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(54) Title: PYRROLOPYRIMIDINES AS FAK AND ALK INHIBITERS FOR TREATMENT OF CANCERS AND OTHER DISEASES

(57) Abstract: Disclosed are compounds which inhibit the activity of focal adhesion kinase (FAK) and anaplastic lymphoma kinase (ALK), compositions containing the compounds, and methods of treating diseases during which FAK and ALK are expressed. The diseases are, for example, cancers.

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PYRROLOPYRAMIDINES AS FAK AND ALK INHIBITORS FOR THE TREATMENT OF CANCER AND OTHER DISEASES

FIELD OF THE INVENTION

This invention pertains to compounds which inhibit the activity of focal adhesion kinase (FAK) and anaphastic lymphoma kinase (ALK), methods of making the compounds, compositions containing the compounds, and methods of treatment using the compounds.

BACKGROUND OF THE INVENTION

Tyrosine kinases play a critical role in signal transduction for several cellular functions including cell proliferation, carcinogenesis, apoptosis, and cell differentiation. Inhibitors of these enzymes are useful for the treatment or prevention of proliferative diseases which are dependent of these enzymes.

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase involved in integrin-mediated signal transduction pathways. FAK co-localizes with integrins in focal contact sites. FAK activation and its tyrosine phosphorylation have been shown in many cell types to be dependent on integrins binding to their extracellular ligands. Results from several studies support the hypothesis that FAK inhibitors could be useful in cancer treatment. For example, FAK-deficient cells migrate poorly in response to chemotactic signals and over-expression of C-terminal domain of FAK blocks cell spreading as well as chemotactic migration (Sieg et al, *J. Cell Science*, **1999**, 112, 2677-2691; Richardson A. and Parsons T., *Cell*, **1997**, 97, 221-231). In addition, studies have demonstrated that an increase in FAK mRNA levels accompanied invasive transformation of tumors and attenuation of the expression of FAK (through the use of antisense oligonucleotides) induces apoptosis in tumor cells (Xu et al, *Cell Growth Differ*. **1996**, 4, 413-418). FAK has been reported to be over-expressed in prostate, breast, thyroid, colon and lung cancers. The level of expression of FAK is directly correlated with tumors demonstrating the most aggressive phenotype.

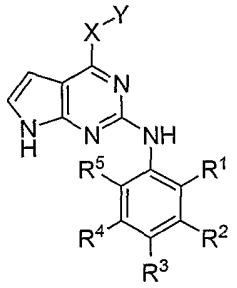
Anaphastic lymphoma kinase (ALK), a member of the insulin receptor super family of receptor tyrosine kinases, has been implicated in oncogenesis in hematopoietic

and non-hematopoietic tumors. The aberrant expression of full-length ALK receptor proteins has been reported in neuroblastomas and glioblastomas (Gascoyne et al, *Blood*, **2003**, 102, 2568-2573; Griffin et al, *Cancer Res.*, **1999**, 59, 2776-2780; Lawrence et al, Am. *J. Pathol.*, **2000**, 157, 377-384). Additionally, ALK fusion proteins have occurred in anaplastic large cell lymphoma.

Accordingly, a need exists for additional selective inhibitors of certain receptor and non-receptor tyrosine kinases, useful in the treatment of abnormal cell growth, such as cancer. The present invention provides novel pyrrolopyrimidines that are selective inhibitors of FAK and ALK. Such compounds can be used to treat subjects suffering from cancer, and can further expand the range of treatment options available for such subjects.

SUMMARY OF THE INVENTION

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as inhibitors of focal adhesion kinase (FAK) and anaphastic lymphoma kinase (ALK), the compounds having Formula (I)



(I);

wherein

X is CH_2NH, CH_2NHCH_2, $CH_2C(R^6)_2$, CH_2CHR^6, CHR^6CH_2, $C(R^6)_2CH_2$, CH_2CH_2, CH=CH, $CH=CR_6$, $CR_6=CH$, or $NHCH_2$;

Y is aryl or heteroaryl; wherein the aryl or heteroaryl is substituted with $NR^7SO_2R^8$; wherein the aryl or heteroaryl is optionally further substituted with one or more R^9;

each R^6 is independently alkyl;

R^7 is hydrogen or alkyl;

R^8 is alkyl;

R^1, R^2, R^3, R^4, R^5, and R^9 are independently selected from the group consisting of hydrogen, R^{10}, OR^{10}, SR^{10}, $S(O)R^{10}$, SO_2R^{10}, $C(O)R^{10}$, $CO(O)R^{10}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, NH_2, NHR^{10}, $N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHS(O)_2R^{10}$, $NR^{10}S(O)_2R^{10}$, $NHC(O)OR^{10}$, $NR^{10}C(O)OR^{10}$, $NHC(O)NH_2$, $NHC(O)NHR^{10}$, $NHC(O)N(R^{10})_2$, $NR^{10}C(O)NHR^{10}$, $NR^{10}C(O)N(R^{10})_2$, $C(O)NH_2$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, C(O)NHOH, $C(O)NHOR^{10}$, $C(O)NHSO_2R^{10}$, $C(O)NR^{10}SO_2R^{10}$, SO_2NH_2, SO_2NHR^{10}, $SO_2N(R^{10})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{10}$, $C(N)N(R^{10})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{10} is independently R^{11}, R^{12}, R^{13}, or R^{14};

R^{11} is aryl;

R^{12} is heteroaryl;

R^{13} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{14} is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{15}, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $C(O)R^{15}$, $CO(O)R^{15}$, $OC(O)R^{15}$, $OC(O)OR^{15}$, NH_2, NHR^{15}, $N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHS(O)_2R^{15}$, $NR^{15}S(O)_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)NHR^{15}$, $NR^{15}C(O)N(R^{15})_2$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, C(O)NHOH, $C(O)NHOR^{15}$, $C(O)NHSO_2R^{15}$, $C(O)NR^{15}SO_2R^{15}$, SO_2NH_2, SO_2NHR^{15}, $SO_2N(R^{15})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{15}$, $C(N)N(R^{15})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{15} is independently R^{16}, R^{17}, R^{18}, or R^{19};

R^{16} is aryl;

R^{17} is heteroaryl;

