*=11.1, 2.4 Hz), 2.51 (2 H, dd, *J*=7.8, 1.2 Hz), 2.15 - 2.37 (4 H, m), 2.05 (2 H, t, *J*=3.4 Hz), 1.87 - 1.97 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 428.2, Calculated 428.2.

EXAMPLE 273

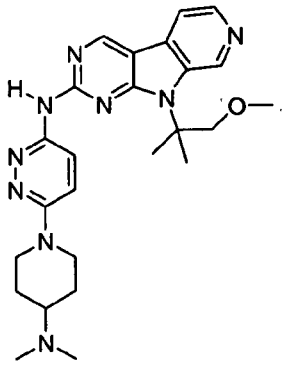


432

N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9-(2-methoxy-1,1-dimethylethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

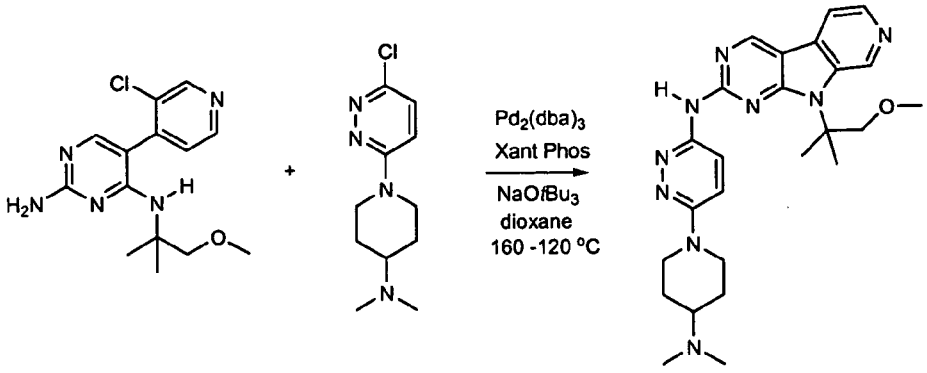
Compound **432** was prepared using chemistry similar to that described in example 20. The yield is 39%. ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 9.22 (1 H, d, *J*=1.0 Hz), 9.08 (1 H, s), 8.47 (1 H, d, *J*=5.1 Hz), 8.30 (1 H, d, *J*=9.0 Hz), 8.06 (1 H, d, *J*=2.9 Hz), 7.92 (1 H, s), 7.83 (1 H, dd, *J*=5.1, 1.2 Hz), 7.41 (1 H, dd, *J*=9.0, 2.9 Hz), 4.16 (2 H, s), 3.66 - 3.73 (2 H, m), 3.52 (1 H, s), 3.33 (6 H, s), 2.79 (2 H, td, *J*=12.0, 2.4 Hz), 2.08 (6 H, s), 1.95 - 2.15 (2 H, m), 1.66 - 1.79 (3 H, m, *J*=12.1, 12.0, 12.0, 4.3 Hz); LCMS-ESI (POS), M/Z, M+1: Found 475.3, Calculated 475.3.

EXAMPLE 274



433

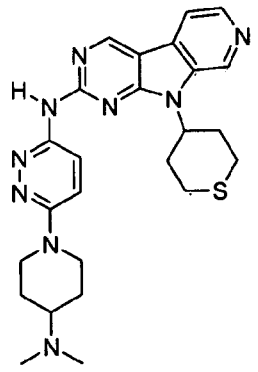
N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(2-methoxy-1,1-dimethylethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



433

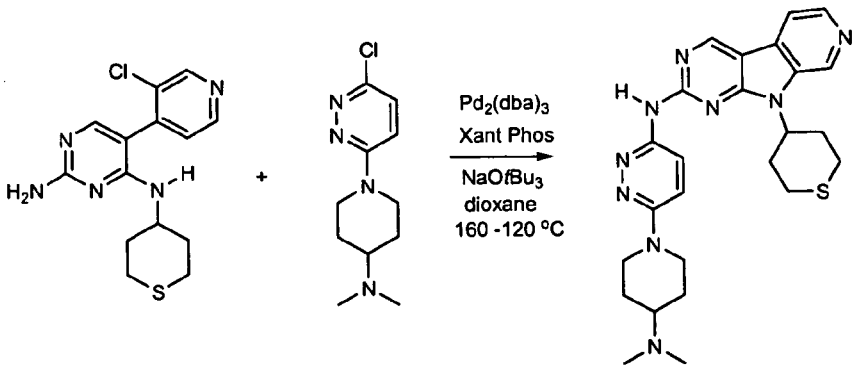
N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(2-methoxy-1,1-dimethylethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (433): Compound **433** was prepared using chemistry similar to that described in example 20. The yield is 45%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.78 (1 H, s), 9.49 (1 H, s), 8.79 (1 H, d, *J*=6.1 Hz), 8.69 (1 H, d, *J*=6.1 Hz), 8.14 (1 H, m), 8.04 (1 H, m), 4.58 (2 H, dddd, *J*=14.0, 4.7, 2.6, 2.4 Hz), 4.19 (2 H, s), 3.54 - 3.64 (1 H, m, *J*=12.0, 12.0, 3.8, 3.7 Hz), 3.37 (3 H, m), 3.20 (2 H, ddd, *J*=14.1, 11.7, 1.6 Hz), 2.94 (6 H, s), 2.29 (2 H, dd, *J*=4.2, 2.0 Hz), 2.15 (6 H, s), 1.87 (2 H, qd, *J*=12.4, 4.3 Hz); LCMS-ESI (POS), M/Z, M+1: Found 476.2, Calculated 476.3.

EXAMPLE 275



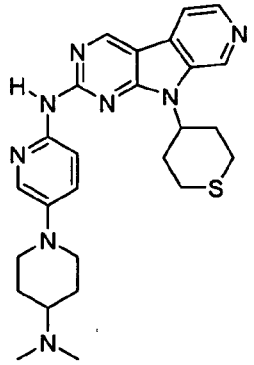
434

N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(tetrahydro-2H-thiopyran-4-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(tetrahydro-2H-thiopyran-4-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (434): Compound **434** was prepared using chemistry similar to that described in example 20. The yield is 14%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.71 (1 H, s), 9.50 (1 H, s), 8.74 (1 H, d, *J*=6.1 Hz), 8.63 (1 H, d, *J*=6.1 Hz), 8.05 - 8.12 (1 H, m), 8.01 (1 H, dd, *J*=11.4, 1.6 Hz), 4.90 (2 H, dt, *J*=11.9, 3.6 Hz), 4.74 (1 H, br. s.), 4.47 - 4.51 (1 H, m), 4.43 - 4.47 (1 H, m), 3.46 - 3.59 (2 H, m), 2.88 - 3.04 (4 H, m), 2.73 - 2.86 (8 H, m), 2.16 - 2.30 (4 H, m), 2.03 - 2.10 (1 H, m), 1.80 (2 H, qd, *J*=12.4, 4.4 Hz), 1.15 - 1.30 (1 H, m); LCMS-ESI (POS), M/Z, M+1: Found 490.1, Calculated 490.2.

EXAMPLE 276

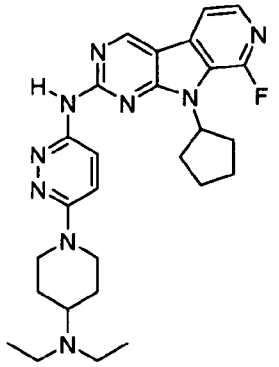


435

N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9-(tetrahydro-2H-thiopyran-4-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9-(tetrahydro-2H-thiopyran-4-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (435): Compound **435** was prepared using chemistry similar to that described in example 20. The yield is 60%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.72 (1 H, s), 9.50 (1 H, s), 8.64 - 8.78 (2 H, m), 8.21 (1 H, dd, *J*=9.5, 2.9 Hz), 8.02 - 8.11 (1 H, m), 7.72 (1 H, d, *J*=9.5 Hz), 3.89 - 4.05 (2 H, m), 3.48 (1 H, tt, *J*=12.1, 3.9 Hz), 3.07(6 H, m), 2.96 (6 H, s), 2.88 (4 H, m), 2.27-2.34 (4 H, m), 1.94 (2 H, qd, *J*=12.3, 4.4 Hz); LCMS-ESI (POS), M/Z, M+1: Found 489.2, Calculated 489.3.

EXAMPLE 277

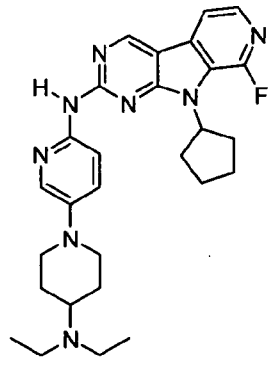


436

9-Cyclopentyl-N-(6-(4-(diethylamino)-1-piperidinyl)-3-pyridazinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **436** was prepared from compound **245** using chemistry similar to that described in example 1. The yield is 86%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.56 (1 H, s), 8.09 - 8.21 (3 H, m), 7.88 - 7.95 (1 H, m), 5.67 (1 H, quin, *J*=9.0 Hz), 4.57 (2 H, dt, *J*=13.9, 2.4 Hz), 3.81 (1 H, m, *J*=12.0, 12.0, 4.2, 3.9 Hz), 3.42 (4 H, m), 3.25 (6 H, m), 2.39 - 2.50 (2 H, m), 2.13 - 2.35 (6 H, m), 1.80 - 2.04 (4 H, m), 1.43 (6 H, t, *J*=7.2 Hz); LCMS-ESI (POS), M/Z, M+1: Found 504.2, Calculated 504.3.

EXAMPLE 278

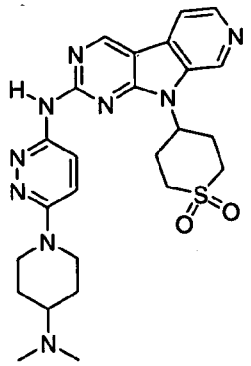


437

9-Cyclopentyl-N-(5-(4-(diethylamino)-1-piperidinyl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

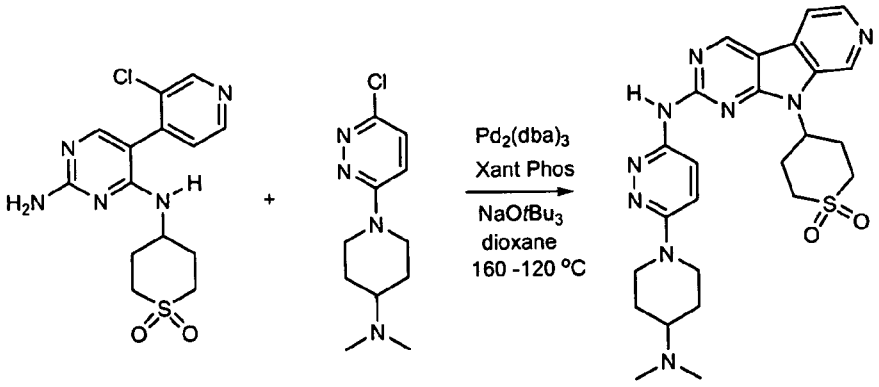
Compound **437** was prepared from compound **245** using chemistry similar to that described in example 1. The yield is 90%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.50 (1 H, s), 8.21 (1 H, dd, *J*=9.5, 2.9 Hz), 8.15 (2 H, s), 8.02 (1 H, d, *J*=2.9 Hz), 7.54 (1 H, d, *J*=9.5 Hz), 4.57 (2 H, dt, *J*=13.9, 2.4 Hz), 3.81 (1 H, m, *J*=12.0, 12.0, 4.2, 3.9 Hz), 3.42 (4 H, m), 3.25 (6 H, m), 2.39 - 2.50 (2 H, m), 2.13 - 2.35 (6 H, m), 1.80 - 2.04 (4 H, m), 1.43 (6 H, t, *J*=7.2 Hz); LCMS-ESI (POS), M/Z, M+1: Found 503.4, Calculated 503.3.

EXAMPLE 279



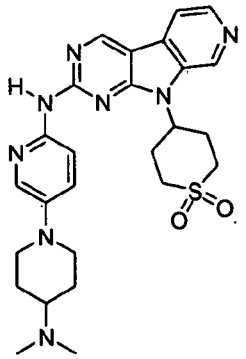
438

N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



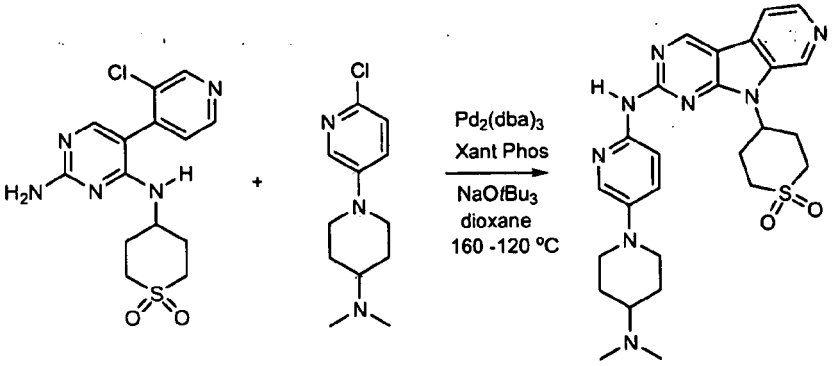
N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (438): Compound **438** was prepared using chemistry similar to that described in example 20. The yield is 8%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.61 (1 H, s), 9.37 (1 H, s), 8.58 - 8.69 (2 H, m), 8.41 (1 H, dd, *J*=10.4, 0.6 Hz), 7.96 (1 H, d, *J*=10.0 Hz), 5.25 (1 H, t, *J*=11.9 Hz), 4.93 (1 H, br. s.), 4.56 - 4.61 (1 H, m), 4.51 - 4.56 (1 H, m), 3.46 - 3.65 (6 H, m), 3.27 - 3.39 (5 H, m), 3.15 - 3.27 (1 H, m), 3.22 (1 H, ddd, *J*=14.0, 11.9, 1.7 Hz), 2.94 (6 H, s), 2.35 - 2.45 (1 H, m), 2.29 (1 H, dd, *J*=4.0, 2.1 Hz), 2.26 (1 H, dd, *J*=2.4, 1.5 Hz), 1.90 (2 H, qd, *J*=12.4, 4.3 Hz); LCMS-ESI (POS), M/Z, M+1: Found 522.2, Calculated 522.2.

EXAMPLE 280



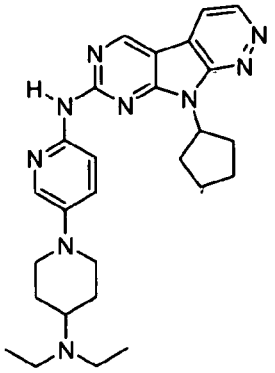
439

N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



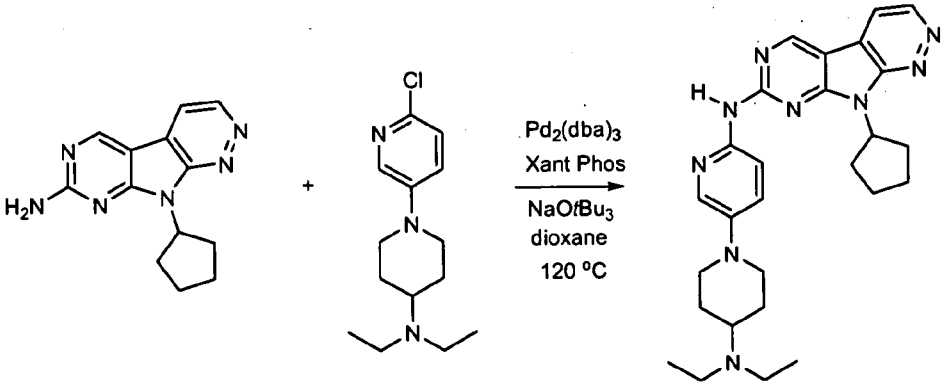
N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (439): Copound **439** was prepared using chemistry similar to that described in example 20. The yield is 30%. ^{1}H NMR (500 MHz, *CD$_3$OD*) δ ppm 9.62 (1 H, s), 9.38 (1 H, s), 8.61 - 8.71 (2 H, m), 8.17 (1 H, br. s.), 8.12 (1 H, dd, *J*=9.7, 0.6 Hz), 7.94 (1 H, d, *J*=4.4 Hz), 5.27 (1 H, dd, *J*=7.8, 3.9 Hz), 3.95 - 4.04 (2 H, m, *J*=12.8, 4.8, 2.3, 2.3 Hz), 3.40 - 3.64 (4 H, m), 3.25 - 3.40 (1 H, m), 2.99 (2 H, m), 2.95 (6 H, s), 2.36 - 2.48 (2 H, m), 2.28 (2 H, dd, *J*=4.3, 2.1 Hz), 2.26 (2 H, dd, *J*=2.7, 1.2 Hz), 1.94 (2 H, qd, *J*=12.3, 4.3 Hz); LCMS-ESI (POS), M/Z, M+1: Found 521.3, Calculated 521.2.

EXAMPLE 281



440

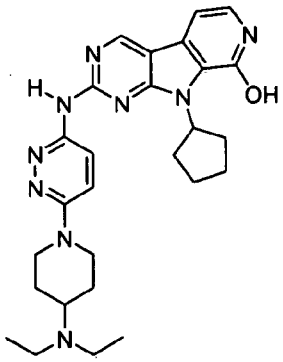
9-Cyclopentyl-N-(5-(4-(diethylamino)-1-piperidinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine



319 440

9-Cyclopentyl-N-(5-(4-(diethylamino)-1-piperidinyl)-2-pyridinyl)-9H-pyrimido-[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (440): Compound **440** was prepared from compound **319** using methods described in Example 1. The yield is 26%. ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 9.13 (1 H, s), 9.12 (1 H, s), 8.60 (1 H, d, *J*=0.5 Hz), 8.39 (1 H, d, *J*=9.0 Hz), 8.13 (1 H, d, *J*=0.5 Hz), 7.88 (1 H, d, *J*=5.1 Hz), 7.41 (1 H, dd, *J*=9.0, 2.9 Hz), 5.72 (1 H, quin, *J*=8.8 Hz), 3.70 - 3.78 (2 H, m, *J*=12.1, 4.8, 2.2, 2.2 Hz), 2.79 (2 H, m), 2.77 (2, H, m), 2.64 (4 H, m), 2.18 (4 H, m), 1.94 (2 H, ddd, *J*=12.7, 2.9, 2.7 Hz), 1.86 (2 H, m), 1.70 (4H, m), 1.10 (6 H, t, *J*=7.1 Hz); LCMS-ESI (POS), M/Z, M+1: Found 486.4, Calculated 486.3.

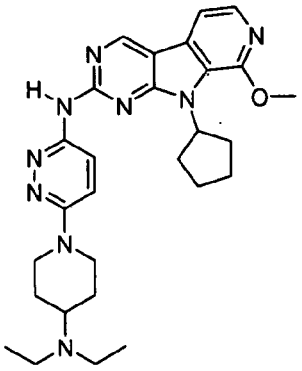
EXAMPLE 282



441

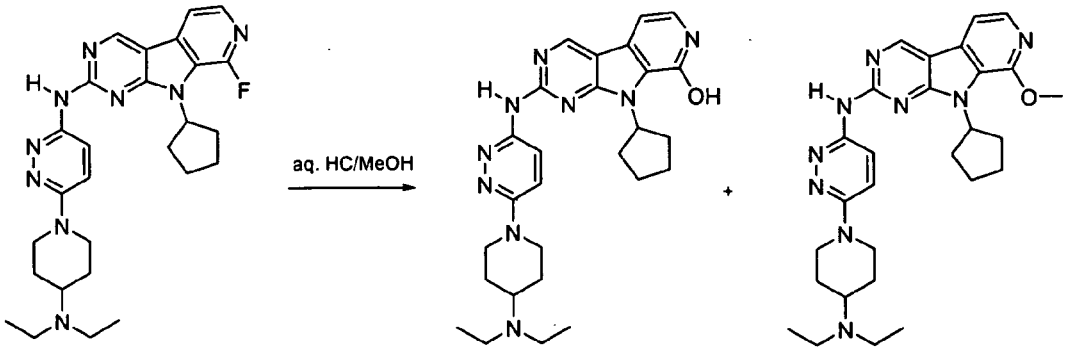
9-cyclopentyl-2-((6-(4-(diethylamino)-1-piperidinyl)-3-pyridazinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol

EXAMPLE 283



442

9-cyclopentyl-N-(6-(4-(diethylamino)-1-piperidinyl)-3-pyridazinyl)-8-methoxy-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine



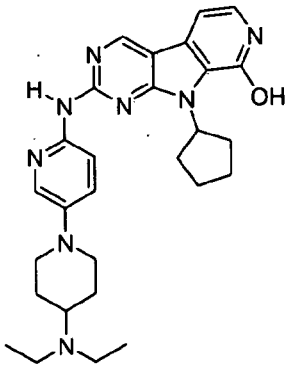
436 **441** **442**

Compound **436** (33mg, 66 μmol) in methanol (2mL) was treated with 0.1 mL of 37% aq. HCl at 60°C for 4 hours. The reaction mixture was diluted with methanol and then purified using HPLC to give compound **441** as a yellow solid (20mg, 60%) and compound **442** as a yellow solid (4.7mg, 14%).

9-cyclopentyl-2-((6-(4-(diethylamino)-1-piperidinyl)-3-pyridazinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol (441): ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.35 (1 H, s), 8.04 (1 H, m, *J*=10.0 Hz), 7.80 (1 H, m, *J*=10.0 Hz), 7.34 (1 H, d, *J*=6.6 Hz), 7.15 (1 H, d, *J*=6.8 Hz), 6.28 (1 H, quin, *J*=8.9 Hz), 4.53 - 4.58 (2 H, m), 3.72 - 3.80 (1 H, m, *J*=12.0, 12.0, 3.8, 3.7 Hz), 3.41 (2 H, dt, *J*=14.1, 7.0 Hz), 3.27 (4 H, m), 3.19 (4 H, m), 2.54 - 2.65 (2 H, m), 2.12 - 2.30 (6 H, m), 1.95 (2 H, m), 1.82 (2 H, m), 1.40 (6 H, t, *J*=7.3 Hz); LCMS-ESI (POS), M/Z, M+1: Found 502.3, Calculated 502.3.