R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{19} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{20}, OR^{20}, SR^{20}, $S(O)R^{20}$, SO_2R^{20}, $C(O)R^{20}$, $CO(O)R^{20}$, $OC(O)R^{20}$, $OC(O)OR^{20}$, NH_2, NHR^{20}, $N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{20}C(O)R^{20}$, $NHS(O)_2R^{20}$, $NR^{20}S(O)_2R^{20}$, $NHC(O)OR^{20}$, $NR^{20}C(O)OR^{20}$, $NHC(O)NH_2$, $NHC(O)NHR^{20}$, $NHC(O)N(R^{20})_2$, $NR^{20}C(O)NHR^{20}$, $NR^{20}C(O)N(R^{20})_2$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, C(O)NHOH, $C(O)NHOR^{20}$, $C(O)NHSO_2R^{20}$, $C(O)NR^{20}SO_2R^{20}$, SO_2NH_2, SO_2NHR^{20}, $SO_2N(R^{20})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{20}$, $C(N)N(R^{20})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I substituents;

each R^{20} is independently alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

wherein the moieties represented by R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, and R^{18} are unsubstituted or substituted with one or two or three or four of independently selected R^{21}, OR^{21}, SR^{21}, $S(O)R^{21}$, SO_2R^{21}, $C(O)R^{21}$, $CO(O)R^{21}$, $OC(O)R^{21}$, $OC(O)OR^{21}$, NH_2, NHR^{21}, $N(R^{21})_2$, $NHC(O)R^{21}$, $NR^{21}C(O)R^{21}$, $NHS(O)_2R^{21}$, $NR^{21}S(O)_2R^{21}$, $NHC(O)OR^{21}$, $NR^{21}C(O)OR^{21}$, $NHC(O)NH_2$, $NHC(O)NHR^{21}$, $NHC(O)N(R^{21})_2$, $NR^{21}C(O)NHR^{21}$, $NR^{21}C(O)N(R^{21})_2$, $C(O)NH_2$, $C(O)NHR^{21}$, $C(O)N(R^{21})_2$, C(O)NHOH, $C(O)NHOR^{21}$, $C(O)NHSO_2R^{21}$, $C(O)NR^{21}SO_2R^{21}$, SO_2NH_2, SO_2NHR^{21}, $SO_2N(R^{21})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{21}$, $C(N)N(R^{21})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{21} is independently R^{22}, R^{23}, R^{24}, or R^{25};

R^{22} is aryl;

R^{23} is heteroaryl;

R^{24} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{25} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{26}, OR^{26}, SR^{26}, $S(O)R^{26}$, SO_2R^{26}, $C(O)R^{26}$, $CO(O)R^{26}$, $OC(O)R^{26}$, $OC(O)OR^{26}$, NH_2, NHR^{26}, $N(R^{26})_2$, $NHC(O)R^{26}$,

$NR^{26}C(O)R^{26}$, $NHS(O)_2R^{26}$, $NR^{26}S(O)_2R^{26}$, $NHC(O)OR^{26}$, $NR^{26}C(O)OR^{26}$, $NHC(O)NH_2$, $NHC(O)NHR^{26}$, $NHC(O)N(R^{26})_2$, $NR^{26}C(O)NHR^{26}$, $NR^{26}C(O)N(R^{26})_2$, $C(O)NH_2$, $C(O)NHR^{26}$, $C(O)N(R^{26})_2$, C(O)NHOH, $C(O)NHOR^{26}$, $C(O)NHSO_2R^{26}$, $C(O)NR^{26}SO_2R^{26}$, SO_2NH_2, SO_2NHR^{26}, $SO_2N(R^{26})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{26}$, $C(N)N(R^{26})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{26} is independently alkyl, alkenyl, alkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; and

the moieties represented by R^{22}, R^{23}, and R^{24} are unsubstituted or substituted with one or two or three or four of independently selected NH_2, $C(O)NH_2$, C(O)NHOH, SO_2NH_2, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I.

In one embodiment of formula (I), X is $NHCH_2$.

In another embodiment of formula (I), X is $NHCH_2$; and Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$.

In another embodiment of formula (I), X is $NHCH_2$; and Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$.

In another embodiment of formula (I), X is $NHCH_2$; Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl.

In another embodiment of formula (I), X is $NHCH_2$; Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl.

In another embodiment of formula (I), X is $NHCH_2$; Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1, R^2, R^4, and R^5, are hydrogen; and R^3 is $C(O)NHR^{10}$.

In another embodiment of formula (I), X is $NHCH_2$; Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1, R^3, R^4, and R^5, are hydrogen; and R^2 is $C(O)NHR^{10}$.

In another embodiment of formula (I), X is $NHCH_2$; Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2, R^4, and R^5 are hydrogen; R^1 is OR^{10}; and R^3 is R^{10} or $C(O)NHR^{10}$.

Still another embodiment pertains to compounds having Formula (I), which are
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(3-morpholin-4-ylpropyl)benzamide;
N-cyclobutyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-morpholin-4-ylethyl)benzamide;
N-[3-(1H-imidazol-1-yl)propyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide;
N-(2-methoxyethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(4-methylpiperazin-1-yl)propyl]benzamide;
N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide;
N-ethyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(tetrahydrofuran-2-ylmethyl)benzamide;
N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]-3-methylphenyl}-N-methylmethanesulfonamide;
N-cyclopropyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(1-methylpiperidin-4-yl)benzamide;

N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide;
N-cyclopentyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide;
N-methyl-N-(2-{[(2-{[4-(morpholin-4-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide;
N-methyl-N-(2-{[(2-{[4-(pyrrolidin-1-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide;
N-ethyl-N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-propylbenzamide;
N-(2-furylmethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-{2-[({2-[(2-methoxy-4-piperazin-1-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide;
N-[3-(1H-imidazol-1-yl)propyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(3-morpholin-4-ylpropyl)benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(1-methylpiperidin-4-yl)benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(pyridin-3-ylmethyl)benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(pyridin-3-ylmethyl)benzamide;
N-[3-(dimethylamino)propyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;

N-[2-(dimethylamino)ethyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-[3-(dimethylamino)propyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N,N-dimethyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
benzyl 4-(3-methoxy-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}phenyl)piperazine-1-carboxylate;
N-cyclopentyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-cyclopropyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-ethyl-N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(4-methylpiperazin-1-yl)propyl]benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-morpholin-4-ylethyl)benzamide;
N-cyclobutyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(tetrahydrofuran-2-ylmethyl)benzamide;
N-methyl-N-(2-{[(2-{[3-(pyrrolidin-1-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide;
N-methyl-N-[2-({[2-({3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide;

N-ethyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-N-(2-{[(2-{[3-(morpholin-4-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide;
N-[2-(dimethylamino)ethyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-[3-(dimethylamino)propyl]-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-propylbenzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide;
N-(2-furylmethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-furylmethyl)-N-methyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N,N-dimethyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-methoxyethyl)-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-furylmethyl)-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-methoxyethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-N-[2-({[2-({4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide;
N-isopropyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;

N-(2-cyanoethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-{2-[({2-[(4-methoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide;
N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide;
N-isopropyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
2-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-methylbenzamide;
N-{6-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide;
2-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzoic acid;
2-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzoic acid;
N-(cyclopropylmethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-ethyl-N-[3-((E)-2-{2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}vinyl)pyridin-2-yl]methanesulfonamide;
N-[3-((E)-2-{2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}vinyl)pyridin-2-yl]-N-methylmethanesulfonamide;
N-methyl-2-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-methoxyethyl)benzamide;
N-(2-methoxyethyl)-4-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-N-(2-{[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]methyl}phenyl)methanesulfonamide;

N-[2-({[2-({3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide;
N-(2-{[(2-{[2-methoxy-4-(piperidin-4-yloxy)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)-N-methylmethanesulfonamide;
N^4-benzyl-N^2-(2-methoxy-4-morpholin-4-ylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine;
N-methyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide;
N-ethyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide;
4-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-(2-methoxyethyl)benzamide;
2-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-methylbenzamide;
N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide;
N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}-N-methylmethanesulfonamide;
2-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzoic acid;
N-(2-methoxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]phenyl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;
N-(2-methoxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;
2-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzoic acid;
N-ethyl-N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide;
4-({4-[({2-[ethyl(methylsulfonyl)amino]phenyl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-(2-methoxyethyl)benzamide; ; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to a composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of a compound of Formula (I).

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound of Formula (I).

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

Variable moieties herein are represented by identifiers (capital letters with numerical and/or alphabetical superscripts) and may be specifically embodied.

It is meant to be understood that proper valences are maintained for all moieties and combinations thereof, that monovalent moieties having more than one atom are

drawn from left to right and are attached through their left ends, and that divalent moieties are also drawn from left to right.

It is also meant to be understood that a specific embodiment of a variable moiety herein may be the same or different as another specific embodiment having the same identifier.

The term "alkenyl" as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkyl" as used herein, means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term "alkynyl" as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited to, acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

The term "aryl," as used herein, means phenyl, a bicyclic aryl or a tricyclic aryl. The bicyclic aryl is naphthyl, or a phenyl fused to a cycloalkyl, or a phenyl fused to a cycloalkenyl, or a phenyl fused to a monocyclic heteroaryl ring as defined herein, or a phenyl fused to a monocyclic heterocycle as defined herein. The bicyclic aryl of the present invention must be attached to the parent molecular moiety through any available carbon atom contained within the phenyl ring. Representative examples of the bicyclic aryl include, but are not limited to, 2,3-dihydro-1,4-benzodioxin-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 3,4-dihydro-2*H*-1,5-benzodioxepin-6-yl, dihydroindenyl, indenyl, indol-4-yl, naphthyl, dihydronaphthalenyl, and tetrahydronaphthalenyl. The tricyclic aryl is anthracene or phenanthrene, or a bicyclic aryl fused to a cycloalkyl, or a bicyclic aryl fused to a cycloalkenyl, or a bicyclic aryl fused to a phenyl. The tricyclic aryl is attached to the parent molecular moiety through any carbon atom contained within the tricyclic

aryl. Representative examples of tricyclic aryl ring include, but are not limited to, azulenyl, dihydroanthracenyl, fluorenyl, and tetrahydrophenanthrenyl.

The term "cycloalkenyl" as used herein, means a monocyclic, bicyclic, tricyclic, spirocyclic, or bridged ring system containing from 3 to 12 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of monocyclic ring systems include, but are not limited to, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl and 3-cyclopenten-1-yl. Bicyclic ring systems are exemplified by a monocyclic cycloalkenyl ring system which is fused to another monocyclic cycloalkyl ring as defined herein, a monocyclic aryl ring as defined herein, a monocyclic heterocycle as defined herein or a monocyclic heteroaryl as defined herein. The bicyclic ring systems of the present invention must be appended to the parent molecular moiety through an available carbon atom within the cycloalkenyl ring. Representative examples of bicyclic ring systems include, but are not limited to, 4,5-dihydro-benzo[1,2,5]oxadiazole, 3a, 4, 5, 6, 7, 7a-hexahydro-1*H*-indenyl, 1, 2, 3, 4, 5, 6-hexahydro-pentalenyl, 1, 2, 3, 4, 4a, 5, 6, 8a-octahydro-pentalenyl.

The term "cycloalkyl" as used herein, means a monocyclic, bicyclic, tricyclic, spirocyclic, or bridged ring system containing a saturated cyclic hydrocarbon group containing from 3 to 12 carbon atoms. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl groups of the present invention are exemplified by a monocyclic cycloalkyl ring fused to another monocyclic cycloalkyl ring, or a monocyclic cycloalkyl ring fused cycloalkenyl, or a monocyclic cycloalkyl ring fused to a phenyl ring, or a monocyclic cycloalkyl ring fused to a monocyclic heteroaryl ring as defined herein, or a monocyclic cycloalkyl ring fused to a monocyclic heterocycle as defined herein. The bicyclic cycloalkyl ring systems of the present invention must be appended to the parent molecular moiety through an available carbon atom within the monocycloalkyl ring.

The term "heteroaryl," as used herein, means a monocyclic heteroaryl, a bicyclic heteroaryl, or a tricyclic heteroaryl. The monocyclic heteroaryl is a 5 or 6 membered ring containing at least one heteroatom independently selected from O, N, or S. The 5 membered ring contains two double bonds may contain one, two, three or four heteroatoms. The 6 membered ring contains three double bonds may contain one, two,

three or four heteroatoms. The 5 or 6 membered heteroaryl is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heteroaryl. Representative examples of monocyclic heteroaryl include, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl consists of a monocyclic heteroaryl fused to a monocyclic aryl ring as defined herein, a monocyclic cycloalkyl ring as defined herein, a monocyclic cycloalkenyl ring as defined herein, another monocyclic heteroaryl or a monocyclic heterocycle ring as defined herein. The bicyclic heteroaryl ring systems of the present invention must be appended to the parent molecular moiety through an available carbon atom within the heteroaryl ring. The bicyclic heteroaryl is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the bicyclic heteroaryl. Representative examples of bicyclic heteroaryl include, but are not limited to, benzofuranyl, benzoxadiazolyl, 1,3-benzothiazolyl, benzimidazolyl, benzodioxolyl, benzothiophenyl, chromenyl, cinnolinyl, furopyridine, indolyl, indazolyl, isoindolyl, isoquinolinyl, naphthyridinyl, oxazolopyridine, quinolinyl, thienopyridine and thienopyridinyl.