9-cyclopentyl-N-(6-(4-(diethylamino)-1-piperidinyl)-3-pyridazinyl)-8-methoxy-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (442): ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.41 (1 H, s), 8.10 (1 H, d, *J*=5.4 Hz), 8.04 - 8.13 (1 H, m), 7.87 (1 H, d, *J*=9.8 Hz), 7.76 (1 H, d, *J*=5.4 Hz), 5.95 (1 H, quin, *J*=8.9 Hz), 4.55 (2 H, dt, *J*=13.9, 2.4 Hz), 4.19 (3 H, s), 3.71 - 3.79 (1 H, m, *J*=12.0, 12.0, 3.8, 3.7 Hz), 3.44 (2 H, m), 3.22 (2 H, m), 3.18 (2 H, m), 2.50 - 2.61 (2 H, m), 2.11 - 2.28 (6 H, m), 1.80 - 1.96 (4 H, m, *J*=12.2, 12.2, 11.9, 4.5 Hz), 1.41 (6 H, t, *J*=7.2 Hz); LCMS-ESI (POS), M/Z, M+1: Found 516.3, Calculated 516.3.

EXAMPLE 284

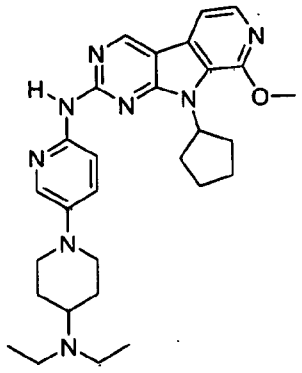


443

9-Cyclopentyl-2-((5-(4-(diethylamino)-1-piperidinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol

Compound **443** was prepared using methods described in examples 282 and 283 beginning with compound **437.** ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.26 (1 H, s), 8.07 (1 H, dd, *J*=9.5, 2.9 Hz), 7.86 (1 H, d, *J*=2.9 Hz), 7.46 (1 H, d, *J*=9.5 Hz), 7.32 (1 H, d, *J*=6.8 Hz), 7.11 (1 H, d, *J*=6.6 Hz), 6.19 (1 H, quin, *J*=8.9 Hz), 3.91 (2 H, ddd, *J*=12.6, 2.4, 2.3 Hz), 3.61 (1 H, tt, *J*=12.1, 3.7 Hz), 3.37 - 3.48 (2 H, m), 3.23 - 3.36 (4 H, m), 2.97 (2 H, ddd, *J*=12.2, 11.0, 0.7 Hz), 2.90 - 3.02 (1 H, m), 2.56 (2 H, ddd, *J*=11.7, 5.9, 3.2 Hz), 2.26)2 H, m), 2.18 (4 H, m), 1.99 (2 H, qd, *J*=12.3, 4.3 Hz), 1.72 - 1.87 (2 H, m), 1.42 (6 H, t, *J*=7.2 Hz); LCMS-ESI (POS), M/Z, M+1: Found 501.2, Calculated 501.3.

EXAMPLE 285

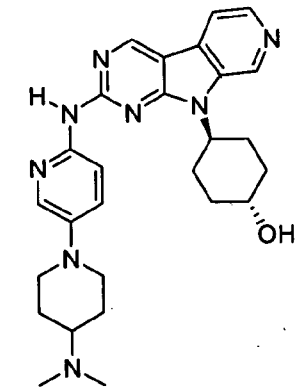


444

9-cyclopentyl-N-(5-(4-(diethylamino)-1-piperidinyl)-2-pyridinyl)-8-methoxy-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound **444**) was prepared using methods described in example 282 and 283 beginning with compound **437**. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.32 (1H, s), 8.03 - 8.11 (2 H, m), 7.97 (1 H, d, *J*=2.9 Hz), 7.74 (1 H, d, *J*=5.4 Hz), 7.53 (1 H, d, *J*=9.3 Hz), 5.90 (1 H, quin, *J*=8.9 Hz), 4.17 (3 H, s), 3.93 - 3.98 (2 H, m), 3.60 (1 H, tt, *J*=12.1, 3.7 Hz), 3.40(2 H, m), 3.27 (2 H, m), 2.97 (2 H, td, *J*=12.2, 1.2 Hz), 2.15 - 2.27 (6 H, m), 1.98 (2 H, qd, *J*=12.3, 4.3 Hz), 1.78 - 1.90 (2 H, m), 1.41 (6 H, t, *J*=7.2 Hz); LCMS-ESI (POS), M/Z, M+1: Found 515.3, Calculated 515.3

EXAMPLE 286



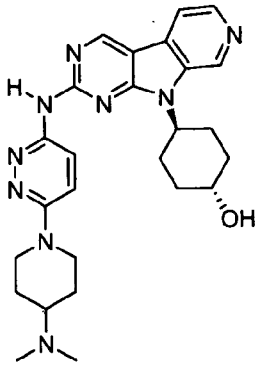
445

Trans-4-(2-((5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)cyclohexanol

Compound **445** was prepared using chemistry similar to that described in example 258. The two step yield is 58%. ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.98 (1 H, s), 8.83 (H, d, *J*=1.0 Hz), 8.42 (1 H, d, *J*=5.1 Hz), 8.24 (1 H, d, *J*=9.0 Hz), 7.97 - 8.04 (2 H, m), 7.74 (1 H, dd, *J*=5.1, 1.2 Hz), 7.30 (1 H, m), 4.67 (1 H, tt, *J*=12.3, 4.0 Hz), 3.79 - 3.87 (1 H, m, *J*=11.1,

11.1, 4.4, 4.3 Hz), 3.54 - 3.67 (2 H, m), 3.27 - 3.34 (1 H, m), 2.54 - 2.76 (4 H, m), 2.27 (6 H, s), 2.16 - 2.20 (3 H, m, *J*=6.6, 6.6, 6.4, 2.6 Hz), 1.86 - 1.96 (6 H, m), 1.49 - 1.73 (6 H, m), 1.38 (1 H, d, *J*=7.3 Hz); LCMS-ESI (POS), M/Z, M+1: Found 487.3, Calculated 487.3.

EXAMPLE 287



446

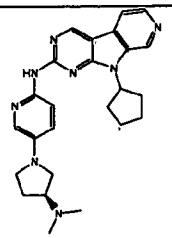
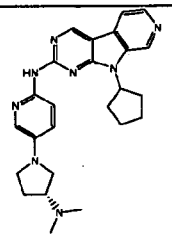
Trans-4-(2-((6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)cyclohexanol

Compound **446** was prepared using chemistry similar to that described in example 258. The two step yield is 53%. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 9.73 (1 H, s), 9.53 (1 H, s), 8.65 - 8.77 (2 H, m), 8.08 (2 H, m), 5.02 (1 H, m, *J*=12.4, 12.4, 4.2, 4.0 Hz), 4.58 - 4.63 (2 H, m), 3.92 (1 H, tt, *J*=11.1, 4.2 Hz), 3.60 (1 H, tt, *J*=12.1, 3.9 Hz), 3.20 (2 H, ddd, *J*=14.2, 12.1, 2.6 Hz), 2.94 (6 H, s), 2.71 - 2.83 (2 H, m, *J*=13.1, 12.9, 12.9, 3.5 Hz), 2.17 - 2.32 (4 H, m), 2.08 (2 H, ddd, *J*=13.3, 2.4, 2.1 Hz), 1.87 (2 H, qd, *J*=12.5, 4.4 Hz), 1.60 - 1.73 (2 H, m); LCMS-ESI (POS), M/Z, M+1: Found 488.2, Calculated 488.3.

Table 5

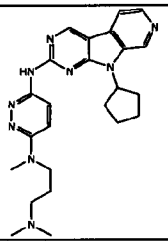
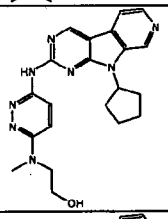
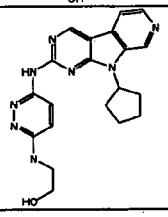
Examples 288-289 (listed in Table 5) were prepared using conditions as described for example 60 with deprotection when necessary, replacing 5-bromo-2-chloropyridine and **97** with proper chemical reagents. The reaction conditions such as temperature and reaction time were the same unless indicated in the table. All LCMS data was obtained using Agilent 1100 series LC/MSD, column: CAPCELL UG120 (3um, 4.6 mm I.D. x 50 mm), solvent system: water-acetonitrile 95:5 with 0.1% formic acid.

Table 5

Example #	Structure	Reaction conditions	LSMS retention time (minutes)	LCMS-ESI (M+1)
288			0.874	443.2
289			0.888	443.2

Examples 290-297 (table 6) were prepared using conditions as described for example 101 with deprotection when necessary, replacing compound **97** with proper amine. The reaction conditions such as solvent, temperature, and reaction time for Step 2 were the same unless indicated

Table 6

Example #	Structure	Reaction Conditions	LSMS retention time (min)	LCMS-ESI (M+1)
290			0.766	446.2
291			0.761	405.1
292			0.742	391.1

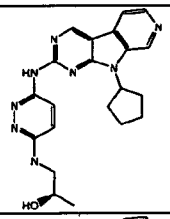
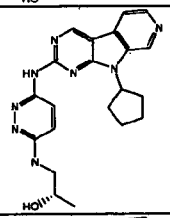
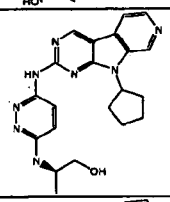
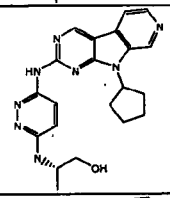
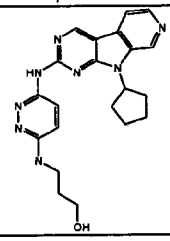
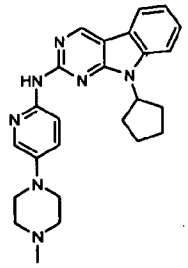
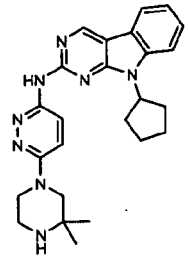
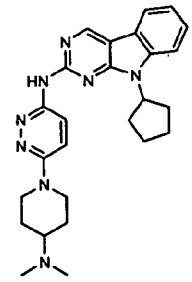
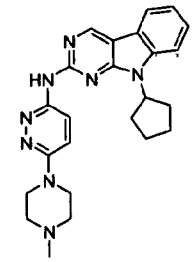
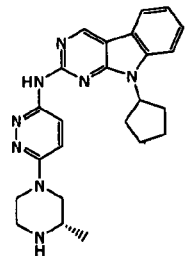
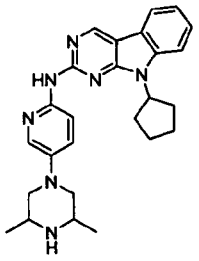
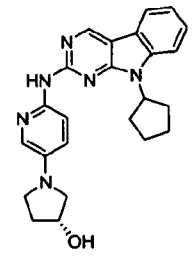
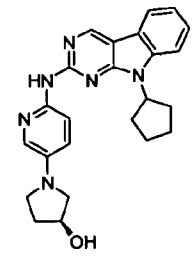
Example #	Structure	Reaction Conditions	LSMS retention time (min)	LCMS-ESI (M+1)
293			0.777	405.2
294			0.781	405.2
295			0.791	405.2
296			0.785	405.2
297			0.768	405.2

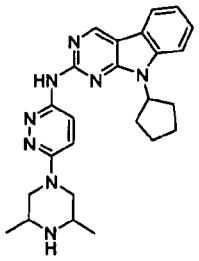
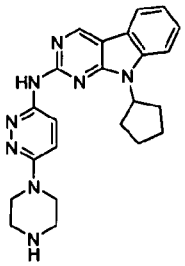
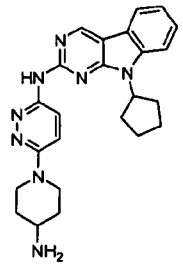
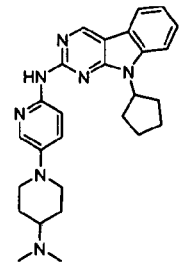
Table 7

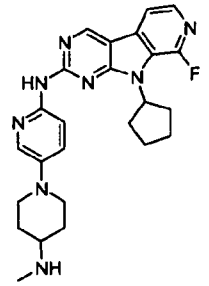
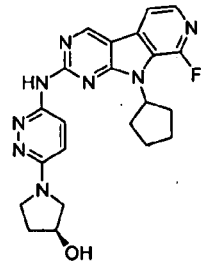
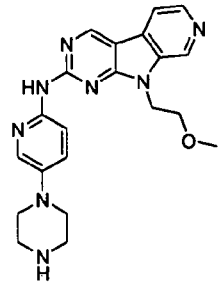
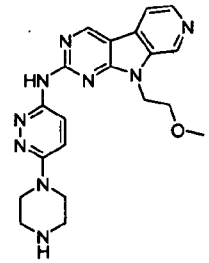
Examples 298-432 (table 7) were prepared using conditions as described for example 122 with deprotection when necessary, replacing components with proper reagents prepared according to examples 1 or 4.

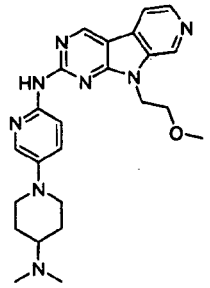
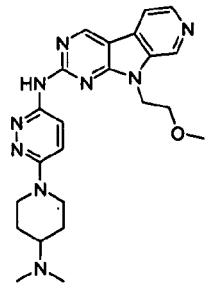
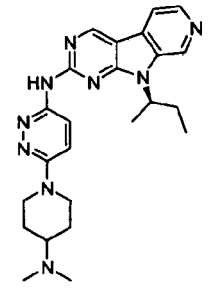
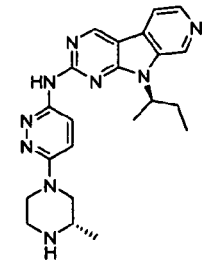
Table 7

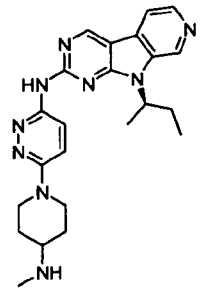
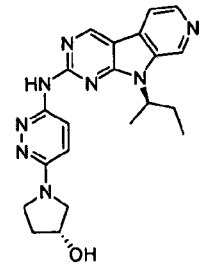
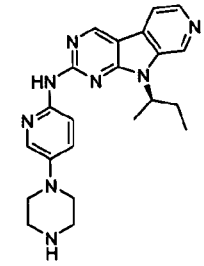
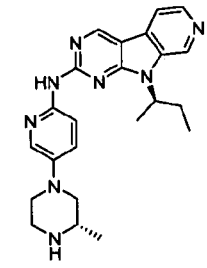
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
298		1.023	428.2
299		1.055	443.2
300		1.082	457.3
301		1.028	429.2

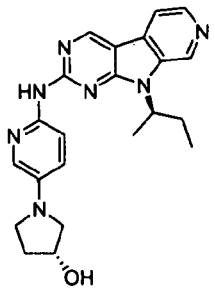
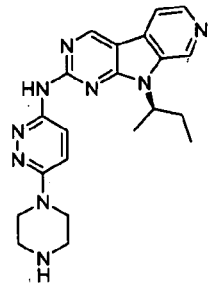
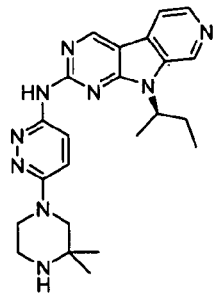
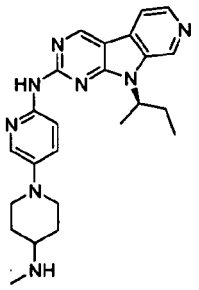
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
302		1.013	429.2
303		1.083	442.3
304		1.360	415.1
305		1.369	415.1

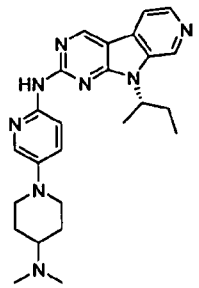
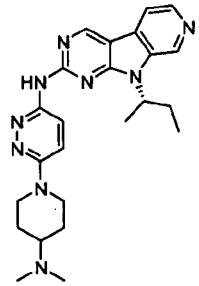
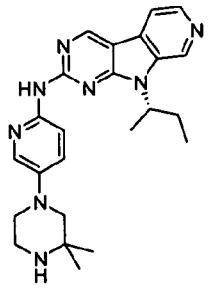
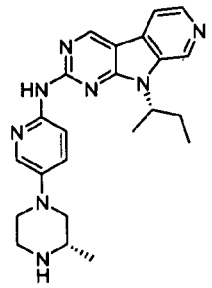
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
306		1.066	443.2
307		1.048	415.1
308		1.080	429.2
309		1.074	456.2

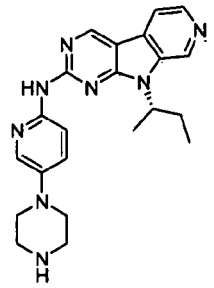
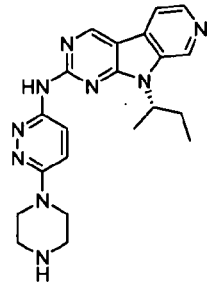
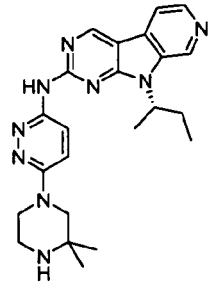
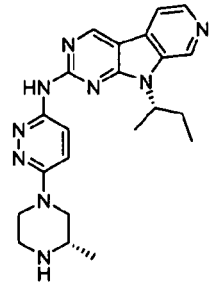
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
310		1.047	461.2
311		1.087	435.1
312		0.574	405.2
313		0.497	406.1

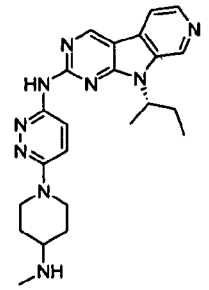
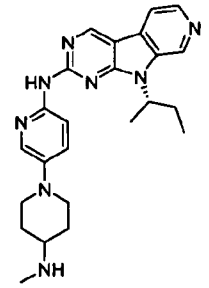
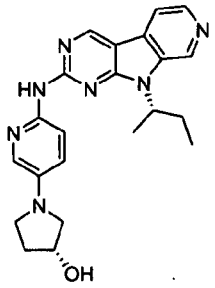
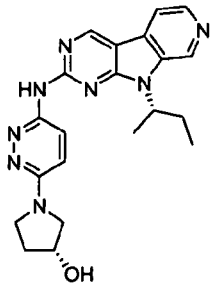
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
314		0.671	447.3
315		0.613	448.1
316		0.701	446.2
317		0.693	418.1

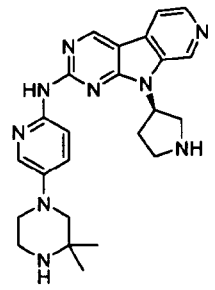
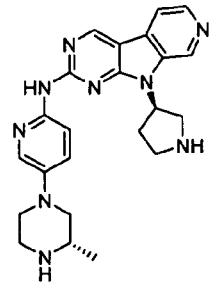
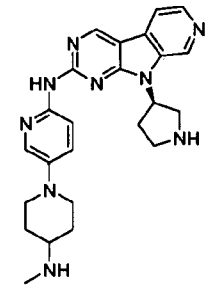
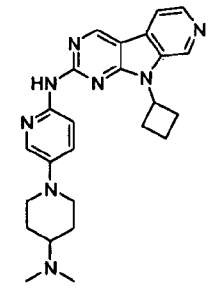
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
318		0.742	432.2
319		0.734	405.1
320		0.706	403.1
321		0.732	417.3

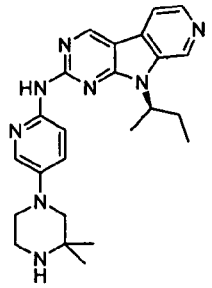
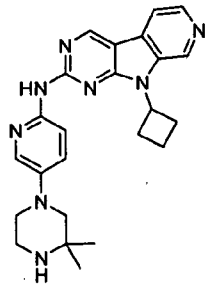
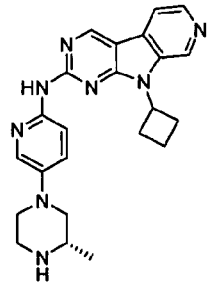
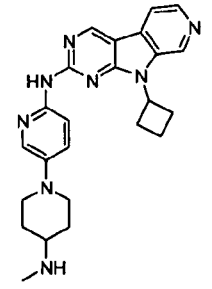
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
322		0.862	404.2
323		0.685	404.2
324		0.728	432.2
325		0.731	431.2

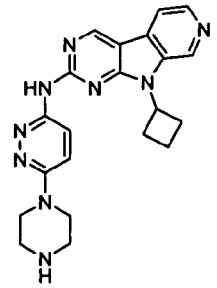
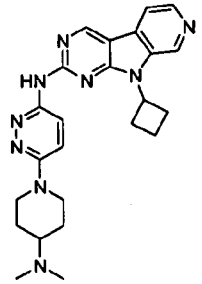
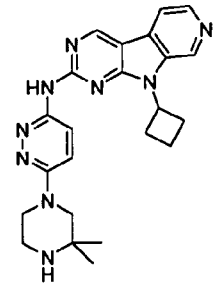
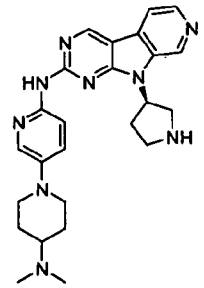
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
326		0.736	445.3
327		0.732	446.2
328		0.783	431.2
329		0.746	417.3

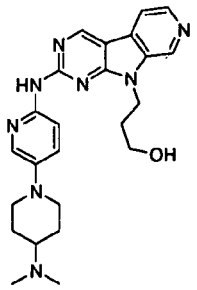
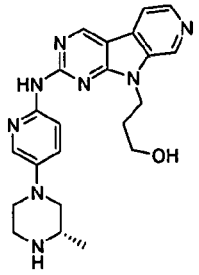
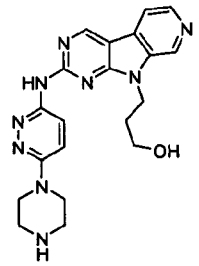
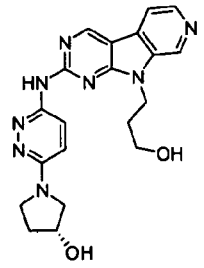
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
330		0.733	403.1
331		0.720	404.2
332		0.753	432.2
333		0.690	418.1