The term "heterocycle" or "heterocyclic" as used herein, refers to a monocyclic, bicyclic, tricyclic, spirocyclic, or bridged ring system that contains at least one heteroatom. The monocyclic heterocycle is a 3, 4, 5, 6 or 7 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S. The 3 or 4 membered ring contains 1 heteroatom selected from the group consisting of O, N and S. The 5 membered ring contains zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The 6 or 7 membered ring contains zero, one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S. The monocyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle. Representative examples of monocyclic heterocycle include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, isoindoline-1,3-dione, morpholinyl,

oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. The bicyclic heterocycle of the present invention is defined as a monocyclic heterocycle fused to a phenyl group, a cycloalkylgroup as defined herein, a cycloalkenyl group as defined herein, another monocyclic heterocycle group as defined herein, or a spirocyclic ring wherein one carbon atom of the monocyclic heterocycle is bridged by two ends of an alkylene chain. The bicyclic heterocycle of the present invention is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heterocyclic ring. Representative examples of bicyclic heterocycle include, but are not limited to, 1,3-benzodioxolyl, 1,3-benzodithiolyl, 2,3-dihydro-1,4-benzodioxinyl, 2,3-dihydro-1-benzofuranyl, 2,3-dihydro-1-benzothienyl, 3,4-dihydro-1*H*-isochromen-4-yl, 2,3-dihydro-1*H*-indolyl, succinmimidyl, and 1,2,3,4-tetrahydroquinolinyl. The tricyclic heterocycle is a bicyclic heterocycle fused to a phenyl, or a bicyclic heterocycle fused to a cycloalkyl, or a bicyclic heterocycle fused to a cycloalkenyl, or a bicyclic heterocycle fused to a monocyclic heterocycle. The tricyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the tricyclic heterocycle. Representative examples of tricyclic heterocycle include, but are not limited to, 2,3,4,4a,9,9a-hexahydro-1*H*-carbazolyl, 5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furanyl, and 5a,6,7,8,9,9a-hexahydrodibenzo[b,d]thienyl.

The term "heterocycloalkyl," as used herein, means a monocyclic, bicyclic, tricyclic, spirocyclic, or bridged heterocycle, as defined herein, wherein the 5 membered ring contains zero double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S, and the 6 or 7 membered ring contains zero double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S.

The term "heterocycloalkenyl," as used herein, means a monocyclic, bicyclic, tricyclic, spirocyclic, or bridged heterocycle,, as defined herein, wherein the 5 membered ring contains one double bond and one, two or three heteroatoms selected from the group

consisting of O, N and S, and the 6 or 7 membered ring contains one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S.

The term "phenyl," as used herein, means a monovalent radical formed by removal of a hydrogen atom from benzene.

The term "spiroalkyl," as used herein, means a spirocyclic cycloalkyl as defined herein.

The term, "spirocyclic," as used herein, means a ring system wherein one atom is common to two different rings.

The term, "bridged," as used herein, means a ring system wherein the rings share at least two common non-adjacent atoms.

The term "NH protecting group," as used herein, means trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, para-nitrobenzylcarbonyl, ortho-bromobenzyloxycarbonyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amyloxycarbonyl, tert-butoxycarbonyl, para-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyl-oxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 2-furfuryl-oxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxy-carbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantyloxycarbonyl, 8-quinolyloxycarbonyl, benzyl, diphenylmethyl, triphenylmethyl, 2-nitrophenylthio, methanesulfonyl, para-toluenesulfonyl, N,N-dimethylaminomethylene, benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthyl-methylene, 3-hydroxy-4-pyridylmethylene, cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxycyclo-hexylidene, diphenylphosphoryl, dibenzylphosphoryl, 5-methyl-2-oxo-2H-1,3-dioxol-4-yl-methyl, trimethylsilyl, triethylsilyl, and triphenylsilyl.

The term "C(O)OH protecting group," as used herein, means methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, tert-butyl, phenyl, naphthyl, benzyl, diphenylmethyl, triphenylmethyl, para-nitrobenzyl, para-methoxybenzyl, bis(para-methoxyphenyl)methyl, acetylmethyl, benzoylmethyl, para-nitrobenzoylmethyl, para-bromobenzoylmethyl, para-methanesulfonylbenzoylmethyl, 2-tetrahydropyranyl 2-tetrahydrofuranyl, 2,2,2-trichloro-ethyl, 2-(trimethylsilyl)ethyl, acetoxymethyl,

propionyloxymethyl, pivaloyloxymethyl, phthalimidomethyl, succinimidomethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, methylthiomethyl, 2-methylthioethyl, phenylthiomethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, and tert-butylmethoxyphenylsilyl.

The term "OH or SH protecting group," as used herein, means benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, S-benzylthiocarbonyl, 4-ethoxy-1-naphthyloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl, methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl (phenylmethyl), para-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloro-ethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, and tert-butylmethoxyphenylsilyl.

Compounds

Geometric isomers may exist in the present compounds. Compounds of this invention may contain carbon-carbon double bonds or carbon-nitrogen double bonds in the E or Z configuration, wherein the term “E” represents higher order substituents on opposite sides of the carbon-carbon or carbon-nitrogen double bond and the term “Z”

represents higher order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond as determined by the Cahn-Ingold-Prelog Priority Rules. The compounds of this invention may also exist as a mixture of "E" and "Z" isomers. Substituents around a cycloalkyl or heterocycloalkyl are designated as being of cis or trans configuration. Furthermore, the invention contemplates the various isomers and mixtures thereof resulting from the disposal of substituents around an adamantane ring system. Two substituents around a single ring within an adamantane ring system are designated as being of Z or E relative configuration. For examples, see C. D. Jones, M. Kaselj, R. N. Salvatore, W. J. le Noble *J. Org. Chem.* **1998**, 63, 2758-2760.

Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms "R" and "S" are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

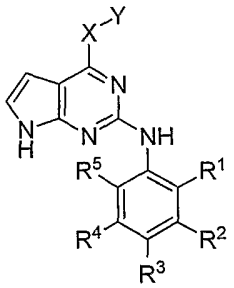
Compounds of this invention containing NH, C(O)OH, OH or SH moieties may have attached thereto prodrug-forming moieties. The prodrug-forming moieties are removed by metabolic processes and release the compounds having the freed hydroxyl, amino or carboxylic acid in vivo. Prodrugs are useful for adjusting such pharmacokinetic properties of the compounds as solubility and/or hydrophobicity, absorption in the gastrointestinal tract, bioavailability, tissue penetration, and rate of clearance.

Compounds of this invention can exist in an isotopic form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur fluorine, chlorine, and iodine include, but are not limited to, ^{2}H, ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I, respectively. Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention. Compounds containing

tritium (^3H) and ^{14}C radioisotopes are preferred in general for their ease in preparation and detectability for radiolabeled compounds. Isotopically labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotopically labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples and Schemes herein by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Suitable groups for X, Y, R^1, R^2, R^3, R^4, and R^5 in compounds of Formula (I) are independently selected. The described embodiments of the present invention may be combined. Such combination is contemplated and within the scope of the present invention. For example, it is contemplated that embodiments for any of X, Y, R^1, R^2, R^3, R^4, and R^5 can be combined with embodiments defined for any other of X, Y, R^1, R^2, R^3, R^4, and R^5.

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as inhibitors of focal adhesion kinase (FAK) and anaphastic lymphoma kinase (ALK), the compounds having Formula (I)



(I);

wherein

X is CH_2NH, CH_2NHCH_2, $CH_2C(R^6)_2$, CH_2CHR^6, CHR^6CH_2, $C(R^6)_2CH_2$, CH_2CH_2, CH=CH, $CH{=}CR_6$, $CR_6{=}CH$, or $NHCH_2$;

Y is aryl or heteroaryl; wherein the aryl or heteroaryl is substituted with $NR^7SO_2R^8$; wherein the aryl or heteroaryl is optionally further substituted with one or more R^9;

each R^6 is independently alkyl;

R^7 is hydrogen or alkyl;

R^8 is alkyl;

R^1, R^2, R^3, R^4, R^5, and R^9 are independently selected from the group consisting of hydrogen, R^{10}, OR^{10}, SR^{10}, $S(O)R^{10}$, SO_2R^{10}, $C(O)R^{10}$, $CO(O)R^{10}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, NH_2, NHR^{10}, $N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHS(O)_2R^{10}$, $NR^{10}S(O)_2R^{10}$, $NHC(O)OR^{10}$, $NR^{10}C(O)OR^{10}$, $NHC(O)NH_2$, $NHC(O)NHR^{10}$, $NHC(O)N(R^{10})_2$, $NR^{10}C(O)NHR^{10}$, $NR^{10}C(O)N(R^{10})_2$, $C(O)NH_2$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, C(O)NHOH, $C(O)NHOR^{10}$, $C(O)NHSO_2R^{10}$, $C(O)NR^{10}SO_2R^{10}$, SO_2NH_2, SO_2NHR^{10}, $SO_2N(R^{10})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{10}$, $C(N)N(R^{10})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{10} is independently R^{11}, R^{12}, R^{13}, or R^{14};

R^{11} is aryl;

R^{12} is heteroaryl;

R^{13} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{14} is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{15}, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $C(O)R^{15}$, $CO(O)R^{15}$, $OC(O)R^{15}$, $OC(O)OR^{15}$, NH_2, NHR^{15}, $N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHS(O)_2R^{15}$, $NR^{15}S(O)_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)NHR^{15}$, $NR^{15}C(O)N(R^{15})_2$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, C(O)NHOH, $C(O)NHOR^{15}$, $C(O)NHSO_2R^{15}$, $C(O)NR^{15}SO_2R^{15}$, SO_2NH_2, SO_2NHR^{15}, $SO_2N(R^{15})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{15}$, $C(N)N(R^{15})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{15} is independently R^{16}, R^{17}, R^{18}, or R^{19};

R^{16} is aryl;

R^{17} is heteroaryl;

R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{19} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{20}, OR^{20}, SR^{20}, $S(O)R^{20}$, SO_2R^{20}, $C(O)R^{20}$, $CO(O)R^{20}$, $OC(O)R^{20}$, $OC(O)OR^{20}$, NH_2, NHR^{20}, $N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{20}C(O)R^{20}$, $NHS(O)_2R^{20}$, $NR^{20}S(O)_2R^{20}$, $NHC(O)OR^{20}$, $NR^{20}C(O)OR^{20}$, $NHC(O)NH_2$, $NHC(O)NHR^{20}$, $NHC(O)N(R^{20})_2$, $NR^{20}C(O)NHR^{20}$, $NR^{20}C(O)N(R^{20})_2$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, C(O)NHOH, $C(O)NHOR^{20}$, $C(O)NHSO_2R^{20}$, $C(O)NR^{20}SO_2R^{20}$, SO_2NH_2, SO_2NHR^{20}, $SO_2N(R^{20})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{20}$, $C(N)N(R^{20})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I substituents;

each R^{20} is independently alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

wherein the moieties represented by R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, and R^{18} are unsubstituted or substituted with one or two or three or four of independently selected R^{21}, OR^{21}, SR^{21}, $S(O)R^{21}$, SO_2R^{21}, $C(O)R^{21}$, $CO(O)R^{21}$, $OC(O)R^{21}$, $OC(O)OR^{21}$, NH_2, NHR^{21}, $N(R^{21})_2$, $NHC(O)R^{21}$, $NR^{21}C(O)R^{21}$, $NHS(O)_2R^{21}$, $NR^{21}S(O)_2R^{21}$, $NHC(O)OR^{21}$, $NR^{21}C(O)OR^{21}$, $NHC(O)NH_2$, $NHC(O)NHR^{21}$, $NHC(O)N(R^{21})_2$, $NR^{21}C(O)NHR^{21}$, $NR^{21}C(O)N(R^{21})_2$, $C(O)NH_2$, $C(O)NHR^{21}$, $C(O)N(R^{21})_2$, C(O)NHOH, $C(O)NHOR^{21}$, $C(O)NHSO_2R^{21}$, $C(O)NR^{21}SO_2R^{21}$, SO_2NH_2, SO_2NHR^{21}, $SO_2N(R^{21})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{21}$, $C(N)N(R^{21})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{21} is independently R^{22}, R^{23}, R^{24}, or R^{25};

R^{22} is aryl;

R^{23} is heteroaryl;

R^{24} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{25} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{26}, OR^{26}, SR^{26}, $S(O)R^{26}$, SO_2R^{26},