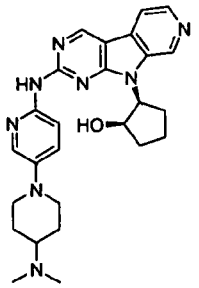
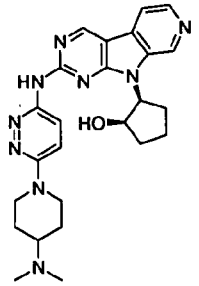
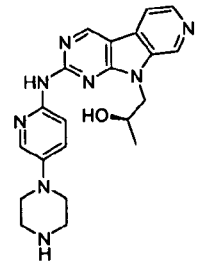
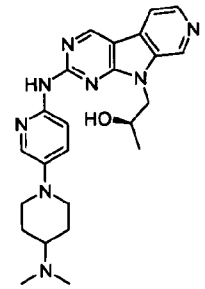
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
334		0.753	432.2
335		0.776	431.2
336		0.925	404.2
337		0.736	405.1

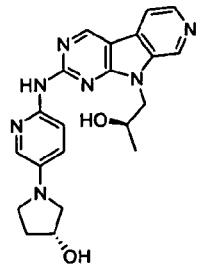
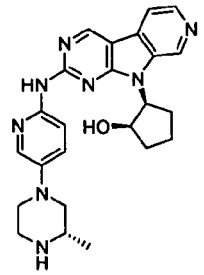
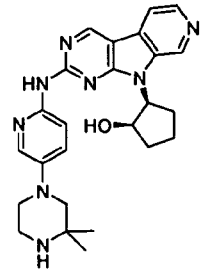
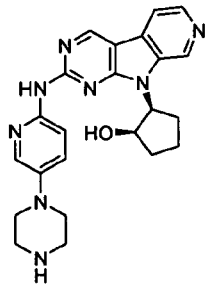
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
338		0.499	444.2
339		0.382	430.1
340		0.411	444.2
341		0.730	443.2

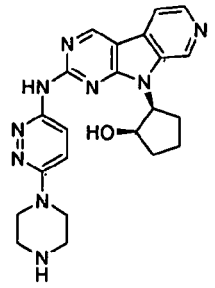
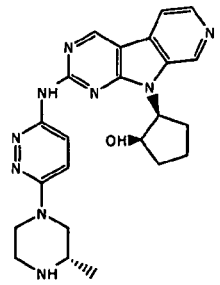
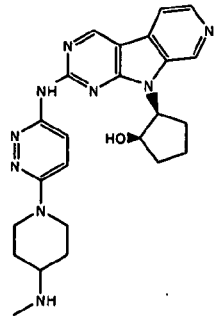
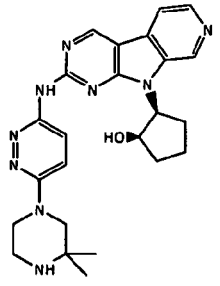
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
342		0.776	431.2
343		0.728	429.2
344		0.723	415.1
345		0.719	429.2

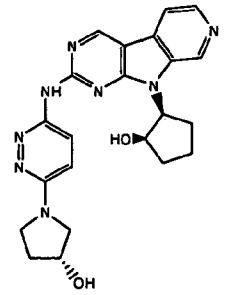
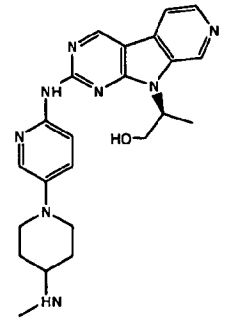
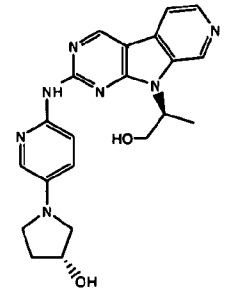
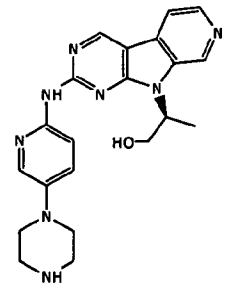
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
346		0.648	402.2
347		0.702	444.2
348		0.719	430.2
349		0.647	458.2

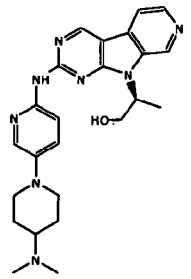
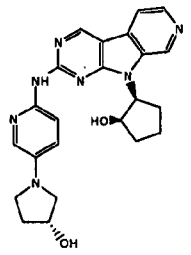
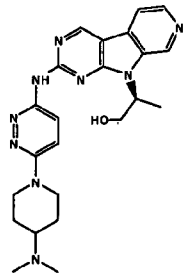
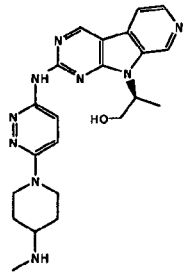
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
350		0.618	447.3
351		0.609	419.2
352		0.422	406.1
353		0.640	407.2

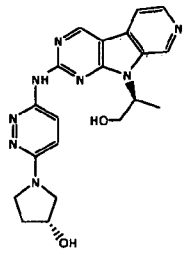
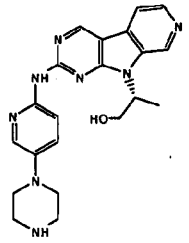
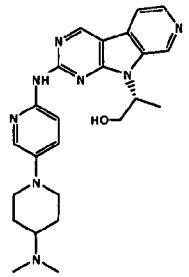
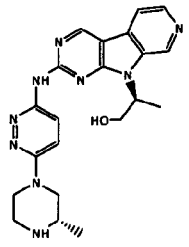
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
354		0.693	473.2
355		0.664	474.2
356		0.565	405.2
357		0.635	447.3

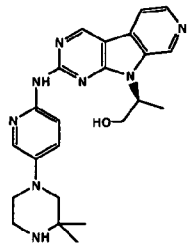
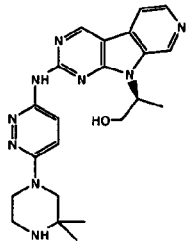
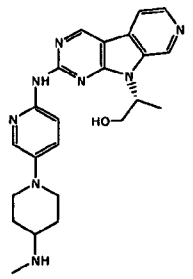
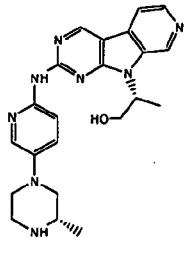
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
358		0.735	406.1
359		0.687	445.3
360		0.714	459.2
361		0.669	431.2

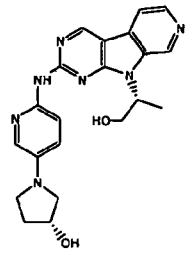
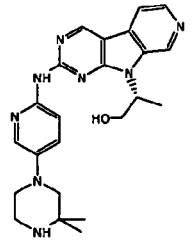
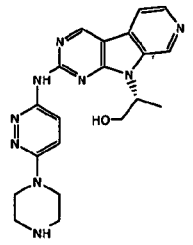
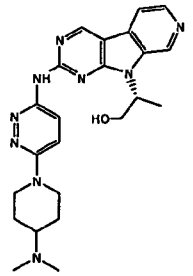
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
362		0.648	432.2
363		0.66	446.2
364		0.683	460.3
365		0.674	460.3

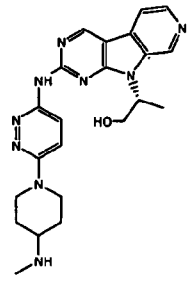
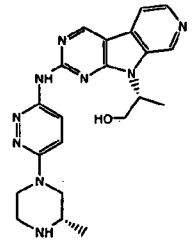
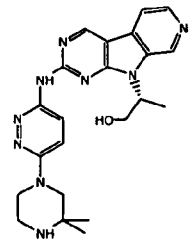
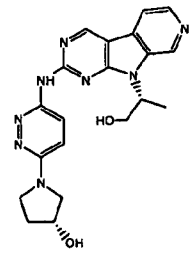
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
366		0.705	433.1
367		0.642	433.2
368		0.757	406.1
369		0.608	405.2

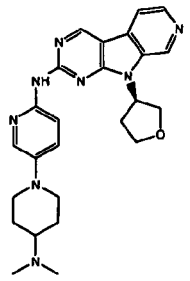
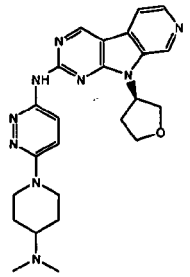
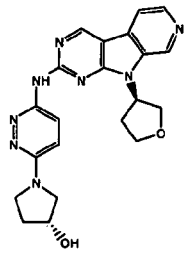
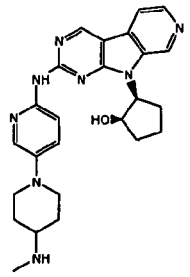
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
370		0.655	447.2
371		0.822	432.1
372		0.642	448.2
373		0.646	434.2

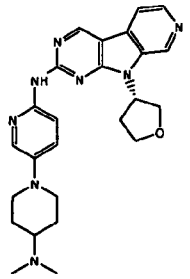
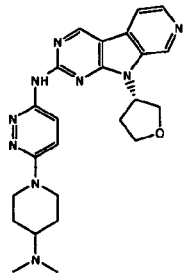
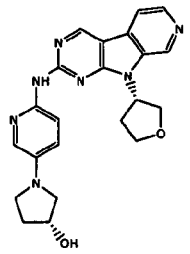
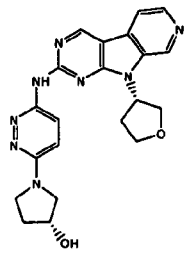
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
374		0.679	407.2
375		0.635	405.1
376		0.658	447.3
377		0.628	420.2

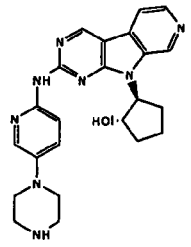
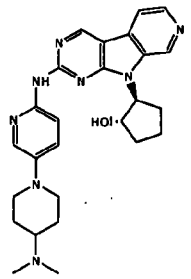
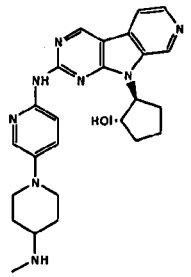
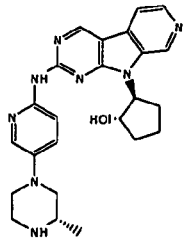
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
378		0.677	433.1
379		0.659	434.2
380		0.664	433.1
381		0.645	419.2

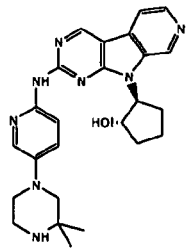
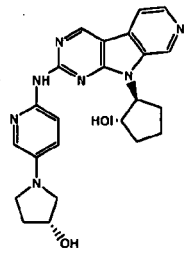
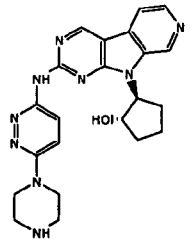
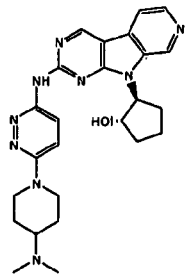
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
382		0.788	406.1
383		0.702	433.1
384		0.648	406.1
385		0.671	448.1

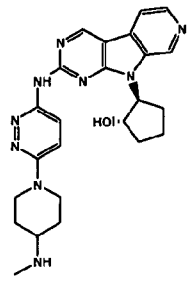
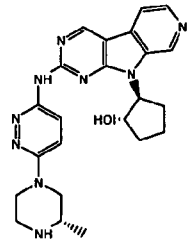
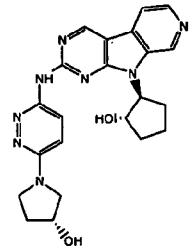
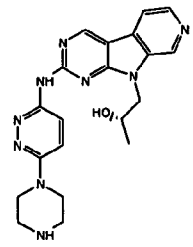
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
386		0.643	434.2
387		0.635	420.1
388		0.646	434.2
389		0.674	407.2

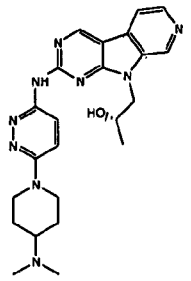
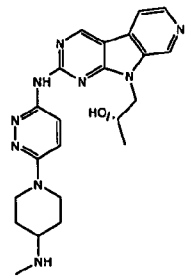
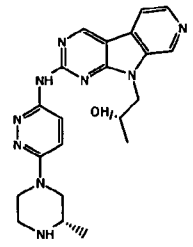
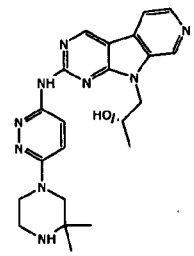
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
390		0.701	470.2
391		0.675	460.1
392		0.696	419.2
393		0.709	459.2

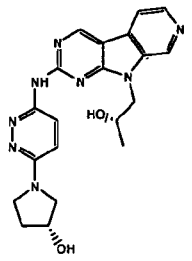
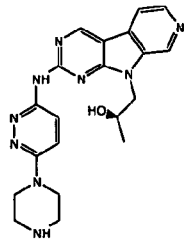
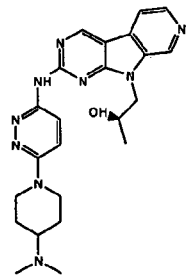
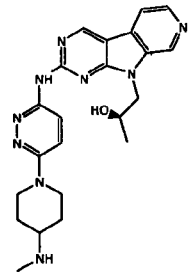
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
394		0.69	459.2
395		0.681	460.1
396		0.766	418.1
397		0.694	419.2

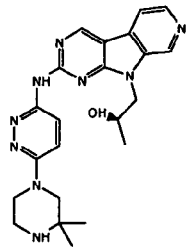
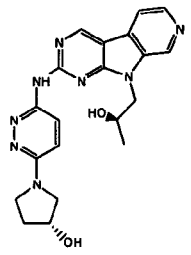
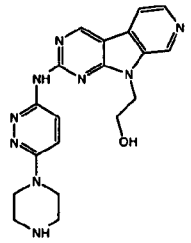
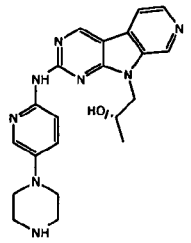
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
398		0.693	431.2
399		0.722	473.2
400		0.708	459.2
401		0.705	445.1

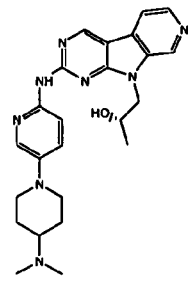
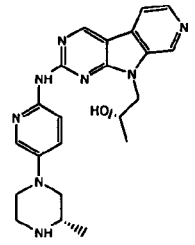
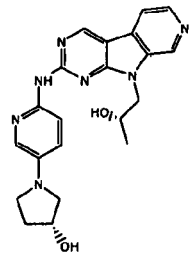
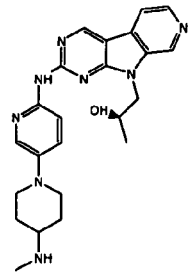
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
402		0.737	459.2
403		0.838	432.1
404		0.653	432.2
405		0.684	474.2

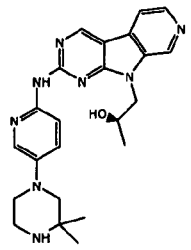
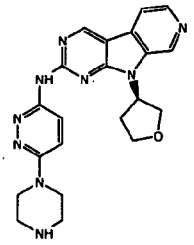
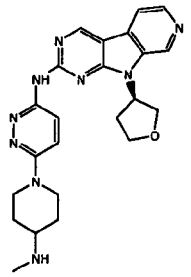
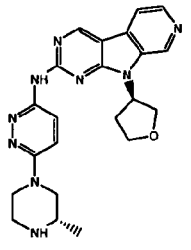
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
406		0.672	460.1
407		0.671	446.2
408		0.715	433.1
409		0.596	406.1

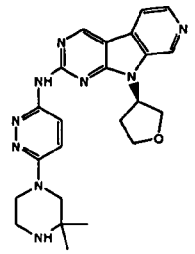
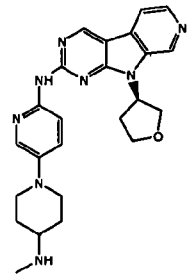
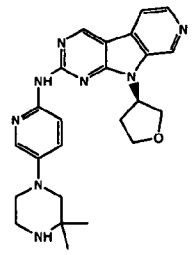
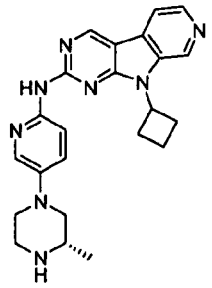
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
410		0.62	448.1
411		0.627	434.2
412		0.622	420.2
413		0.633	434.2

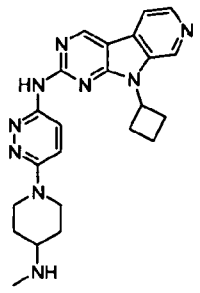
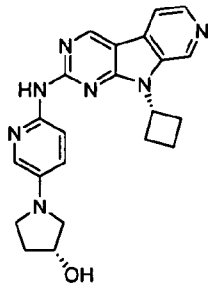
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
414		0.66	407.2
415		0.606	406.1
416		0.634	448.3
417		0.669	434.2

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
418		0.679	434.2
419		0.652	407.2
420		0.587	391.1
421		0.708	405.2

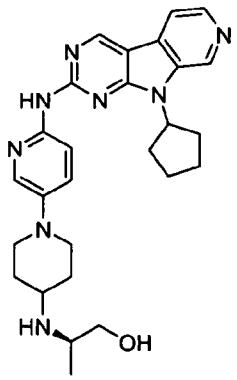
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
422		0.759	447.3
423		0.603	419.2
424		0.712	406.1
425		0.685	433.2

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
426		0.672	433.2
427		0.595	418.1
428		0.635	446.2
429		0.618	432.2

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
430		0.638	446.2
431		0.658	445.3
432		0.674	445.3
433		0.671	416.2

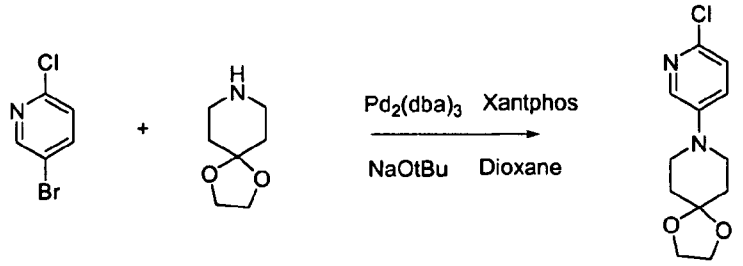
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
434		0.680	430.1
435		0.891	402.1

EXAMPLE 436



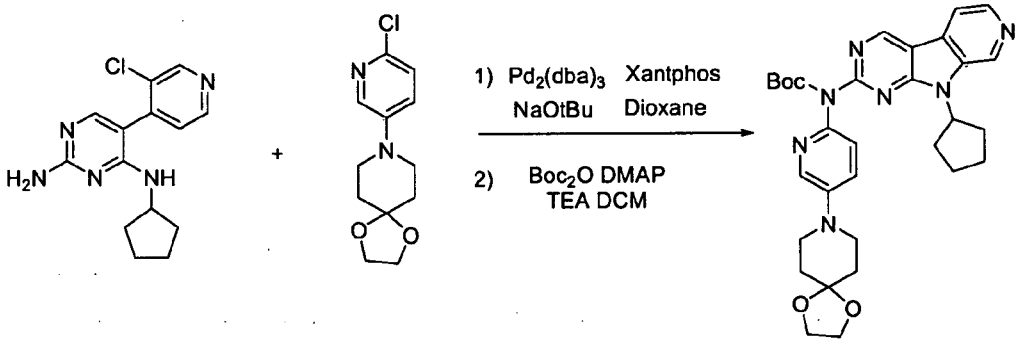
448

(2R)-2-((1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)amino)-1-propanol



303

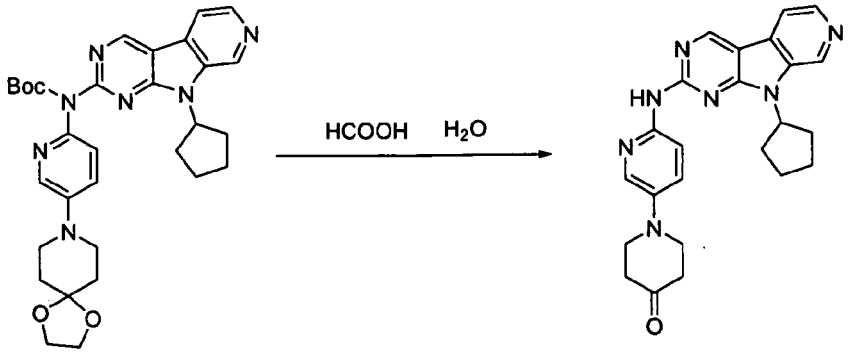
8-(6-chloro-3-pyridinyl)-1,4-dioxa-8-azaspiro[45]decane: A mixture of 5-bromo-2-chloropyridine (3.84 g, 20.0 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (3.14 g, 21.9 mmol), Xantphos (1.73 g, 2.99 mmol), $Pd_2(dba)_3$ (1.37 g, 1.5 mmol), and sodium *tert*-butoxide (2.88 g, 29.9 mmol) in dioxane was purged with nitrogen gas for 10 minutes and then heated at 80°C for 2 hours. After cooling to room temperature, the mixture was filtered through a celite pad and concentrated on a rotary evaporator. The crude product was purified via flash chromatography on silica gel eluting with a gradient of 0-40% ethyl acetate in hexane to give compound **303** (2.8 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (1H, d, J = 3.1 Hz), 7.24 (1H, dd, J = 3.1 Hz, J = 8.8 Hz), 7.18 (1H, d, J = 8.8 Hz), 4.02 (4H, s), 3.36 (4H, m), 1.87 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 255.1, Calculated 255.1.



3 303 450

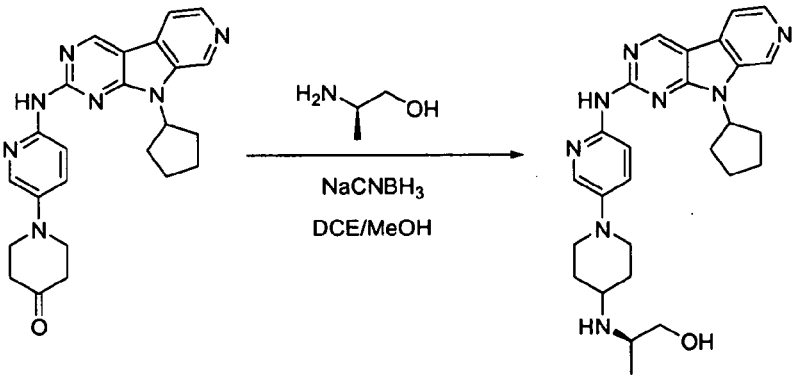
***tert*-Butyl (9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)(5-(1,4-dioxa-8-azaspiro[45]dec-8-yl)-2-pyridinyl)carbamate (450):** A mixture of compound **3** (3.18 g, 11.0 mmol), compound **303** (2.80 g, 11.0 mmol), Xantphos (1.27 g, 2.19 mmol), $Pd_2(dba)_3$ (1.00 g, 1.1 mmol), and sodium *tert*-butoxide (1.58 g, 16.5 mmol) in dioxane was purged with nitrogen gas for 10 minutes and then heated at 125°C for 2 hours. After cooling to room temperature, the mixture was diluted with 100 mL of DCM and partitioned over 200 mL of brine. The aqueous layer was extracted with two 100 mL portions of DCM and the combined DCM phases were dried over sodium sulfate. After concentration on a rotary evaporator, the crude product was treated with di-*tert*-butyl dicarbonate (2.4 g, 11.0 mmol), triethylamine (1.65 g, 0.17 mmol) and DMAP (0.25 g, 2.2 mmol) in DCM and stirred overnight at rt. The mixture was then washed with 3 portions of brine, dried over sodium sulfate and concentrated. The crude product was purified via flash chromatography on silica gel eluting with a gradient of 0-5%

methanol in DCM in the presence of 0.5% NH_4OH to give compound **450** (2.8 g, 46%). LCMS-ESI (POS), M/Z, M+1: Found 572.2, Calculated 572.3.



450 **451**

1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinone (451): A mixture of compound **450** (2.85 g, 5.0 mmol) and 50 mL of 50% aqueous formic acid was heated to 100 °C for 1h. After cooling to room temperature, the reaction mixture was titrated to pH 12 with concentrated aqueous NaOH, while cooling through the addition of ice. The precipitated product was filtered, washed with water followed by a minimal volume of methanol and dried under vacuum to give compound **451** (2.1 g, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (1H, s), 8.84 (1H, s), 8.44 (1H, d, J = 5.9 Hz), 8.38 (1H, d, J = 9 Hz), 8.09 (1H, d, J = 2.7 Hz), 7.81 (1H, d, J = 5.9 Hz), 7.38 (1H, dd, J = 9.0 Hz, J = 2.7 Hz), 5.31 (1H, m), 3.52 (4H, m), 3.42 (1H, s), 2.56 (4H, m), 2.37 (2H, m), 2.10 (4H, m), 1.82 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 428.2, Calculated 428.2.



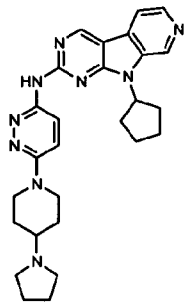
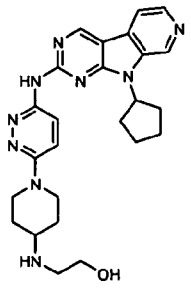
451 **448**

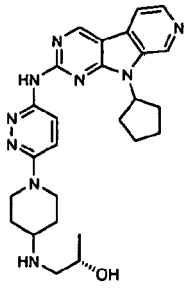
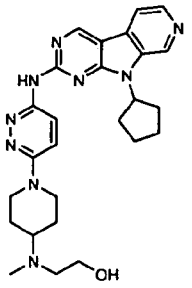
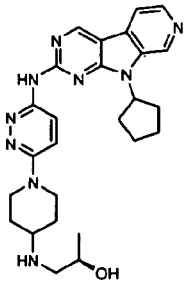
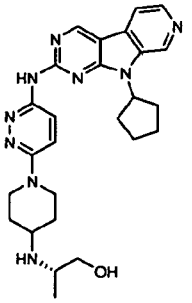
(2R)-2-((1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)amino)-1-propanol: A mixture of compound **451** (43 mg, 0.10 mmol), (R)-2-aminopropan-1-ol (38 mg, 0.50 mmol) and sodium cyanoborohydride (1M/THF: 0.26 mL, 0.26 mmol) in 3 mL of methanol/dichloroethane 2:1 was heated at 80°C for 2h. After concentration, the

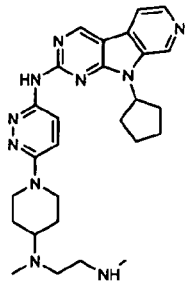
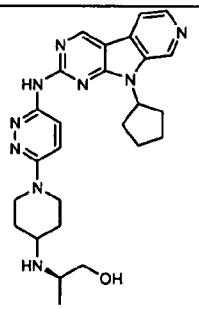
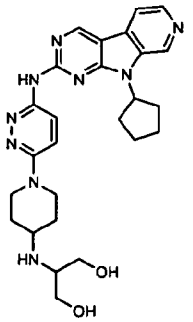
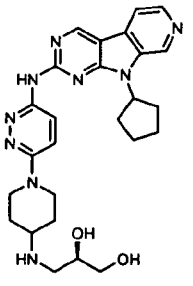
crude mixture was diluted with 2 mL of methanol/DMSO (1:1) and purified via reverse phase HPLC to give compound **448** (28 mg, 39%) ^{1}H NMR (400 MHz, *CD_3OD*) δ 9.71 (1H, s), 9.37 (1H, s) 8.74 (1H, d, *J* = 6.5 Hz), 8.69 (1H, d, *J* = 6.5 Hz), 8.20 (1H, dd, *J* = 9.6 Hz, *J* = 2.9 Hz), 8.02 (1H, d, *J* = 2.9 Hz), 7.68 (1H, d, *J* = 9.6 Hz), 5.48 (1H, m), 3.94 (2H, d, *J* = 12.5), 3.87 (1H, dd, *J* = 11.7 Hz, *J* = 3.5 Hz), 3.64 (1H, dd, *J* = 11.7 Hz, *J* = 5.5 Hz), 3.55 (2H, m), 3.00 (2H, t, *J* = 12.5 Hz), 2.53 (2H, m), 2.24 (7H, m), 1.88 (4H, m), 1.38 (3H, d, *J* = 6.7 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 487.3, Calculated 487.3.

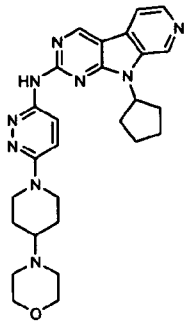
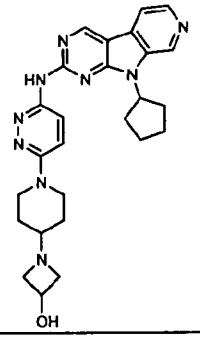
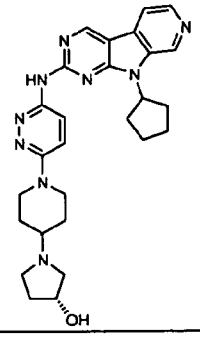
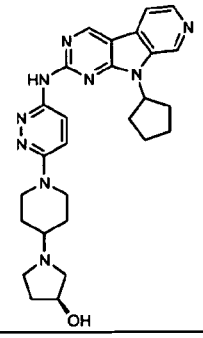
Examples 437-481 (table 8) were prepared using conditions as described for example 436 using the appropriate primary or secondary amine followed by deprotection when necessary.

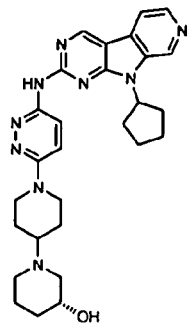
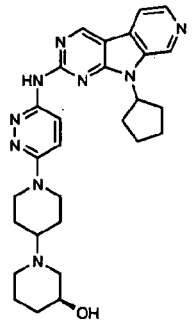
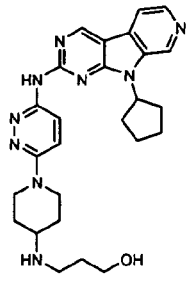
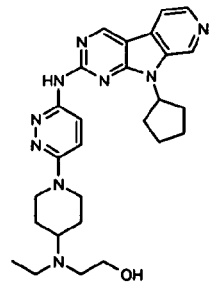
Table 8

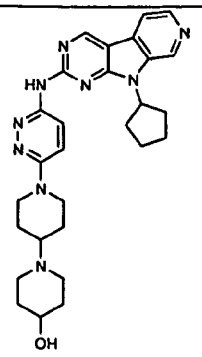
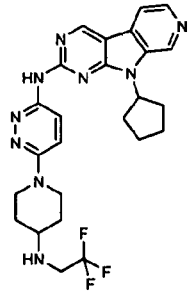
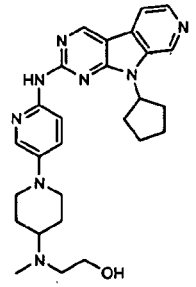
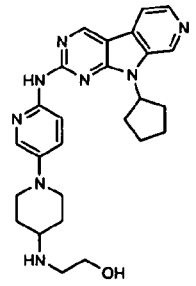
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
437		0.73	484.3
438		0.702	474.2

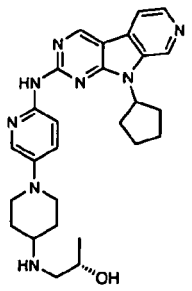
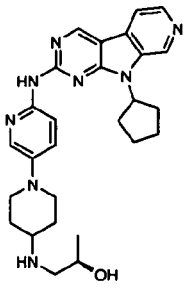
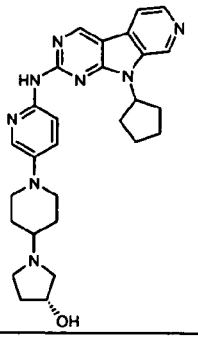
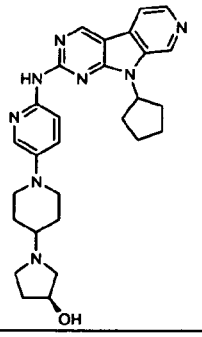
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
439		0.726	488.2
440		0.707	488.2
441		0.716	488.2
442		0.723	488.2

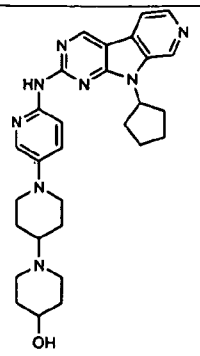
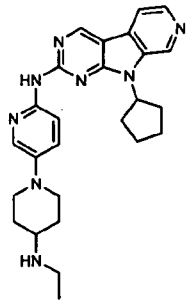
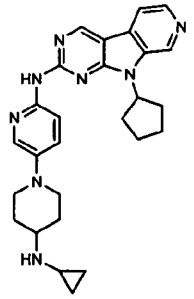
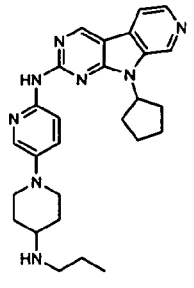
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
443		0.664	501.2
444		0.717	488.2
445		0.784	504.2
446		0.789	504.2

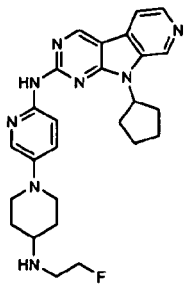
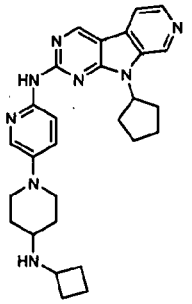
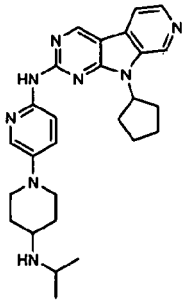
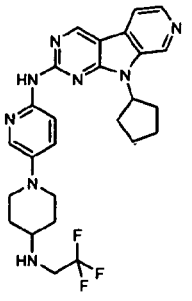
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
447		0.809	500.2
448		0.78	486.2
449		0.786	500.2
450		0.765	500.2

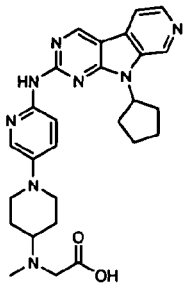
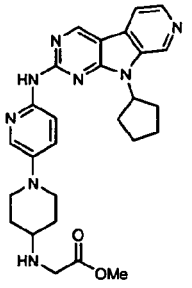
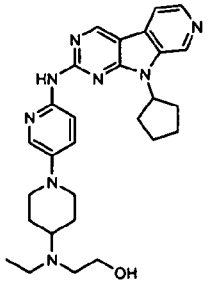
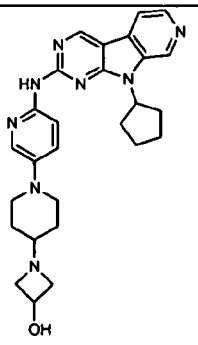
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
451		0.794	514.3
452		0.809	514.3
453		0.794	488.2
454		0.808	502.3

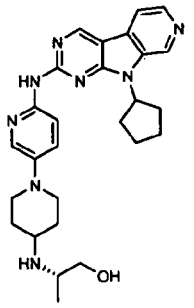
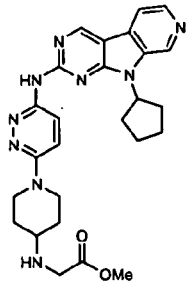
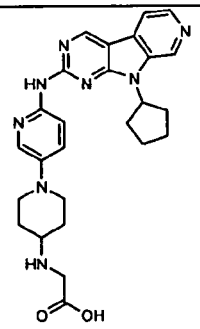
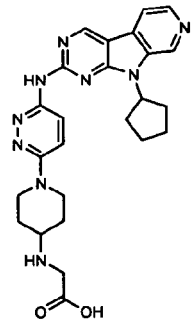
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
455		0.791	514.3
456		0.89	512.2
457		0.782	487.3
458		0.766	473.2

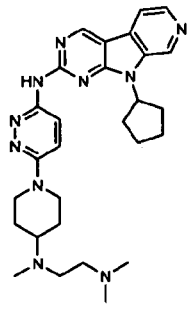
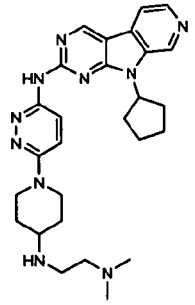
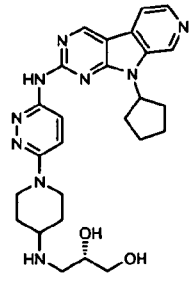
Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
459		0.825	487.3
460		0.772	487.3
461		0.732	499.2
462		0.729	499.2

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
463		0.733	513.3
464		0.75	457.3
465		0.777	469.3
466		0.774	471.3

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
467		0.738	475.3
468		0.795	483.3
469		0.779	471.3
470		0.873	511.1

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
471		0.798	501.2
472		0.771	501.2
473		0.766	501.2
474		0.762	485.2

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
475		0.764	487.1
476		0.745	502.1
477		0.773	487.3
478		0.729	488.2

Example #	Structure	LCMS retention time (min)	LCMS-ESI (M+1)
479		0.731	515.3
480		0.715	501.2
481		0.698	504.2

BIOLOGICAL TESTING

The pharmacological properties of the compounds of this invention may be confirmed by *in vitro* assays such as those described below.

The Cdk4 and Cdk6 inhibitory activity of the compounds is measured with a kinase inhibition assay using recombinant Cdk4/CyclinD1 or Cdk6/CyclinD3 protein complexes. The protein substrate used in the assay is the retinoblastoma protein (Rb). The kinase reactions are carried out in a 96-well filter plate (MSDV N6B50, Millipore). Compounds are serially diluted in kinase buffer (20 mM Tris-HCl, pH 7.4, 50 mM NaCl, 1 mM DTT, 1 mg/ml BSA) and added to the reaction mixture containing

2.5 ng/ml Cdk4/CyclinD1 or Cdk6/CyclinD3, 25 μM ATP, 10 μCi/ml [^{33}P]-ATP, 0.1 μg/ml Rb in the kinase buffer. The mixture is incubated at room temperature for 1 hour and the proteins precipitated with an equal volume of 20% TCA. The plates are washed with 10% TCA according to the manufacturer's instruction and dried at room temperature. The amount of the phophorylated Rb is determined with a TopCount (PerkinElmer). The IC_{50} of a compound is determined by nonlinear regression curve fitting using software program Prism 5 (GraphPad Software).

The cellular activity of the compounds is measured with a cell-based DNA synthesis inhibition assay. Rb positive (e.g. Colo-205, MDA-MB-435) or Rb negative (e.g. MDA-MB-436, H2009) cancer cells are seeded in the 96-well Cytostar plates (GE Healthcare, Cat# RPNQ0163) at a density of 3000-5000 cells/well. Dilutions of compounds are added to the cells. After 24 hour incubation at 37 C, ^{14}C-thymidine is added (0.1 μCi/well). After additional 48 hour incubation at 37 C, incorporation of ^{14}C-thymidine into the DNA of the cells was measured with a TopCount (PerkinElmer). The IC_{50} of a compound is determined by nonlinear regression curve fitting using software program Prism 5 (GraphPad Software).

The Cdk4 or Cdk6 inhibitory activity of the compounds may also be measured with kinase assays of a different format, e.g., a homogeneous time-resolved fluorescence energy transfer (HTRF) assay (Jia Y. et al , *Anal Biochem.* 2006; 356:273-281) or a fluorescence polarization (FP) assay (Sportsman JR, et al. *Comb Chem High Throughput Screen.* 2003; 6:195-200).

The compounds exemplified herein have been assayed and exhibit Cdk 4 IC_{50}s in a range from 0.13 nm to 430 nm, and exhibit Cdk 6 IC_{50}s , where determined from 0.36 nm to 500 nm. Illustrative activity values are provided in the following Table 9.

TABLE 9

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
1	0.0032	0.0044
2	0.013	0.01
3	0.00045	0.0029
4	0.0039	0.0115
5	0.00091	0.0042
6	0.0015	0.0066
7	0.0014	0.0013
8	0.00013	0.0011
9	0.0038	0.0195
10	0.0022	
11	0.0031	0.01
12	0.0096	
13	0.001	0.0026
14	0.0022	0.008
15	0.0075	0.013

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
16	0.01	0.021
17	0.00032	0.00036
18	0.0016	0.0015
19	0.004	0.01
20	0.0081	0.057
21	0.001	0.00041
22	0.0013	0.0025
23	0.011	0.0131
24	0.00094	0.0051
25	0.03	0.038
26	0.0016	0.0035
27	0.0055	0.007
28	0.057	0.061
29	0.0039	0.0057
30	0.0046	0.0061
31	0.0025	0.0059
32	0.013	0.0304
33	0.0053	0.0089
34	0.011	0.021
35	0.0082	0.021
36	0.00083	0.0044
37	0.0043	0.0012
38	0.0021	0.0153
39	0.0021	0.0031
40	0.0049	0.0026
41	0.0027	0.0072
42	0.237	0.5
43	0.136	0.218
44	0.011	0.025
45	0.073	0.129
46	0.002	0.00075
47	0.002	0.0037
48	0.0016	0.0056
49	0.0025	0.0065
50	0.066	0.112
51	0.126	0.406
52	0.012	0.022
53	0.0047	0.011
54	0.02	0.047
55	0.0012	0.0044
56	0.00097	
57	0.002	0.017
58	0.0052	
59	0.015	
60	0.004	
61	0.0017	
62	0.002	
63	0.0034	0.02
64	0.0028	0.024
65	0.0096	0.024
66	0.0054	0.073
67	0.0013	

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
68	0.0041	
69	0.017	0.031
70	0.0036	
71	0.0041	
72	0.0023	
73	0.017	
74	0.056	
75	0.0014	
76	0.0059	
77	0.003	0.011
78	0.015	
79	0.012	
80	0.0035	
81	0.0092	
82	0.0026	
83	0.012	
84	0.022	
85	0.02	
86	0.0064	
87	0.043	
88	0.477	
89	0.0076	
90	0.0056	
91	0.0061	0.0112
92	0.0088	0.0151
93	0.0031	0.0159
94	0.0049	0.0092
95	0.0044	
96	0.0162	0.0124
97	0.43	0.396
98	0.0025	0.0266
99	0.0049	
100	0.0062	
101	0.004	0.0088
102	0.0031	0.0111
103	0.0056	0.0026
104	0.0033	0.014
105	0.0067	0.0071
106	0.004	0.0243
107	0.0084	0.048
108	0.012	0.0157
109	0.0019	0.011
110	0.0034	
111	0.0044	0.0197
112	0.0059	
113	0.0042	
114	0.0016	0.01
115	0.0023	
116	0.002	
117	0.0055	0.0068
118	0.0042	
119	0.0051	

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
120	0.019	
121	0.0043	
122	0.0087	
123	0.0481	
124	0.017	
125	0.012	
126	0.002	
127	0.0053	
128	0.029	
129	0.016	
130	0.02	
131	0.174	
132	0.302	
133	0.1	
134	0.19	
135	10	
136	0.0069	
137	0.011	0.027
138	0.0012	
139	0.016	0.0064
140	0.093	10
141	0.0022	0.0026
142	0.0018	0.0049
143	0.0038	0.0158
144	0.0034	0.0046
145	0.001	0.0058
146	0.05	0.033
147	0.041	
148	0.015	
149	0.017	
150	0.011	
151	0.003	
152	0.002	0.0043
153	0.001	0.0028
154	0.02	
155	0.0041	
156	0.007	0.014
157	0.03	0.025
158	0.0054	0.0053
159	0.003	
160	0.0025	0.0048
161	0.0036	0.016
162	10	0.11
163	0.017	0.016
164	0.0036	0.0062
165	0.0085	0.017
166	0.0055	
167	0.011	0.021
168	10	10
169	0.14	0.15
170	0.0025	
171	0.019	

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
172	0.0056	
173	0.056	
174	0.033	
175	0.037	
176	0.93	
177	0.005	
178	0.005	
179	0.0034	
180	0.002	
181	0.015	0.026
182	0.113	0.016
183	0.142	0.104
184	0.0086	0.031
185	0.145	0.149
186A	0.0019	0.002
186B	0.002	0.0048
187	0.0029	0.0028
188	0.027	0.0134
189	0.02	0.022
190	0.0064	0.0076
191	0.0044	0.0049
192	0.0262	
193	0.068	
194	0.6	
195	0.013	
196	0.0024	
197	0.0042	
198	0.0046	
199	0.0045	
200	0.036	0.013
201	0.026	
202	0.141	0.52
203		
204	0.0035	0.0011
205	0.0026	
206	0.014	
207	0.01	
208	0.0018	
209	0.011	
210	0.0066	
211	0.0098	
212	0.034	0.033
213	0.203	0.052
214	0.014	0.021
215	0.0044	0.0082
216	0.01	0.015
217	0.0036	0.0098
218	0.00139	0.0036
219	0.0053	0.011
220	0.001	0.0033
221	0.0014	0.008
222	0.006	