$C(O)R^{26}$, $CO(O)R^{26}$, $OC(O)R^{26}$, $OC(O)OR^{26}$, NH_2, NHR^{26}, $N(R^{26})_2$, $NHC(O)R^{26}$, $NR^{26}C(O)R^{26}$, $NHS(O)_2R^{26}$, $NR^{26}S(O)_2R^{26}$, $NHC(O)OR^{26}$, $NR^{26}C(O)OR^{26}$, $NHC(O)NH_2$, $NHC(O)NHR^{26}$, $NHC(O)N(R^{26})_2$, $NR^{26}C(O)NHR^{26}$, $NR^{26}C(O)N(R^{26})_2$, $C(O)NH_2$, $C(O)NHR^{26}$, $C(O)N(R^{26})_2$, C(O)NHOH, $C(O)NHOR^{26}$, $C(O)NHSO_2R^{26}$, $C(O)NR^{26}SO_2R^{26}$, SO_2NH_2, SO_2NHR^{26}, $SO_2N(R^{26})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{26}$, $C(N)N(R^{26})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{26} is independently alkyl, alkenyl, alkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; and

the moieties represented by R^{22}, R^{23}, and R^{24} are unsubstituted or substituted with one or two or three or four of independently selected NH_2, $C(O)NH_2$, C(O)NHOH, SO_2NH_2, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I.

In another embodiment of formula (I),

X is CH_2NH, CH_2NHCH_2, CH=CH, or $NHCH_2$;

Y is aryl or heteroaryl; wherein the aryl or heteroaryl is substituted with $NR^7SO_2R^8$; wherein the aryl or heteroaryl is optionally further substituted with one or more R^9;

R^7 is hydrogen or alkyl;

R^8 is alkyl;

R^1, R^2, R^3, R^4, R^5, and R^9 are independently selected from the group consisting of hydrogen, R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH;

each R^{10} is independently R^{11}, R^{13}, or R^{14};

R^{11} is aryl;

R^{13} is cycloalkyl, or heterocycloalkyl;

R^{14} is alkyl, which is unsubstituted or substituted with R^{15}, OR^{15}, $N(R^{15})_2$, or CN;

each R^{15} is independently R^{17}, R^{18}, or R^{19};

R^{17} is heteroaryl;

R^{18} is cycloalkyl, or heterocycloalkyl;

R^{19} is alkyl;

wherein the moieties represented by R^{11}, R^{13} and R^{18} are unsubstituted or substituted with one or two or three or four of independently selected R^{21}, OR^{21}, $CO(O)R^{21}$;

each R^{21} is independently R^{25};

R^{25} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with R^{26}; and

each R^{26} is aryl.

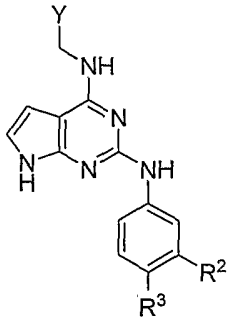
In one embodiment of formula (I), X is CH_2NH, CH_2NHCH_2, CH=CH, or $NHCH_2$. In another embodiment of formula (I), X is CH_2NH. In another embodiment of formula (I), X is CH_2NHCH_2. In another embodiment of formula (I), X is CH=CH. In another embodiment of formula (I), X is $NHCH_2$.

In one embodiment of formula (I), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In one embodiment of formula (I), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In another embodiment of formula (I), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In another embodiment of formula (I), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl.

In one embodiment of formula (I), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl, and X is $NHCH_2$. In one embodiment of formula (I), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; and X is $NHCH_2$. In another embodiment of formula (I), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; and X is $NHCH_2$. In another embodiment of formula (I), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; and X is $NHCH_2$.

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as

inhibitors of focal adhesion kinase (FAK) and anaphastic lymphoma kinase (ALK), the compounds having Formula (II)



(II);

wherein

Y is aryl or heteroaryl; wherein the aryl or heteroaryl is substituted with $NR^7SO_2R^8$; wherein the aryl or heteroaryl is optionally further substituted with one or more R^9;

R^7 is hydrogen or alkyl;

R^8 is alkyl;

R^2, R^3, and R^9 are independently selected from the group consisting of hydrogen, R^{10}, OR^{10}, SR^{10}, $S(O)R^{10}$, SO_2R^{10}, $C(O)R^{10}$, $CO(O)R^{10}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, NH_2, NHR^{10}, $N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHS(O)_2R^{10}$, $NR^{10}S(O)_2R^{10}$, $NHC(O)OR^{10}$, $NR^{10}C(O)OR^{10}$, $NHC(O)NH_2$, $NHC(O)NHR^{10}$, $NHC(O)N(R^{10})_2$, $NR^{10}C(O)NHR^{10}$, $NR^{10}C(O)N(R^{10})_2$, $C(O)NH_2$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, C(O)NHOH, $C(O)NHOR^{10}$, $C(O)NHSO_2R^{10}$, $C(O)NR^{10}SO_2R^{10}$, SO_2NH_2, SO_2NHR^{10}, $SO_2N(R^{10})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{10}$, $C(N)N(R^{10})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{10} is independently R^{11}, R^{12}, R^{13}, or R^{14};

R^{11} is aryl;

R^{12} is heteroaryl;

R^{13} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{14} is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{15}, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $C(O)R^{15}$, $CO(O)R^{15}$, $OC(O)R^{15}$, $OC(O)OR^{15}$, NH_2, NHR^{15}, $N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHS(O)_2R^{15}$, $NR^{15}S(O)_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)NHR^{15}$, $NR^{15}C(O)N(R^{15})_2$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, C(O)NHOH, $C(O)NHOR^{15}$, $C(O)NHSO_2R^{15}$, $C(O)NR^{15}SO_2R^{15}$, SO_2NH_2, SO_2NHR^{15}, $SO_2N(R^{15})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{15}$, $C(N)N(R^{15})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{15} is independently R^{16}, R^{17}, R^{18}, or R^{19};

R^{16} is aryl;

R^{17} is heteroaryl;

R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{19} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{20}, OR^{20}, SR^{20}, $S(O)R^{20}$, SO_2R^{20}, $C(O)R^{20}$, $CO(O)R^{20}$, $OC(O)R^{20}$, $OC(O)OR^{20}$, NH_2, NHR^{20}, $N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{20}C(O)R^{20}$, $NHS(O)_2R^{20}$, $NR^{20}S(O)_2R^{20}$, $NHC(O)OR^{20}$, $NR^{20}C(O)OR^{20}$, $NHC(O)NH_2$, $NHC(O)NHR^{20}$, $NHC(O)N(R^{20})_2$, $NR^{20}C(O)NHR^{20}$, $NR^{20}C(O)N(R^{20})_2$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, C(O)NHOH, $C(O)NHOR^{20}$, $C(O)NHSO_2R^{20}$, $C(O)NR^{20}SO_2R^{20}$, SO_2NH_2, SO_2NHR^{20}, $SO_2N(R^{20})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{20}$, $C(N)N(R^{20})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I substituents;

each R^{20} is independently alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

wherein the moieties represented by R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, and R^{18} are unsubstituted or substituted with one or two or three or four of independently selected R^{21}, OR^{21}, SR^{21}, $S(O)R^{21}$, SO_2R^{21}, $C(O)R^{21}$, $CO(O)R^{21}$, $OC(O)R^{21}$, $OC(O)OR^{21}$, NH_2,