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
223	0.013	
224	0.52	0.86
225	0.004	0.003
226	0.0032	0.0027
227	0.003	0.0031
228	0.015	0.0039
229	0.0212	0.0205
230	0.016	0.016
231	0.0033	
232	0.0072	
233	0.0046	0.012
234	0.015	0.026
235	0.125	0.257
236	0.034	0.112
237	0.049	0.131
238	0.035	0.178
239	0.0068	0.017
240	0.0044	0.0046
241	0.177	
242	0.062	
243	0.007	
244	0.011	
245	0.0074	
246	0.07	
247	0.0034	
248	0.018	
249	0.0044	
250	0.016	
251	0.0032	
252	0.002	0.005
253	0.0039	0.027
254	0.022	0.04
255	0.0056	0.06
256	0.0013	0.007
257	0.007	0.0053
258	0.0062	0.0133
258a	0.001	0.041
258b	0.005	0.024
259	0.049	0.101
260	0.045	0.06
261	0.233	0.36
262	0.032	0.038
263	0.014	
264	0.0093	0.0166
265	0.0022	0.0022
266	0.0031	0.0065
267	0.073	
268	0.011	
269	0.035	
270	0.04	0.035
271	0.016	0.016
272	0.027	0.101

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
273	0.019	
274	1	
275	0.017	
276	0.096	
277	0.018	
278	0.0046	
279	0.59	
280	0.059	
281	0.011	
282	0.0028	
283	0.011	
284	0.005	
285	0.0026	
286		
287	0.123	
288	0.014	0.04
289	0.0072	0.04
290	0.035	0.085
291	0.0039	0.0069
292	0.0049	0.0161
293	0.0046	0.016
294	0.0059	0.026
295	0.0068	0.0337
296	0.0055	0.014
297	0.0014	0.013
298	0.04	0.008
299	0.06	0.034
300	0.022	0.048
301	0.031	0.022
302	0.047	0.023
303	0.031	0.03
304	0.046	0.027
305	0.149	0.111
306	0.013	0.039
307	0.011	0.0088
308	0.011	0.008
309	0.011	0.012
310	0.005	0.013
311	0.0086	0.024
312	0.37	0.79
313	0.34	0.4
314	0.38	1.5
315	1.38	
316	0.036	0.059
317	0.012	0.021
318	0.0029	0.027
319	0.022	0.049
320	0.0036	0.011
321	0.007	0.011
322	0.015	0.05
323	0.0096	0.023
324	0.011	0.02

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
325	0.011	0.042
326	0.62	
327	0.63	
328	0.051	
329	0.5	
330	0.248	
331	0.39	
332	0.016	
333	0.3	
334	0.8	
335	1.63	
336	0.002	
337	0.022	
338	0.302	
339	0.3	
340	0.37	
341	0.021	0.016
342	0.087	0.077
343	0.044	0.028
344	0.016	0.01
345	0.021	0.015
346	0.054	0.016
347	0.027	0.027
348	0.017	0.012
349	0.144	0.34
350	0.074	0.102
351	0.08	0.176
352	0.146	0.053
353	0.09	0.103
354	0.58	0.83
355	0.177	0.275
356	0.36	0.37
357	0.294	0.314
358	0.47	0.59
359	0.071	
360	0.066	
361	0.044	0.058
362	0.162	
363	0.211	
364	0.258	
365	0.159	
366	0.33	
367	0.35	
368	0.284	
369	0.045	0.029
370	0.161	
371	0.123	
372	0.129	
373	0.045	
374	0.086	
375	0.04	
376	0.05	

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
377	0.073	
378	0.085	
379	0.011	
380	0.261	
381	2	
382	0.152	
383	0.062	
384	0.143	
385	0.216	
386	0.053	
387	0.227	
388	0.218	
389	0.166	
390	0.032	
391	0.184	
392	0.219	
393	0.3	
394	1.19	
395	0.3	
396	0.238	
397	0.34	
398	0.33	
399	0.057	
400	0.301	
401	0.17	
402	0.175	
403	0.35	
404	0.82	
405	0.75	
406	0.36	
407	0.035	
408	0.044	
409	0.281	
410	0.24	
411	0.43	
412	0.014	
413	0.033	
414	0.0026	
415	0.259	
416	0.271	
417	0.151	
418	0.112	
419	0.162	
420	0.08	
421	0.077	
422	0.069	
423	0.075	
424	0.072	
425	0.073	
426	0.115	
427	0.024	
428	0.059	

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
429	0.092	
430	0.021	
431	0.012	
432	0.017	
433	0.02	0.08
434	0.013	0.019
435	0.042	0.092
436	0.013	0.0051
437	0.023	0.03
438	0.0042	0.012
439	0.0037	0.0057
440	0.0058	0.014
441	0.0017	0.0038
442	0.0015	0.013
443	0.0048	0.016
444	0.0019	0.011
445	0.0022	0.0063
446	0.0013	0.0048
447	0.0028	0.026
448	0.01	0.022
449	0.012	0.036
450	0.01	0.016
451	0.013	0.018
452	0.007	0.03
453	0.0046	0.013
454	0.0052	0.011
455	0.007	0.009
456	0.11	0.38
457	0.019	0.037
458	0.0048	0.0051
459	0.012	0.014
460	0.0045	0.012
461	0.189	0.119
462	0.34	0.35
463	0.015	0.018
464	0.002	0.0031
465	0.0041	0.012
466	0.0047	0.014
467	0.0072	0.021
468	0.0042	0.019
469	0.0057	0.02
470	0.011	0.038
471	0.0041	0.018
472	0.024	0.034
473	0.0097	0.028
474	0.005	0.012
475	0.0026	0.008
476	0.0017	0.026
477	0.002	0.0051
478	0.002	0.0057
479	0.008	0.017
480	0.0049	0.01

Example Number	Cdk 4 IC_{50} (μM)	Cdk 6 IC_{50} (μM)
481	0.008	0.012

FORMULATIONS

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of Formula I-II in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, preferably between about 0.01 and about 50 mg/kg, and more preferably about 0.01 and about 30 mg/kg body weight may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids,

cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include DMSO and related analogs.

The compounds of this invention can also be administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span

80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. Tween 80).

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 diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary

temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes, which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

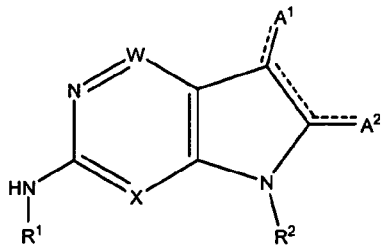
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

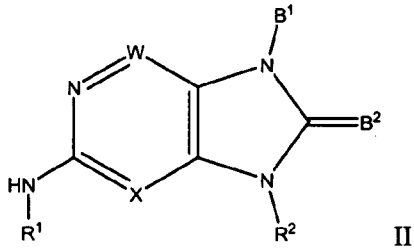
All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.

WE CLAIM:

1. A compound of Formula I or II



I



II

enantiomers, diastereomers, salts and solvates thereof wherein

W and X are independently CH or N;

A^1 and A^2 together with ring carbon atoms to which they are attached combine to form benzene, cyclopentadiene, pyridine, pyridone, pyrimidine, pyrazine, pyridazine, 2H-pyran, pyrrole, imidazole, pyrazole, triazole, furan, oxazole, isoxazole, oxadiazole, thiophene, thiazole, isothiazole or thiadiazole any of which may be optionally partially saturated, and any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

B^1 and B^2 together with the ring atoms to which they are attached combine to form dihydropyridine, dihydropyridone, dihydropyrimidine, dihydropyrimidone, dihydropyrazine, dihyrdopyridazine, pyrrole, imidazole, pyrazole, triazole, or tetrazole any of which may be optionally partially saturated, and any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^1 is $-Y-(alkylene)_m-R^a$;

Y is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl or heteroaryl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^a is heterocyclo, heteroaryl, $-NR^3R^4$, $-C(=O)NR^3R^4$; $-O-R^5$, $-S(O)_n-R^5$, or $-S(O)_n-NR^3R^4$ any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring;

R^2 is alkyl, cycloalkyl, heterocyclo, aryl, $-S(O)_nR^5$, $-C(=O)R^5$, $-C(=S)R^5$, $-C(=O)OR^5$, $-C(=S)OR^5$, $-C(=O)NR^3R^4$, $-C(=S)NR^3R^4$, $-SO_2NR^3R^4$, any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^3 and R^4 at each occurance are independently

(i) hydrogen or

(ii) alkyl, cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring;

or R^3 and R^4 together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring;

R^3* and R^4* at each occurance are independently

(i) hydrogen or

(ii) alkyl, alkenyl, alkynyl cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

or R^3* and R^4* together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more R^x groups as allowed by valance;

R^5 and R^5* at each occurance is

(i) hydrogen or

(ii) alkyl, alkenyl, alkynyl cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^x at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^5$, $-(alkylene)_m-S(O)_nR^5$, $-(alkylene)_m-NR^3R^4$, $-(alkylene)_m-C(=O)R^5$, $-(alkylene)_m-C(=S)R^5$, $-(alkylene)_m-C(=O)OR^5$, $-(alkylene)_m-OC(=O)R^5$, $-(alkylene)_m-C(=S)OR^5$, $-(alkylene)_m-C(=O)NR^3R^4$, $-(alkylene)_m-C(=S)NR^3R^4$, $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$, $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$, $-(alkylene)_m-N(R^3)C(=O)R^5$, $-(alkylene)_m-N(R^3)C(=S)R^5$, $-(alkylene)_m-OC(=O)NR^3R^4$, $-(alkylene)_m-OC(=S)NR^3R^4$, $-(alkylene)_m-SO_2NR^3R^4$, $-(alkylene)_m-N(R^3)SO_2R^5$, $-(alkylene)_m-N(R^3)SO_2NR^3R^4$, $-(alkylene)_m-N(R^3)C(=O)OR^5$, $-(alkylene)_m-N(R^3)C(=S)OR^5$, or $-(alkylene)_m-N(R^3)SO_2R^5$;

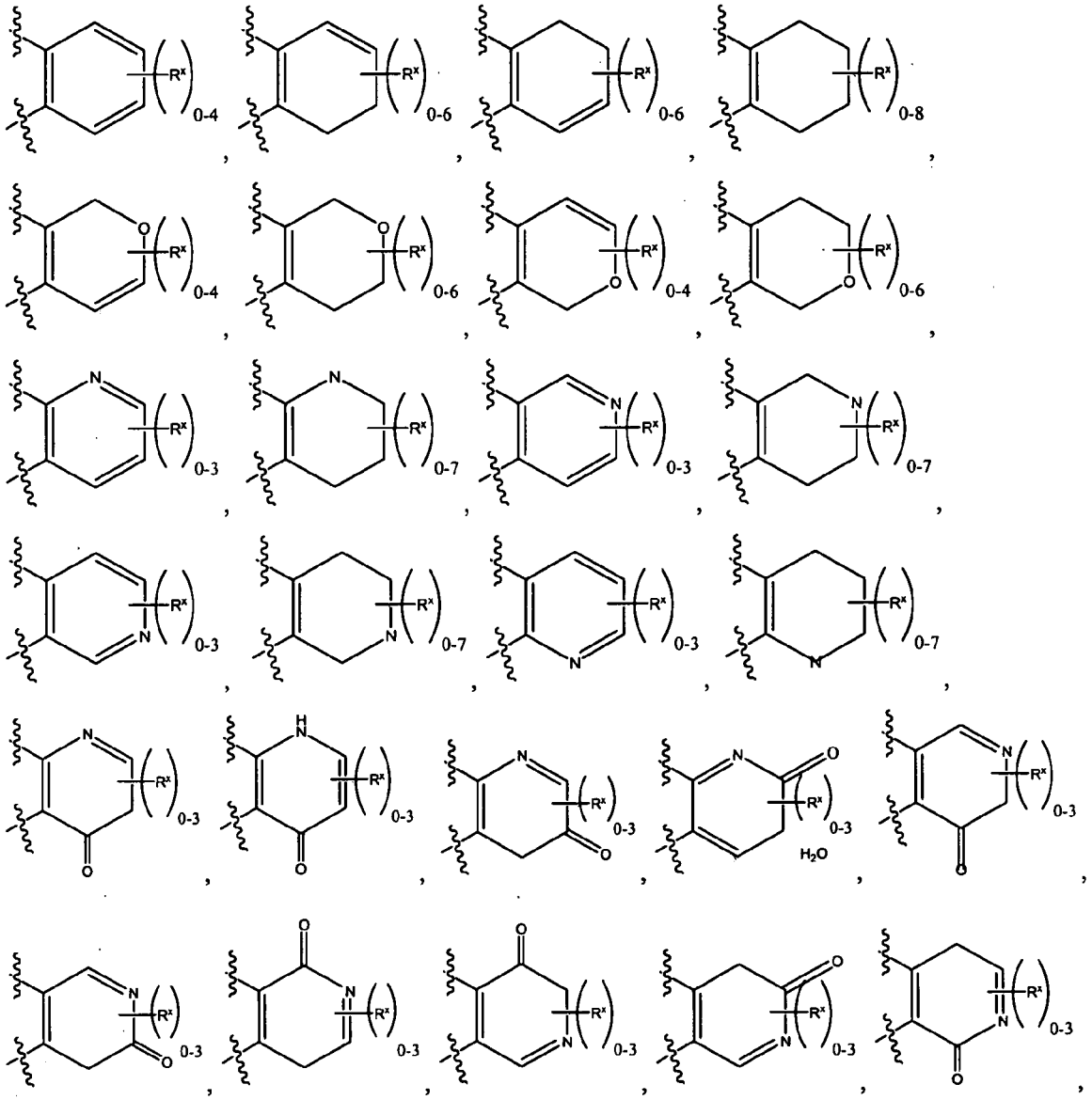
wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(alkylene)_m-CN$, $-(alkylene)_m-OR^5*$, $-(alkylene)_m-S(O)_nR^5*$, $-(alkylene)_m-NR^3*R^4*$, $-(alkylene)_m-C(=O)R^5*$, $-(alkylene)_m-C(=S)R^5*$, $-(alkylene)_m-C(=O)O\ R^5*$, $-(alkylene)_m-OC(=O)R^5*$,

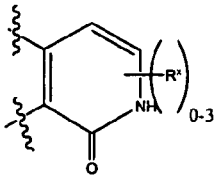
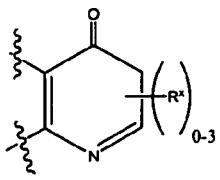
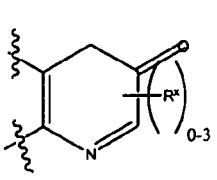
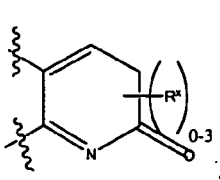
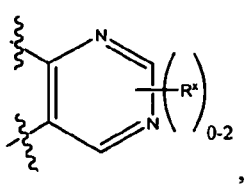
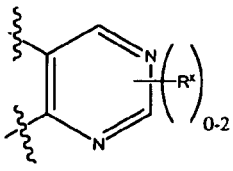
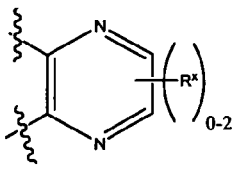
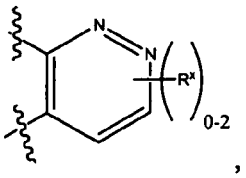
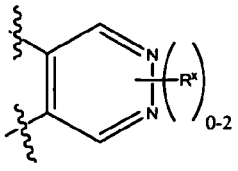
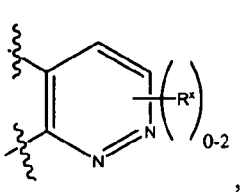
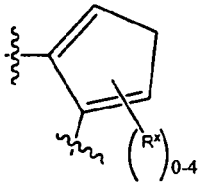
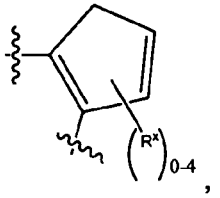
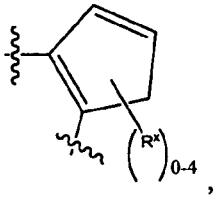
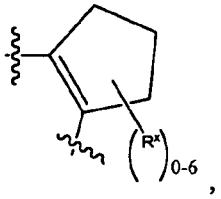
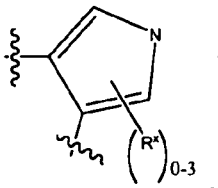
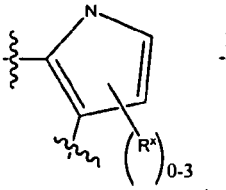
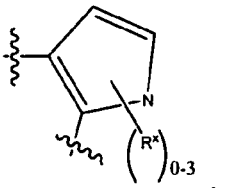
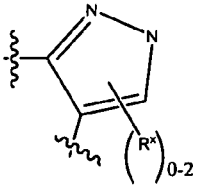
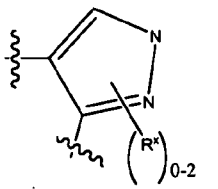
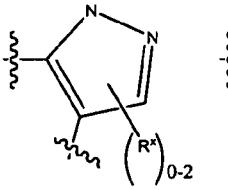
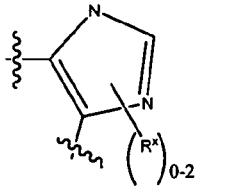
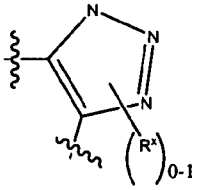
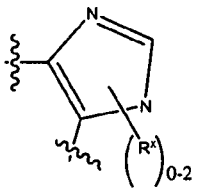
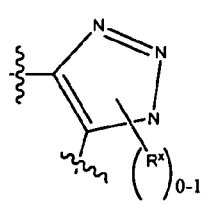
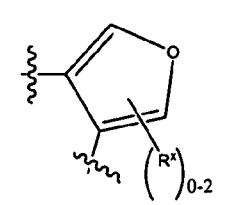
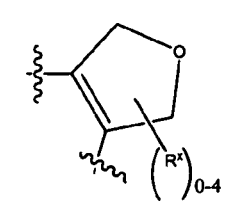
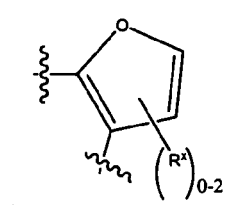
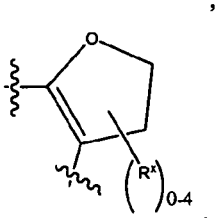
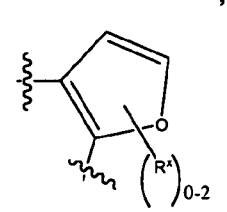
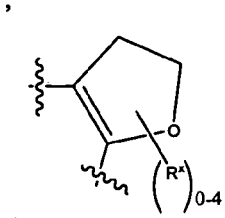
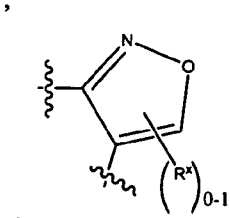
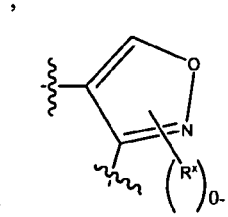
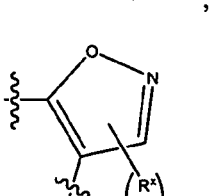
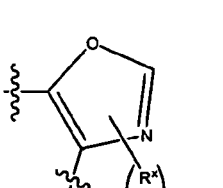
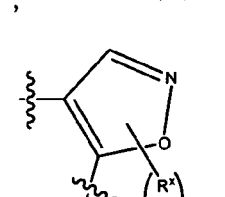
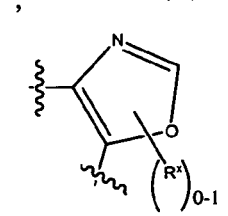
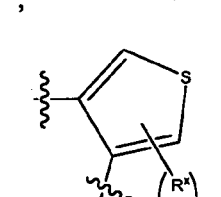
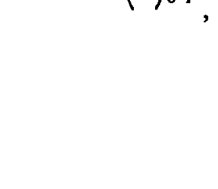
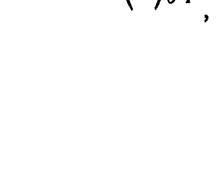
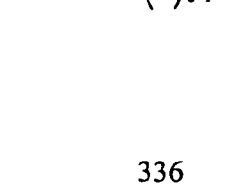
-(alkylene)$_m$-C(=S)OR^5*, —(alkylene)$_m$-C(=O)NR^3*R^4*, -(alkylene)$_m$-C(=S)NR^3*R^4*,
-(alkylene)$_m$-N(R^3*)C(=O)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=S)NR^3*R^4*,
-(alkylene)$_m$-N(R^3*)C(=O)R^5*, -(alkylene)$_m$-N(R^3*)C(=S)R^5*, -(alkylene)$_m$-OC(=O)NR^3*R^4*,
-(alkylene)$_m$-OC(=S)NR^3*R^4*, -(alkylene)$_m$-SO$_2$NR^3*R^4*, -(alkylene)$_m$-N(R^3*)SO$_2$R^5*,
-(alkylene)$_m$-N(R^3*)SO$_2$NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)OR^5*,
-(alkylene)$_m$-N(R^3*)C(=S)OR^5*, or -(alkylene)$_m$-N(R^3*)SO$_2$R^5*;

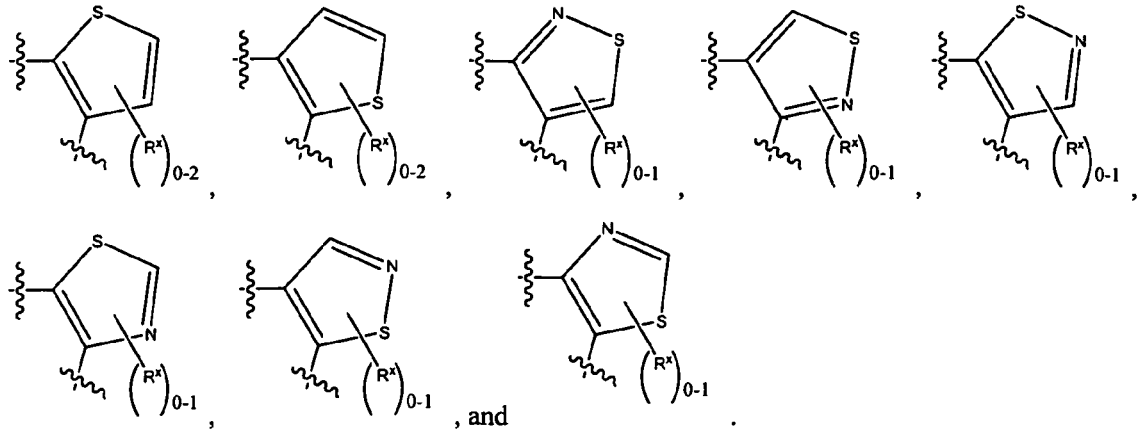
n is independently 0, 1 or 2; and

m is independently 0 or 1.

2. A compound of claim 1 wherein A^1 and A^2 together with the ring atoms to which they are attached combine to form

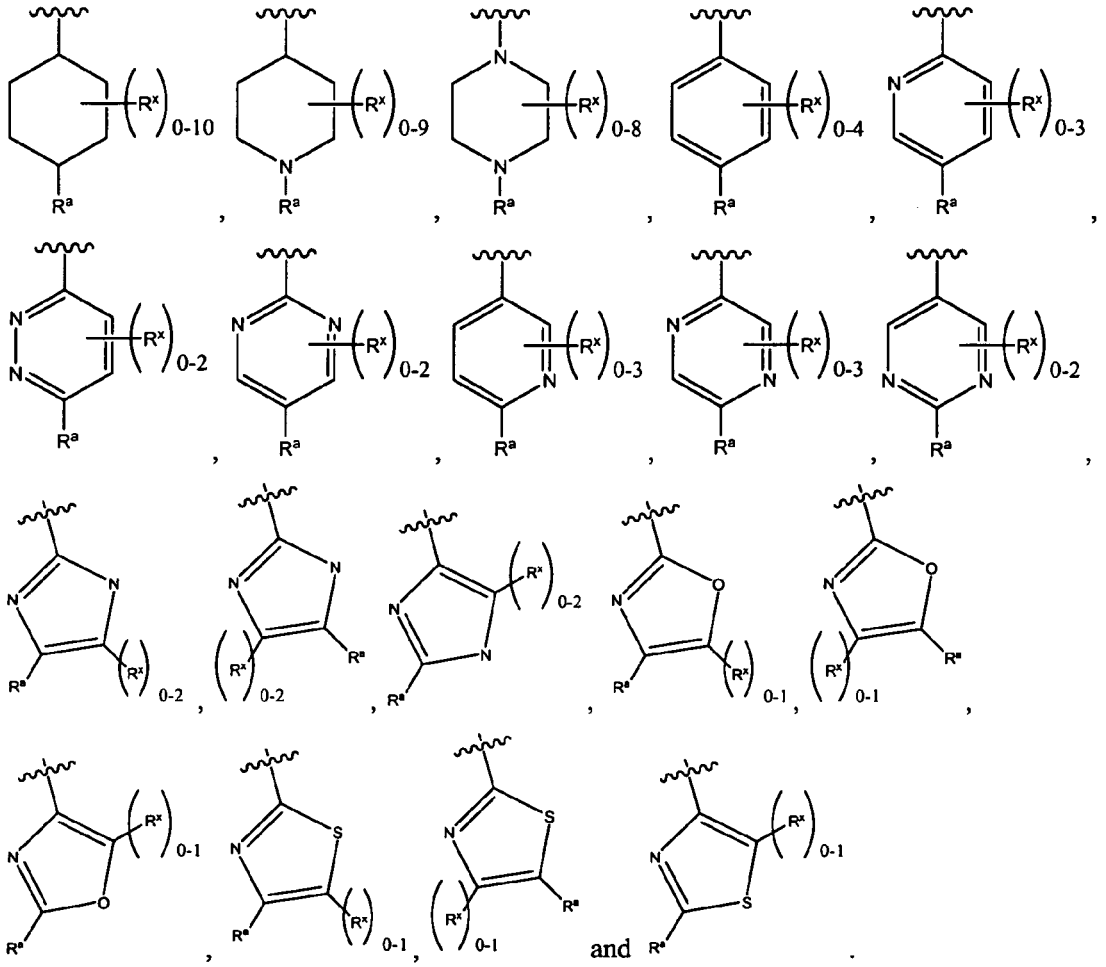




3. A compound of claim 1 wherein Y is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, phenyl, pyridinyl, pyrimidinyl, cyclopentadienyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl, any of which may be optionally substituted with one or more R^x as allowed by valance.

4. A compound of claim 3 wherein R^1 is selected from

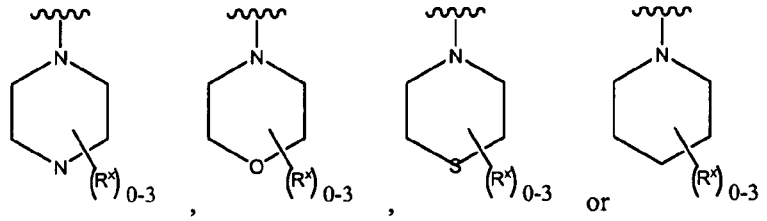


5. A compound of claim 4 where R^a is selected from

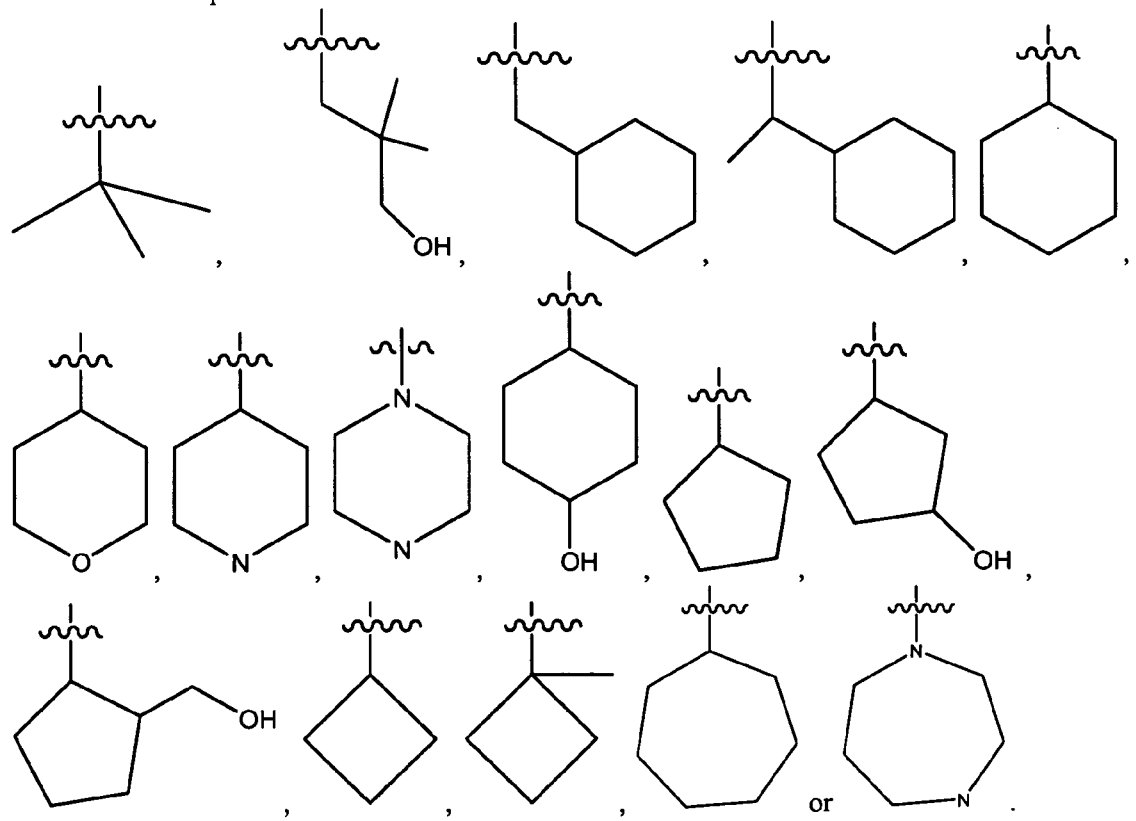
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

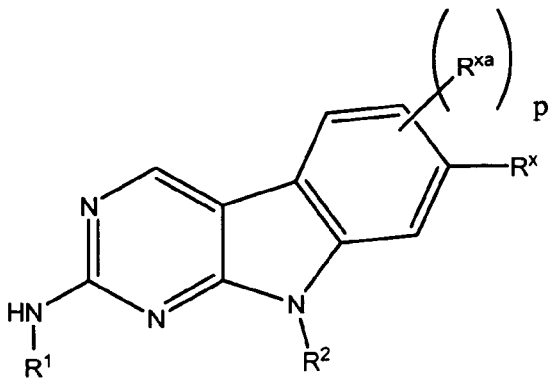
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



6. A compound of claim 5 wherein R^2 is



7. A compound of claim 1 having the following formula IA



IA

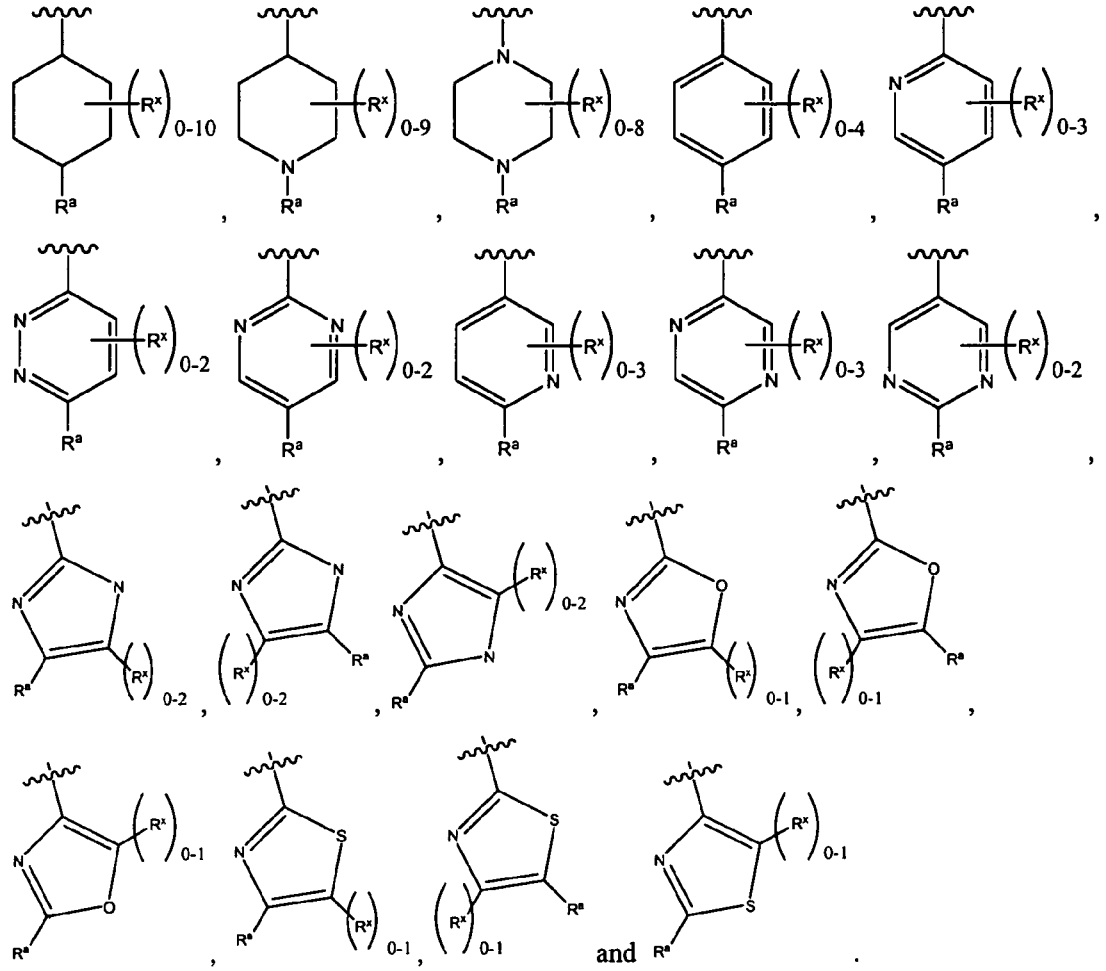
wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, -(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-$S(O)_nR^5$*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-$C(=O)R^5$*, -(alkylene)$_m$-$C(=S)R^5$*, -(alkylene)$_m$-$C(=O)OR^5$*, -(alkylene)$_m$-$OC(=O)R^5$*, -(alkylene)$_m$-$C(=S)OR^5$*, -(alkylene)$_m$-$C(=O)NR^3$*R^4*, -(alkylene)$_m$-$C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=S)NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)R^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)R^5$*, -(alkylene)$_m$-$OC(=O)NR^3$*R^4*, -(alkylene)$_m$-$OC(=S)NR^3$*R^4*, -(alkylene)$_m$-SO_2NR^3*R^4*, -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*, -(alkylene)$_m$-$N(R^3$*$)SO_2NR^3$*R^4*, -(alkylene)$_m$-$N(R^3$*$)C(=O)OR^5$*, -(alkylene)$_m$-$N(R^3$*$)C(=S)OR^5$*, or -(alkylene)$_m$-$N(R^3$*$)SO_2R^5$*;

m is 0 or 1 ; and
p is zero to three.

8. A compound of claim 7 whereinY is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, phenyl, pyridinyl, pyrimidinyl, cyclopentadienyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl, any of which may be optionally substituted with one or more R^x as allowed by valance.

9. A compound of claim 8 wherein R^1 is selected from

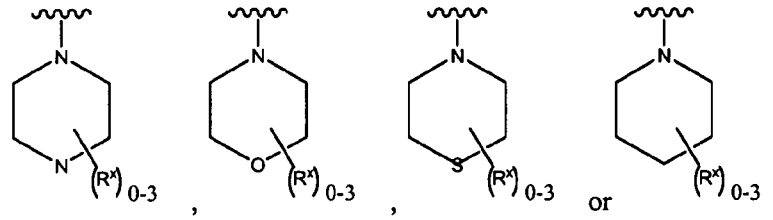


10. A compound of claim 9 where R^a is selected from

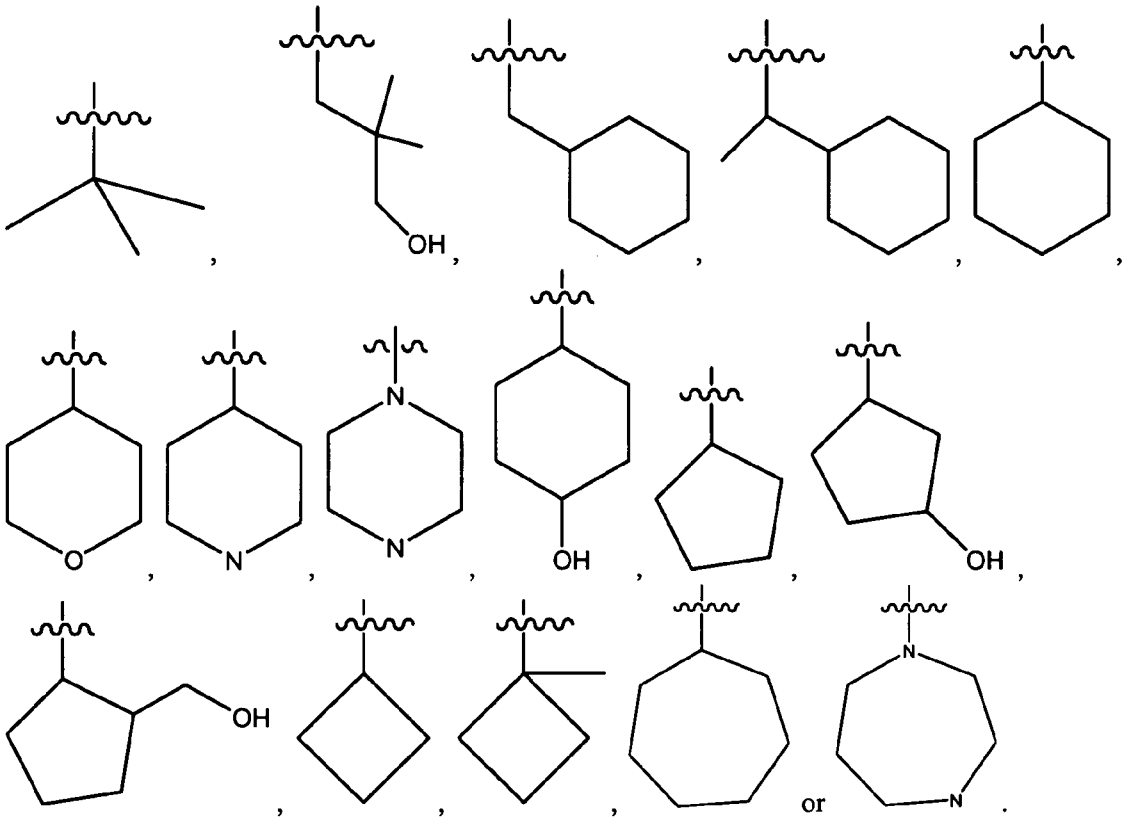
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^5*$, or $-NR^3*R^4*$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^5*$, or $-NR^3*R^4*$;

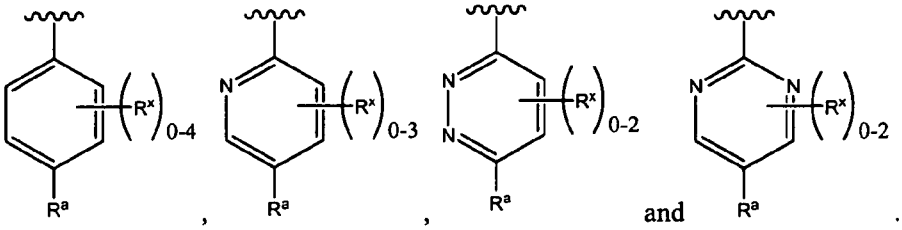
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



11. A compound of claim 10 wherein R^2 is



12. A compound of claim 9 wherein R^1 is selected from

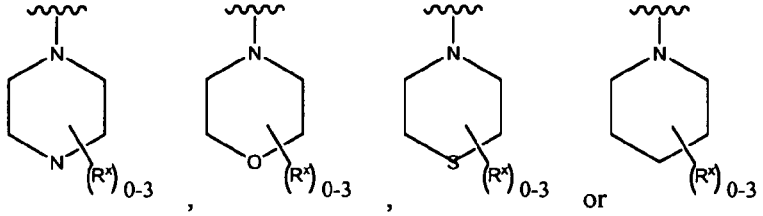


13. A compound of claim 12 where R^a is selected from

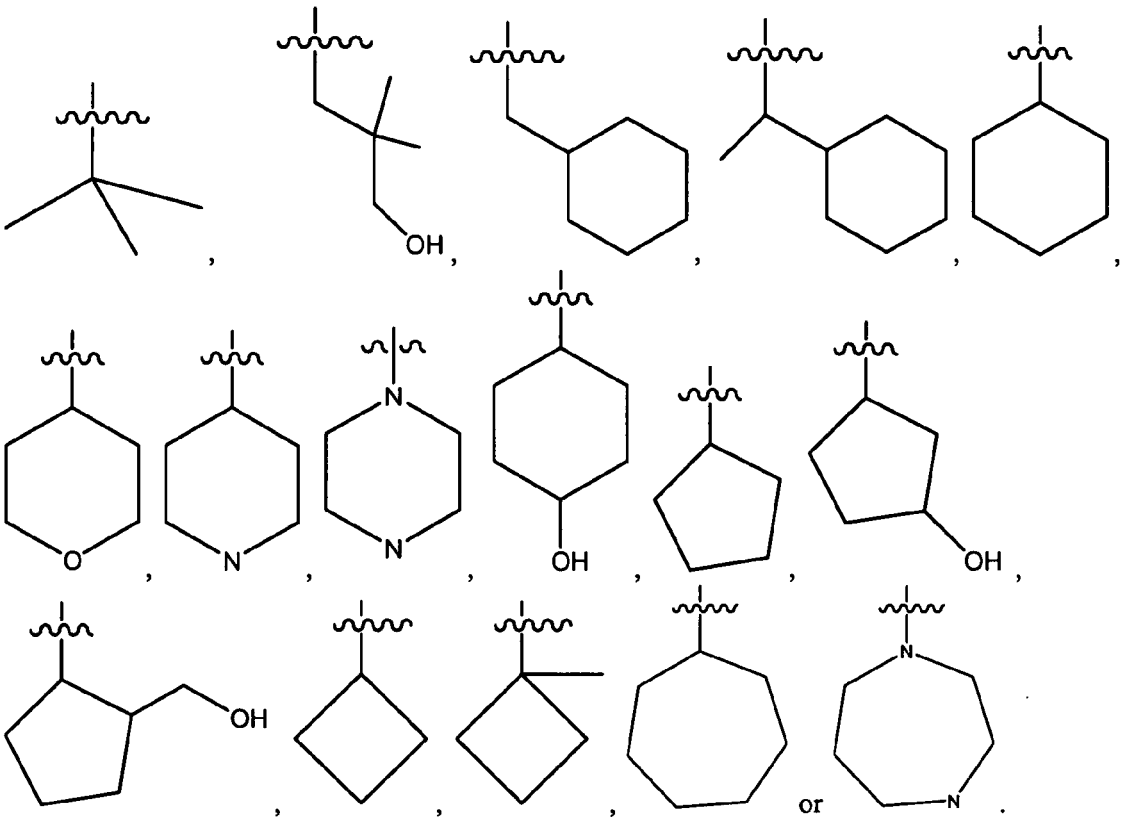
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

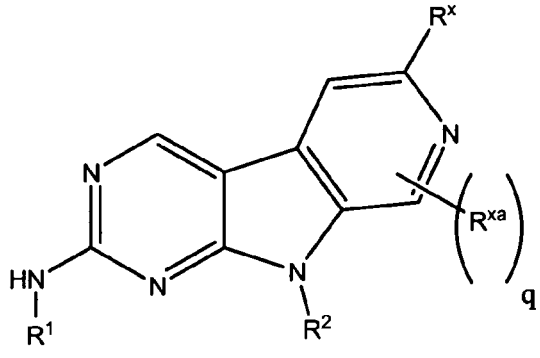
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