NHR^{21}, $N(R^{21})_2$, $NHC(O)R^{21}$, $NR^{21}C(O)R^{21}$, $NHS(O)_2R^{21}$, $NR^{21}S(O)_2R^{21}$, $NHC(O)OR^{21}$, $NR^{21}C(O)OR^{21}$, $NHC(O)NH_2$, $NHC(O)NHR^{21}$, $NHC(O)N(R^{21})_2$, $NR^{21}C(O)NHR^{21}$, $NR^{21}C(O)N(R^{21})_2$, $C(O)NH_2$, $C(O)NHR^{21}$, $C(O)N(R^{21})_2$, C(O)NHOH, $C(O)NHOR^{21}$, $C(O)NHSO_2R^{21}$, $C(O)NR^{21}SO_2R^{21}$, SO_2NH_2, SO_2NHR^{21}, $SO_2N(R^{21})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{21}$, $C(N)N(R^{21})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{21} is independently R^{22}, R^{23}, R^{24}, or R^{25};

R^{22} is aryl;

R^{23} is heteroaryl;

R^{24} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{25} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{26}, OR^{26}, SR^{26}, $S(O)R^{26}$, SO_2R^{26}, $C(O)R^{26}$, $CO(O)R^{26}$, $OC(O)R^{26}$, $OC(O)OR^{26}$, NH_2, NHR^{26}, $N(R^{26})_2$, $NHC(O)R^{26}$, $NR^{26}C(O)R^{26}$, $NHS(O)_2R^{26}$, $NR^{26}S(O)_2R^{26}$, $NHC(O)OR^{26}$, $NR^{26}C(O)OR^{26}$, $NHC(O)NH_2$, $NHC(O)NHR^{26}$, $NHC(O)N(R^{26})_2$, $NR^{26}C(O)NHR^{26}$, $NR^{26}C(O)N(R^{26})_2$, $C(O)NH_2$, $C(O)NHR^{26}$, $C(O)N(R^{26})_2$, C(O)NHOH, $C(O)NHOR^{26}$, $C(O)NHSO_2R^{26}$, $C(O)NR^{26}SO_2R^{26}$, SO_2NH_2, SO_2NHR^{26}, $SO_2N(R^{26})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{26}$, $C(N)N(R^{26})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{26} is independently alkyl, alkenyl, alkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; and

the moieties represented by R^{22}, R^{23}, and R^{24} are unsubstituted or substituted with one or two or three or four of independently selected NH_2, $C(O)NH_2$, C(O)NHOH, SO_2NH_2, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I.

In another embodiment of formula (II),

Y is aryl or heteroaryl; wherein the aryl or heteroaryl is substituted with $NR^7SO_2R^8$; wherein the aryl or heteroaryl is optionally further substituted with one or more R^9;

R^7 is hydrogen or alkyl;

R^8 is alkyl;

R^2, R^3, and R^9 are independently selected from the group consisting of hydrogen, R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH;

each R^{10} is independently R^{11}, R^{13}, or R^{14};

R^{11} is aryl;

R^{13} is cycloalkyl, or heterocycloalkyl;

R^{14} is alkyl, which is unsubstituted or substituted with R^{15}, OR^{15}, $N(R^{15})_2$, or CN;

each R^{15} is independently R^{17}, R^{18}, or R^{19};

R^{17} is heteroaryl;

R^{18} is cycloalkyl, or heterocycloalkyl;

R^{19} is alkyl;

wherein the moieties represented by R^{11}, R^{13} and R^{18} are unsubstituted or substituted with one or two or three or four of independently selected R^{21}, OR^{21}, $CO(O)R^{21}$;

each R^{21} is independently R^{25};

R^{25} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with R^{26}; and

each R^{26} is aryl.

In one embodiment of formula (II), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In one embodiment of formula (II), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In another embodiment of formula (II), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In another embodiment of formula (II), Y is

pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl.

In one embodiment of formula (II), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2 is hydrogen; and R^3 is R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH. In one embodiment of formula (II), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2 is hydrogen; and R^3 is R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH. In another embodiment of formula (II), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2 is hydrogen; and R^3 is R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH. In another embodiment of formula (II), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2 is hydrogen; and R^3 is R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH.

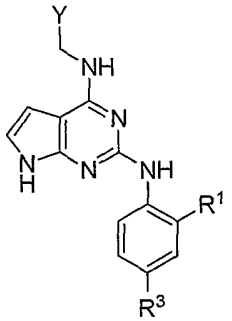
In one embodiment of formula (II), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2 is hydrogen; and R^3 is $C(O)NHR^{10}$. In one embodiment of formula (II), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2 is hydrogen; and R^3 is $C(O)NHR^{10}$. In another embodiment of formula (II), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2 is hydrogen; and R^3 is $C(O)NHR^{10}$. In another embodiment of formula (II), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^2 is hydrogen; and R^3 is $C(O)NHR^{10}$.

In one embodiment of formula (II), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^3 is hydrogen; and R^2 is R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH. In one embodiment of formula (II), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^3 is hydrogen; and R^2 is R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH. In another embodiment of formula (II), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^3 is hydrogen; and R^2 is R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH. In another embodiment

of formula (II), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^3 is hydrogen; and R^2 is R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH.

In one embodiment of formula (II), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^3 is hydrogen; and R^2 is $C(O)NHR^{10}$. In one embodiment of formula (II), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^3 is hydrogen; and R^2 is $C(O)NHR^{10}$. In another embodiment of formula (II), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^3 is hydrogen; and R^2 is $C(O)NHR^{10}$. In another embodiment of formula (II), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^3 is hydrogen; and R^2 is $C(O)NHR^{10}$.