14. A compound of claim 13 wherein R^2 is



15. A compound of claim 1 having the following formula IB



IB

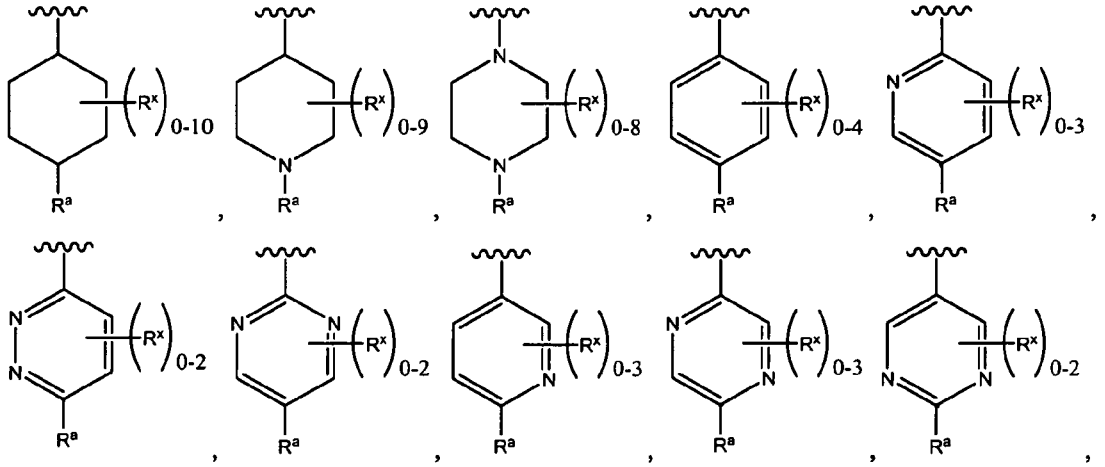
wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-S(O)$_n$$R^5$, -(alkylene)$_m$-$NR^3R^4$, -(alkylene)$_m$-C(=O)$R^5$, -(alkylene)$_m$-C(=S)$R^5$, -(alkylene)$_m$-C(=O)$OR^5$, -(alkylene)$_m$-OC(=O)$R^5$, -(alkylene)$_m$-C(=S)$OR^5$, —(alkylene)$_m$-C(=O)$NR^3R^4$, -(alkylene)$_m$-C(=S)$NR^3R^4$, -(alkylene)$_m$-N($R^3$)C(=O)$NR^3R^4$, -(alkylene)$_m$-N($R^3$)C(=S)$NR^3R^4$, -(alkylene)$_m$-N($R^3$)C(=O)$R^5$, -(alkylene)$_m$-N($R^3$)C(=S)$R^5$, -(alkylene)$_m$-OC(=O)$NR^3R^4$, -(alkylene)$_m$-OC(=S)$NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-N($R^3$)$SO_2R^5$, -(alkylene)$_m$-N($R^3$)$SO_2NR^3R^4$, -(alkylene)$_m$-N($R^3$)C(=O)$OR^5$, -(alkylene)$_m$-N($R^3$)C(=S)$OR^5$, or -(alkylene)$_m$-N($R^3$)$SO_2R^5$;

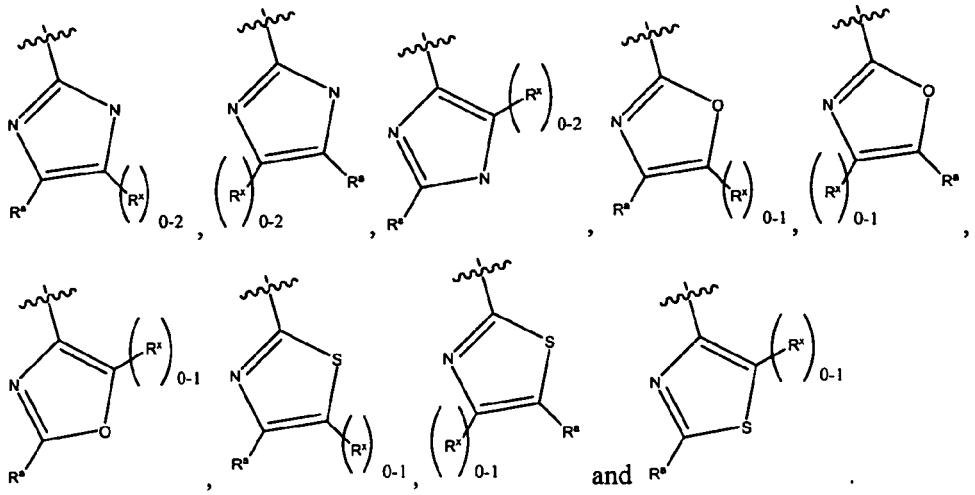
wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-S(O)$_n$R^5*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-C(=O)R^5*, -(alkylene)$_m$-C(=S)R^5*, -(alkylene)$_m$-C(=O)OR^5*, -(alkylene)$_m$-OC(=O)R^5*, -(alkylene)$_m$-C(=S)OR^5*, —(alkylene)$_m$-C(=O)NR^3*R^4*, -(alkylene)$_m$-C(=S)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=S)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)R^5*, -(alkylene)$_m$-N(R^3*)C(=S)R^5*, -(alkylene)$_m$-OC(=O)NR^3*R^4*, -(alkylene)$_m$-OC(=S)NR^3*R^4*, -(alkylene)$_m$-SO$_2$NR^3*R^4*, -(alkylene)$_m$-N(R^3*)SO$_2$R^5*, -(alkylene)$_m$-N(R^3*)SO$_2$NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)OR^5*, -(alkylene)$_m$-N(R^3*)C(=S)OR^5*, or -(alkylene)$_m$-N(R^3*)SO$_2$R^5*;

m is 0 or 1 ; and
q is zero to two.

16. A compound of claim 15 whereinY is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, phenyl, pyridinyl, pyrimidinyl, cyclopentadienyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl, any of which may be optionally substituted with one or more R^x as allowed by valance.

17. A compound of claim 16 wherein R^1 is selected from



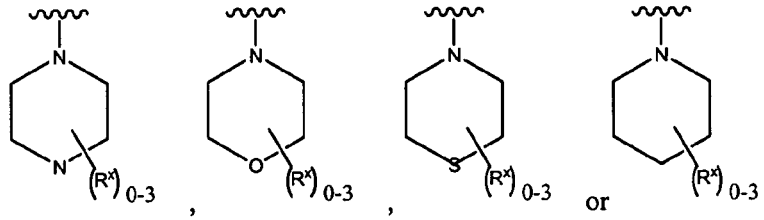


18. A compound of claim 17 where R^a is selected from

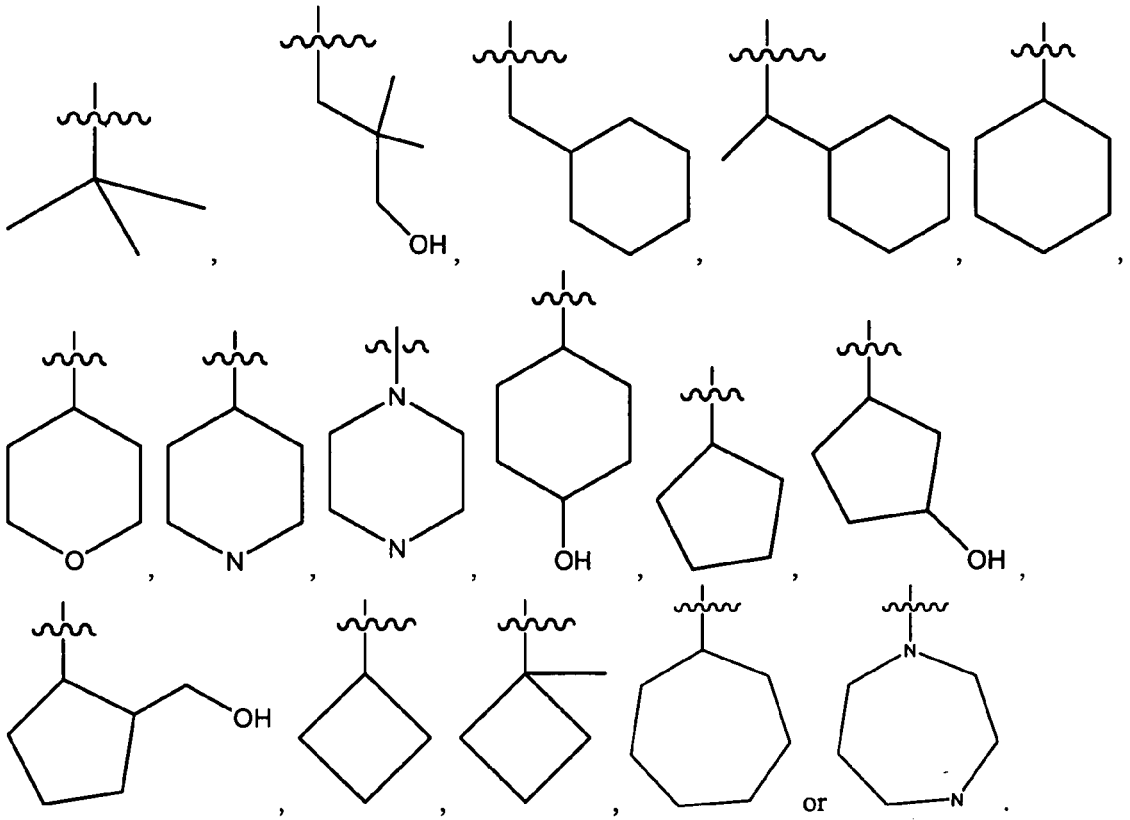
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^5*$, or $-NR^3*R^4*$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^5*$, or $-NR^3*R^4*$;

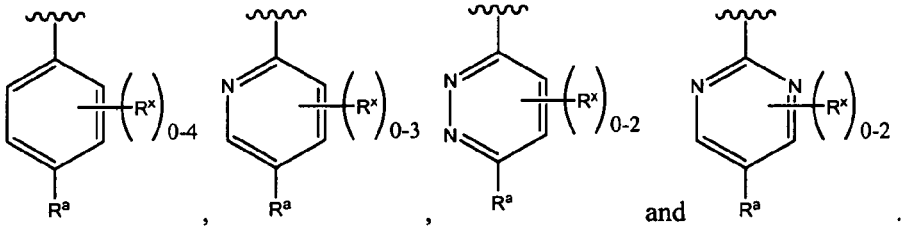
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



19. A compound of claim 18 wherein R^2 is



20. A compound of claim 17 wherein R^1 is selected from

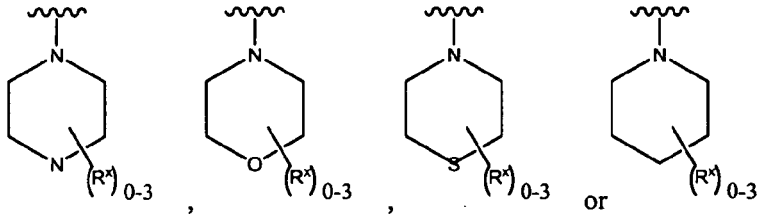


21. A compound of claim 20 where R^a is selected from

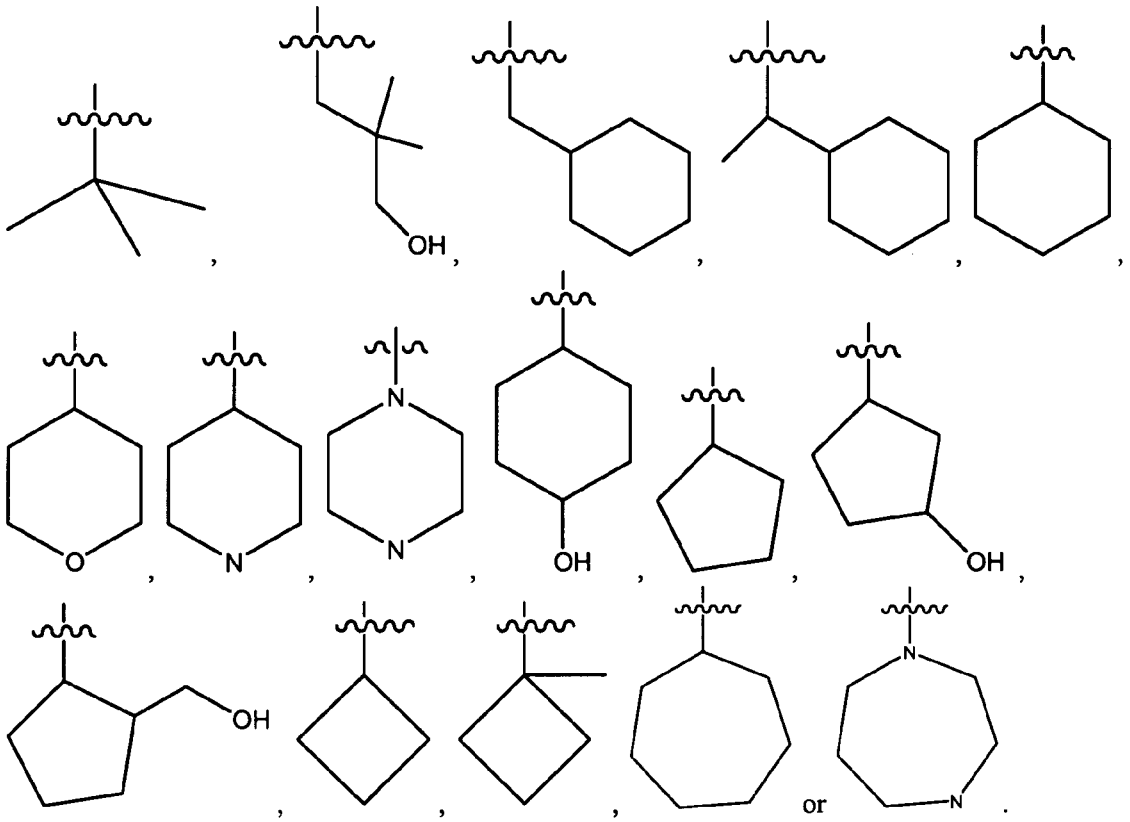
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

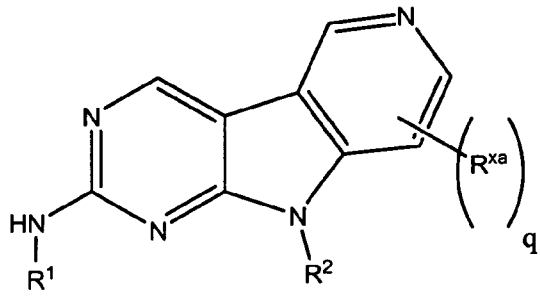
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



22. A compound of claim 21 wherein R^2 is



23. A compound of claim 1 having the following formula IC



IC

wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, -(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

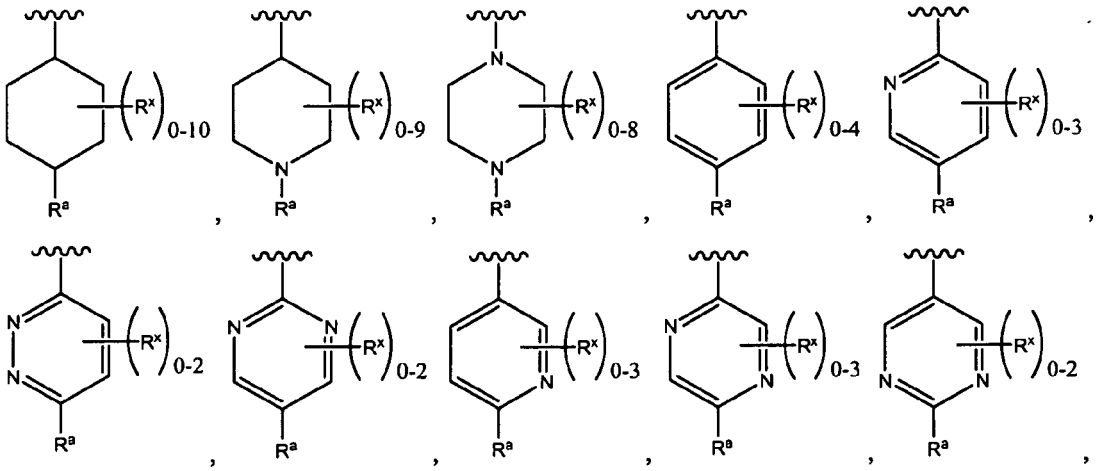
wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-S(O)$_n$R^5*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-C(=O)R^5*, -(alkylene)$_m$-C(=S)R^5*, -(alkylene)$_m$-C(=O)OR^5*, -(alkylene)$_m$-OC(=O)R^5*, -(alkylene)$_m$-C(=S)OR^5*, -(alkylene)$_m$-C(=O)NR^3*R^4*, -(alkylene)$_m$-C(=S)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=S)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)R^5*, -(alkylene)$_m$-N(R^3*)C(=S)R^5*, -(alkylene)$_m$-OC(=O)NR^3*R^4*, -(alkylene)$_m$-OC(=S)NR^3*R^4*, -(alkylene)$_m$-SO$_2$NR^3*R^4*, -(alkylene)$_m$-N(R^3*)SO$_2$R^5*, -(alkylene)$_m$-N(R^3*)SO$_2$NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)OR^5*, -(alkylene)$_m$-N(R^3*)C(=S)OR^5*, or -(alkylene)$_m$-N(R^3*)SO$_2$R^5*;

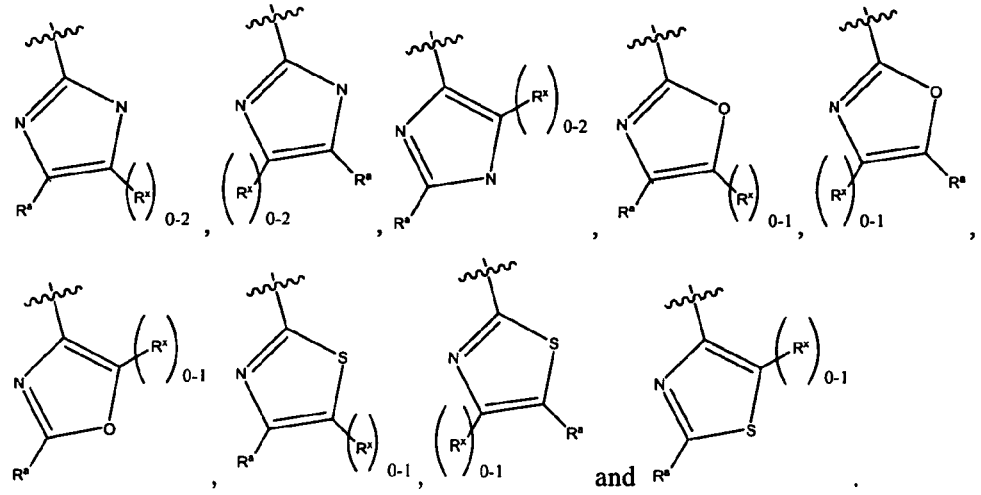
m is 0 or 1 ; and

q is zero to two.

24. A compound of claim 23 whereinY is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, phenyl, pyridinyl, pyrimidinyl, cyclopentadienyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl, any of which may be optionally substituted with one or more R^x as allowed by valance.

25. A compound of claim 24 wherein R^1 is selected from



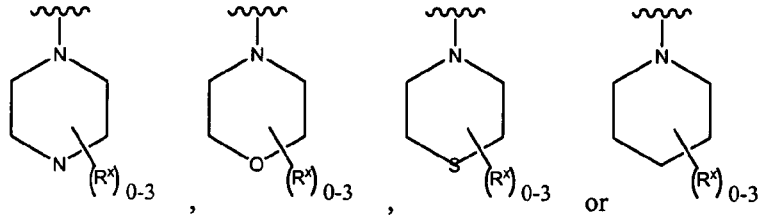


26. A compound of claim 25 where R^a is selected from

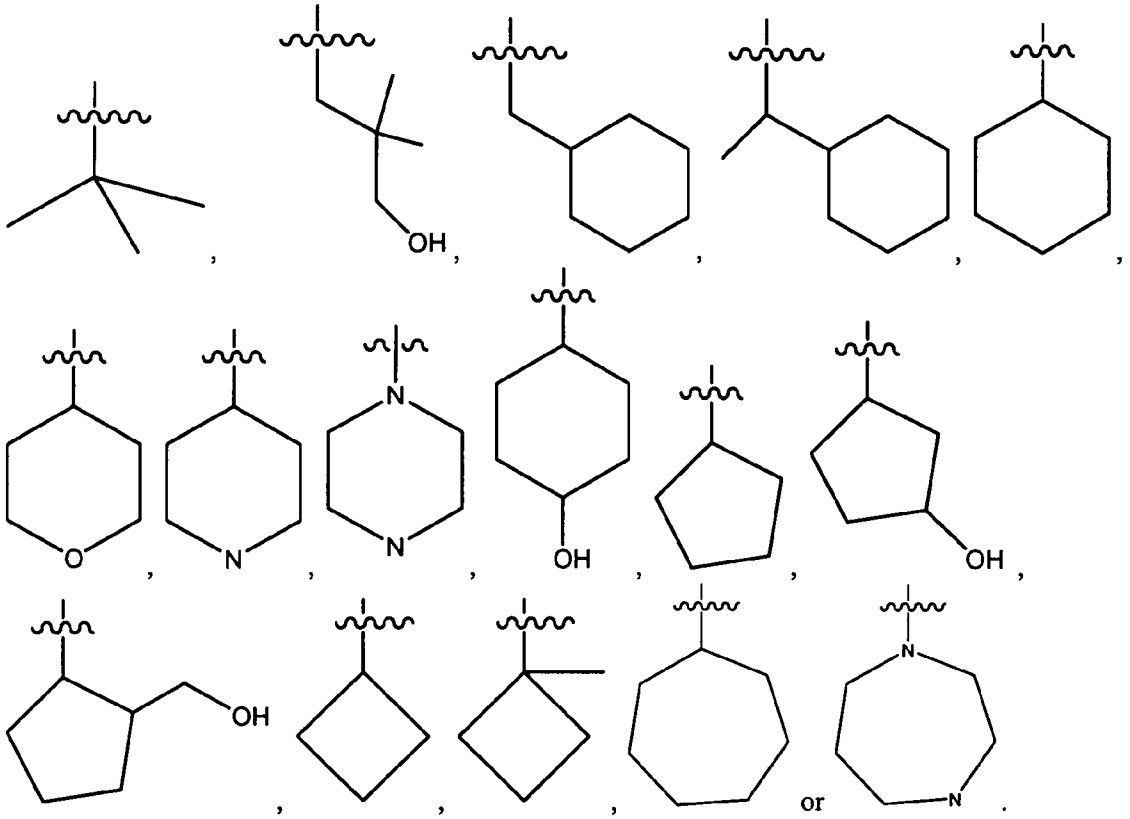
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^5*$, or $-NR^3*R^4*$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^5*$, or $-NR^3*R^4*$;

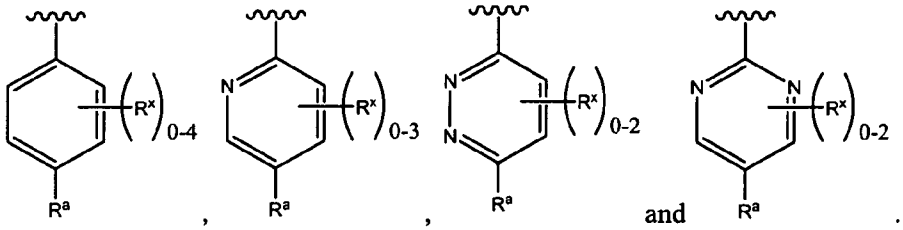
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



27. A compound of claim 26 wherein R^2 is



28. A compound of claim 25 wherein R^1 is selected from

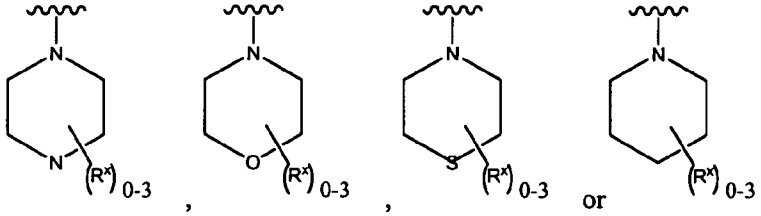


29. A compound of claim 28 where R^a is selected from

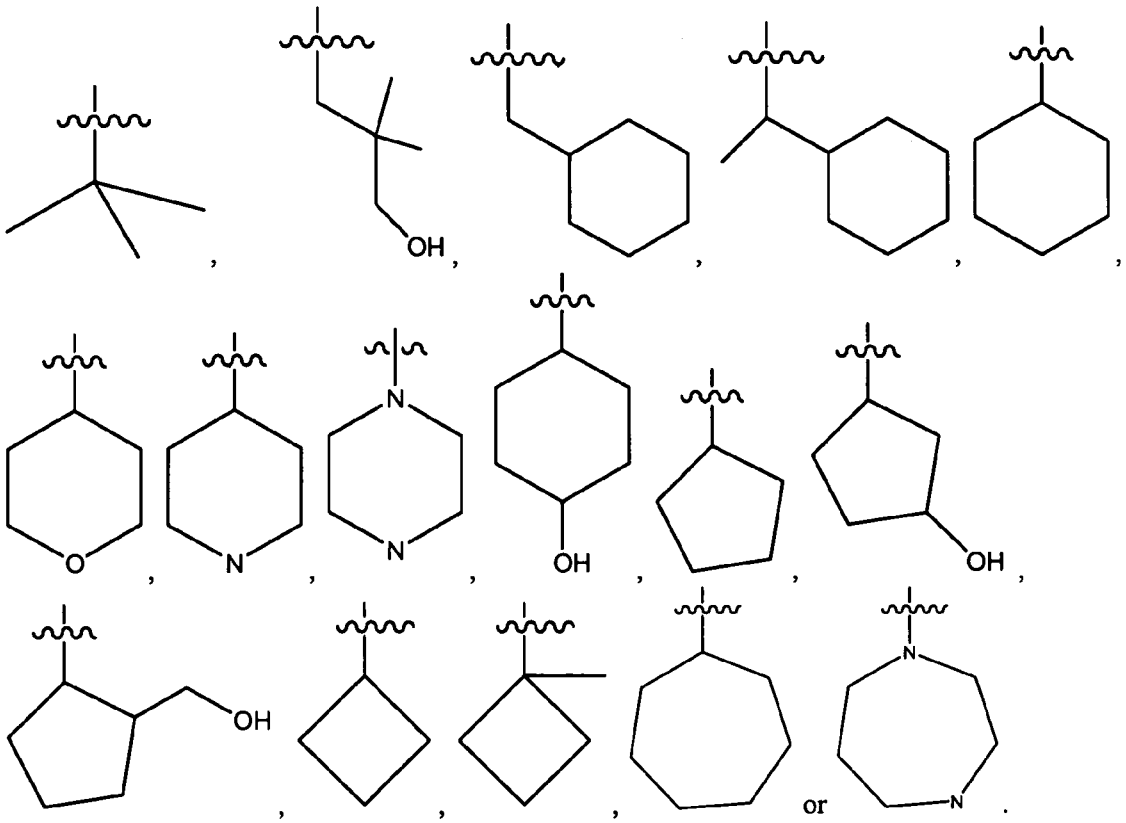
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

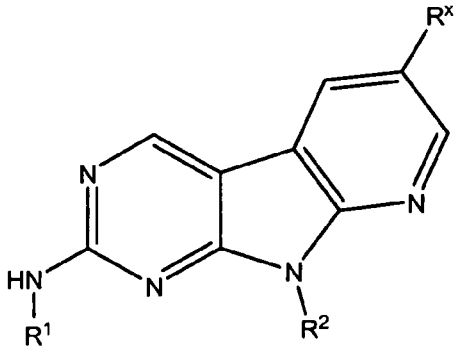
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



30. A compound of claim 29 wherein R^2 is



31. A compound of claim 1 having the following formula ID



ID

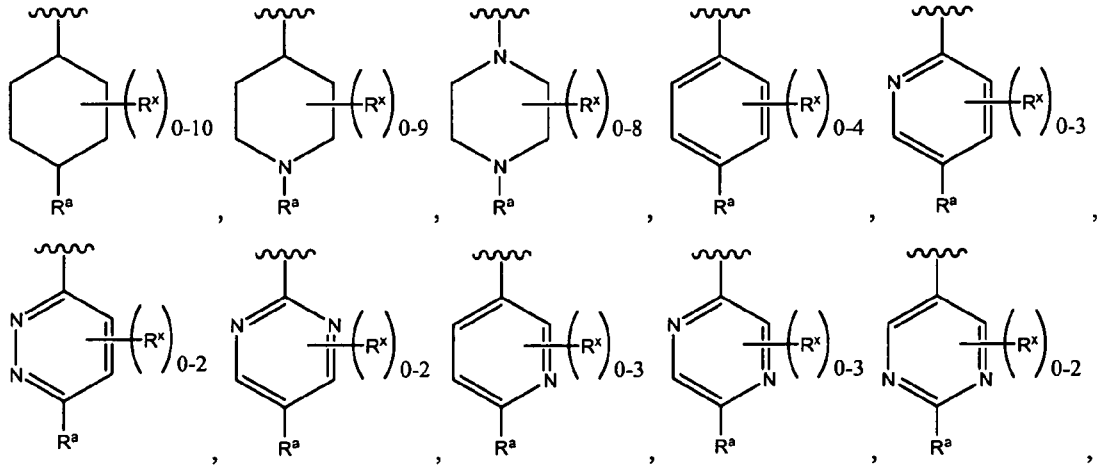
wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, —(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$, -(alkylene)$_m$-$N(R^3)SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)OR^5$, -(alkylene)$_m$-$N(R^3)C(=S)OR^5$, or -(alkylene)$_m$-$N(R^3)SO_2R^5$;

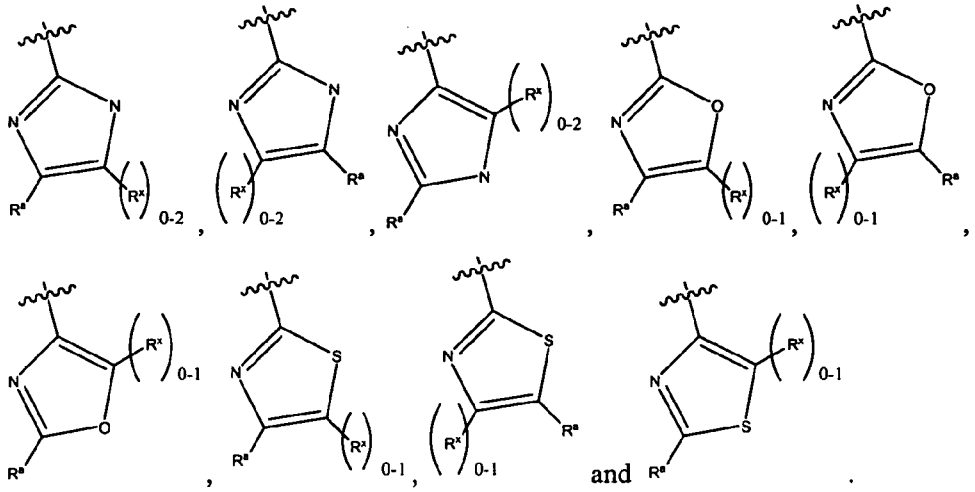
wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-S(O)$_n$R^5*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-C(=O)R^5*, -(alkylene)$_m$-C(=S)R^5*, -(alkylene)$_m$-C(=O)OR^5*, -(alkylene)$_m$-OC(=O)R^5*, -(alkylene)$_m$-C(=S)OR^5*, -(alkylene)$_m$-C(=O)NR^3*R^4*, -(alkylene)$_m$-C(=S)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=S)NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)R^5*, -(alkylene)$_m$-N(R^3*)C(=S)R^5*, -(alkylene)$_m$-OC(=O)NR^3*R^4*, -(alkylene)$_m$-OC(=S)NR^3*R^4*, -(alkylene)$_m$-SO$_2$NR^3*R^4*, -(alkylene)$_m$-N(R^3*)SO$_2$R^5*, -(alkylene)$_m$-N(R^3*)SO$_2$NR^3*R^4*, -(alkylene)$_m$-N(R^3*)C(=O)OR^5*, -(alkylene)$_m$-N(R^3*)C(=S)OR^5*, or -(alkylene)$_m$-N(R^3*)SO$_2$R^5*;

m is independently 0 or 1 ; and
q is zero to two.

32. A compound of claim 31 wherein Y is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, phenyl, pyridinyl, pyrimidinyl, cyclopentadienyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl, any of which may be optionally substituted with one or more R^x as allowed by valance.

33. A compound of claim 32 wherein R^1 is selected from



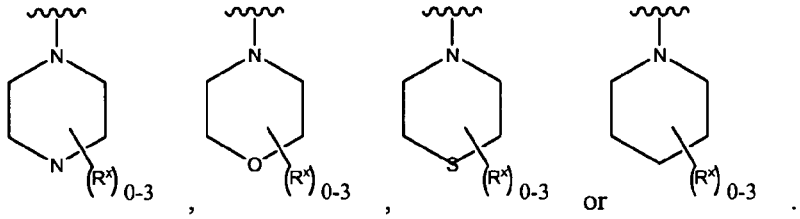


34. A compound of claim 33 where R^a is selected from

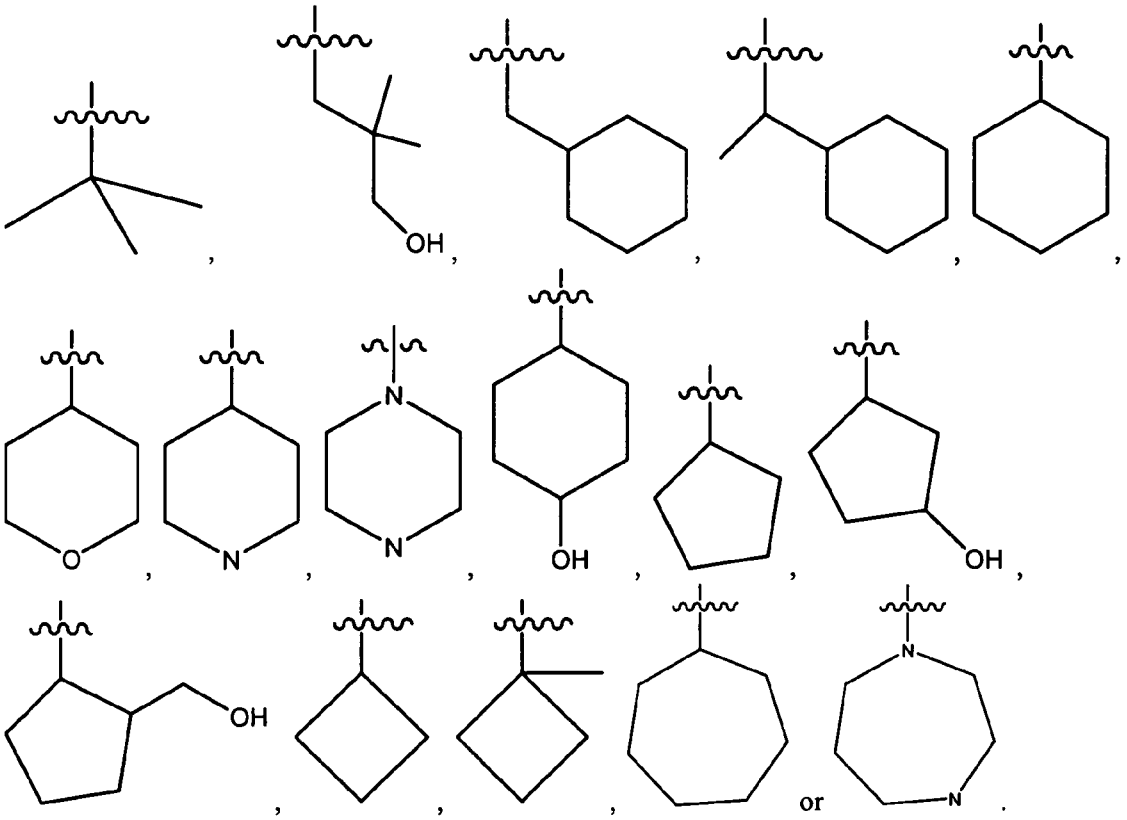
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^5*$, or $-NR^3*R^4*$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^5*$, or $-NR^3*R^4*$;

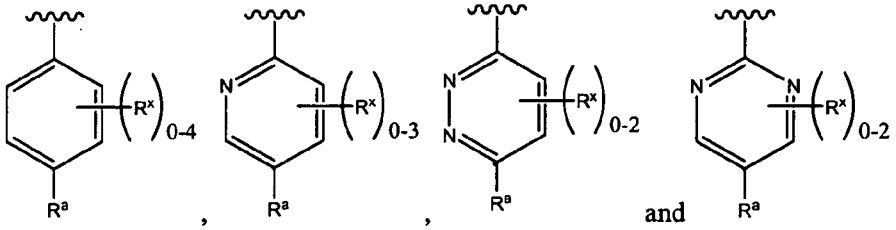
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



35. A compound of claim 34 wherein R^2 is



36. A compound of claim 33 wherein R^1 is selected from

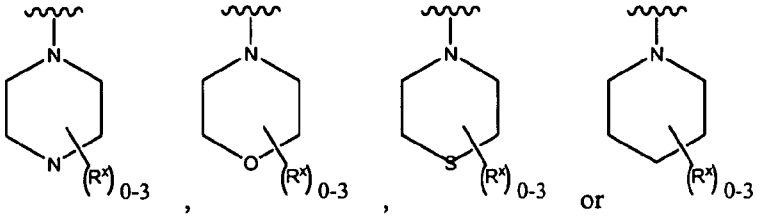


37. A compound of claim 36 where R^a is selected from

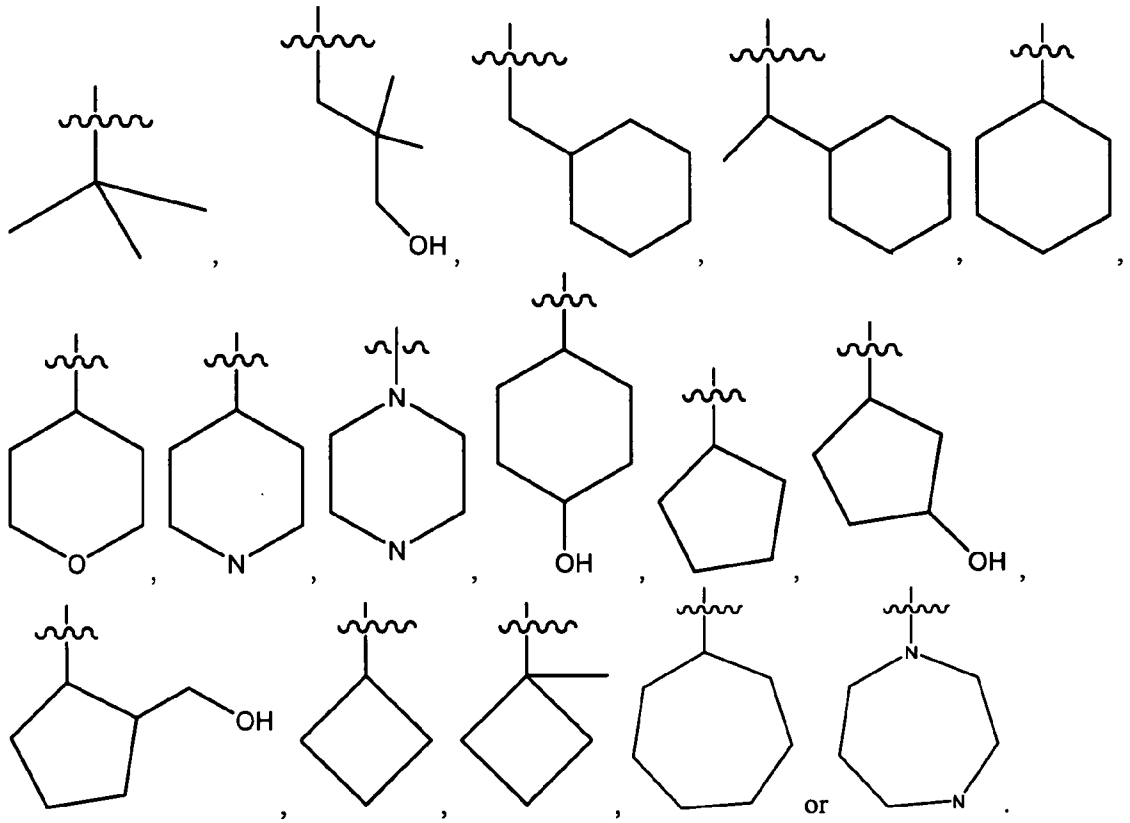
(a) $-OR^5$ or $-S(O)_nR^5$ where R^5 is alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

(b) $-C(=O)NR^3R^4$ or $-NR^3R^4$ where R^3 and R^4 are independently alkyl optionally independently substituted with one or more $-OR^{5*}$, or $-NR^{3*}R^{4*}$;

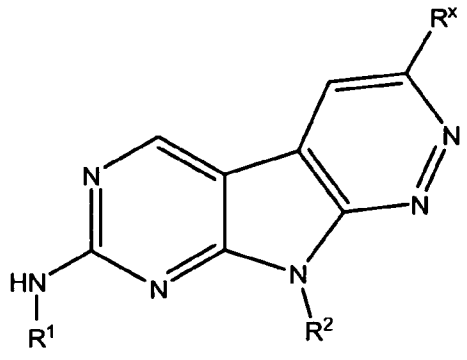
or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form



38. A compound of claim 37 wherein R^2 is



39. A compound of claim 1 having the following formula IE



IE

wherein R^{xa} is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-$S(O)_nR^5$, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-$C(=O)R^5$, -(alkylene)$_m$-$C(=S)R^5$, -(alkylene)$_m$-$C(=O)OR^5$, -(alkylene)$_m$-$OC(=O)R^5$, -(alkylene)$_m$-$C(=S)OR^5$, —(alkylene)$_m$-$C(=O)NR^3R^4$, -(alkylene)$_m$-$C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=S)NR^3R^4$, -(alkylene)$_m$-$N(R^3)C(=O)R^5$, -(alkylene)$_m$-$N(R^3)C(=S)R^5$, -(alkylene)$_m$-$OC(=O)NR^3R^4$, -(alkylene)$_m$-$OC(=S)NR^3R^4$, -(alkylene)$_m$-$SO_2NR^3R^4$, -(alkylene)$_m$-$N(R^3)SO_2R^5$,

-(alkylene)$_m$-N(R^3)$SO_2NR^3R^4$, -(alkylene)$_m$-N(R^3)C(=O)OR^5, -(alkylene)$_m$-N(R^3)C(=S)OR^5, or -(alkylene)$_m$-N(R^3)SO_2R^5;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-S(O)$_n$$R^5$*, -(alkylene)$_m$-$NR^3$*$R^4$*, -(alkylene)$_m$-C(=O)$R^5$*, -(alkylene)$_m$-C(=S)$R^5$*, -(alkylene)$_m$-C(=O)O$R^5$*, -(alkylene)$_m$-OC(=O)$R^5$*, -(alkylene)$_m$-C(=S)$OR^5$*, —(alkylene)$_m$-C(=O)$NR^3$*$R^4$*, -(alkylene)$_m$-C(=S)$NR^3$*$R^4$*, -(alkylene)$_m$-N($R^3$*)C(=O)$NR^3$*$R^4$*, -(alkylene)$_m$-N($R^3$*)C(=S)$NR^3$*$R^4$*, -(alkylene)$_m$-N($R^3$*)C(=O)$R^5$*, -(alkylene)$_m$-N($R^3$*)C(=S)$R^5$*, -(alkylene)$_m$-OC(=O)$NR^3$*$R^4$*, -(alkylene)$_m$-OC(=S)$NR^3$*$R^4$*, -(alkylene)$_m$-$SO_2NR^3$*$R^4$*, -(alkylene)$_m$-N($R^3$*)$SO_2R^5$*, -(alkylene)$_m$-N($R^3$*)$SO_2NR^3$*$R^4$*, -(alkylene)$_m$-N($R^3$*)C(=O)$OR^5$*, -(alkylene)$_m$-N($R^3$*)C(=S)$OR^5$*, or -(alkylene)$_m$-N($R^3$*)$SO_2R^5$*;

m is independently 0 or 1 ; and

q is zero to two.

40. A pharmaceutical composition comprising a compound of claim 1 together with a pharmaceutically acceptable vehicle adjuvant or diluent.

41. A method of treating cancer in a subject, said method comprising administering an effective amount of a compound as in claim 1.

42. The method of claim 41 wherein said compound of claim 1 is administered in combination with at least one compound selected from antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and miscellaneous agents.

43. A method of reducing tumor size in a subject, said method comprising administering an effective amount of a compound as in claim 1.

44. A method of treating cdk4 or cdk6 mediated disorders in a subject, said method comprising administering an effective amount of a compound as in claim 1.

45. A method of reducing metastasis in a tumor in a subject, said method comprising administering an effective amount of a compound as in claim 1.