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as inhibitors of focal adhesion kinase (FAK) and anaphastic lymphoma kinase (ALK), the compounds having Formula (III)



(III);

wherein

Y is aryl or heteroaryl; wherein the aryl or heteroaryl is substituted with $NR^7SO_2R^8$; wherein the aryl or heteroaryl is optionally further substituted with one or more R^9;

R^7 is hydrogen or alkyl;

R^8 is alkyl;

R^1, R^3, and R^9 are independently selected from the group consisting of hydrogen, R^{10}, OR^{10}, SR^{10}, $S(O)R^{10}$, SO_2R^{10}, $C(O)R^{10}$, $CO(O)R^{10}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, NH_2, NHR^{10}, $N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHS(O)_2R^{10}$, $NR^{10}S(O)_2R^{10}$, $NHC(O)OR^{10}$, $NR^{10}C(O)OR^{10}$, $NHC(O)NH_2$, $NHC(O)NHR^{10}$, $NHC(O)N(R^{10})_2$, $NR^{10}C(O)NHR^{10}$, $NR^{10}C(O)N(R^{10})_2$, $C(O)NH_2$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, C(O)NHOH, $C(O)NHOR^{10}$, $C(O)NHSO_2R^{10}$, $C(O)NR^{10}SO_2R^{10}$, SO_2NH_2, SO_2NHR^{10}, $SO_2N(R^{10})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{10}$, $C(N)N(R^{10})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{10} is independently R^{11}, R^{12}, R^{13}, or R^{14};

R^{11} is aryl;

R^{12} is heteroaryl;

R^{13} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{14} is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{15}, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $C(O)R^{15}$, $CO(O)R^{15}$, $OC(O)R^{15}$, $OC(O)OR^{15}$, NH_2, NHR^{15}, $N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHS(O)_2R^{15}$, $NR^{15}S(O)_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)NHR^{15}$, $NR^{15}C(O)N(R^{15})_2$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, C(O)NHOH, $C(O)NHOR^{15}$, $C(O)NHSO_2R^{15}$, $C(O)NR^{15}SO_2R^{15}$, SO_2NH_2, SO_2NHR^{15}, $SO_2N(R^{15})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{15}$, $C(N)N(R^{15})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{15} is independently R^{16}, R^{17}, R^{18}, or R^{19};

R^{16} is aryl;

R^{17} is heteroaryl;

R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{19} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{20}, OR^{20}, SR^{20}, $S(O)R^{20}$, SO_2R^{20},

$C(O)R^{20}$, $CO(O)R^{20}$, $OC(O)R^{20}$, $OC(O)OR^{20}$, NH_2, NHR^{20}, $N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{20}C(O)R^{20}$, $NHS(O)_2R^{20}$, $NR^{20}S(O)_2R^{20}$, $NHC(O)OR^{20}$, $NR^{20}C(O)OR^{20}$, $NHC(O)NH_2$, $NHC(O)NHR^{20}$, $NHC(O)N(R^{20})_2$, $NR^{20}C(O)NHR^{20}$, $NR^{20}C(O)N(R^{20})_2$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, C(O)NHOH, $C(O)NHOR^{20}$, $C(O)NHSO_2R^{20}$, $C(O)NR^{20}SO_2R^{20}$, SO_2NH_2, SO_2NHR^{20}, $SO_2N(R^{20})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{20}$, $C(N)N(R^{20})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I substituents;

each R^{20} is independently alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

wherein the moieties represented by R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, and R^{18} are unsubstituted or substituted with one or two or three or four of independently selected R^{21}, OR^{21}, SR^{21}, $S(O)R^{21}$, SO_2R^{21}, $C(O)R^{21}$, $CO(O)R^{21}$, $OC(O)R^{21}$, $OC(O)OR^{21}$, NH_2, NHR^{21}, $N(R^{21})_2$, $NHC(O)R^{21}$, $NR^{21}C(O)R^{21}$, $NHS(O)_2R^{21}$, $NR^{21}S(O)_2R^{21}$, $NHC(O)OR^{21}$, $NR^{21}C(O)OR^{21}$, $NHC(O)NH_2$, $NHC(O)NHR^{21}$, $NHC(O)N(R^{21})_2$, $NR^{21}C(O)NHR^{21}$, $NR^{21}C(O)N(R^{21})_2$, $C(O)NH_2$, $C(O)NHR^{21}$, $C(O)N(R^{21})_2$, C(O)NHOH, $C(O)NHOR^{21}$, $C(O)NHSO_2R^{21}$, $C(O)NR^{21}SO_2R^{21}$, SO_2NH_2, SO_2NHR^{21}, $SO_2N(R^{21})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{21}$, $C(N)N(R^{21})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{21} is independently R^{22}, R^{23}, R^{24}, or R^{25};

R^{22} is aryl;

R^{23} is heteroaryl;

R^{24} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{25} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{26}, OR^{26}, SR^{26}, $S(O)R^{26}$, SO_2R^{26}, $C(O)R^{26}$, $CO(O)R^{26}$, $OC(O)R^{26}$, $OC(O)OR^{26}$, NH_2, NHR^{26}, $N(R^{26})_2$, $NHC(O)R^{26}$, $NR^{26}C(O)R^{26}$, $NHS(O)_2R^{26}$, $NR^{26}S(O)_2R^{26}$, $NHC(O)OR^{26}$, $NR^{26}C(O)OR^{26}$, $NHC(O)NH_2$, $NHC(O)NHR^{26}$, $NHC(O)N(R^{26})_2$, $NR^{26}C(O)NHR^{26}$, $NR^{26}C(O)N(R^{26})_2$,

$C(O)NH_2$, $C(O)NHR^{26}$, $C(O)N(R^{26})_2$, C(O)NHOH, $C(O)NHOR^{26}$, $C(O)NHSO_2R^{26}$, $C(O)NR^{26}SO_2R^{26}$, SO_2NH_2, SO_2NHR^{26}, $SO_2N(R^{26})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{26}$, $C(N)N(R^{26})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{26} is independently alkyl, alkenyl, alkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; and

the moieties represented by R^{22}, R^{23}, and R^{24} are unsubstituted or substituted with one or two or three or four of independently selected NH_2, $C(O)NH_2$, C(O)NHOH, SO_2NH_2, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I.

In another embodiment of formula (III),

Y is aryl or heteroaryl; wherein the aryl or heteroaryl is substituted with $NR^7SO_2R^8$; wherein the aryl or heteroaryl is optionally further substituted with one or more R^9;

R^7 is hydrogen or alkyl;

R^8 is alkyl;

R^1, R^3, and R^9 are independently selected from the group consisting of hydrogen, R^{10}, OR^{10}, $C(O)R^{10}$, NHR^{10}, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, or C(O)OH;

each R^{10} is independently R^{11}, R^{13}, or R^{14};

R^{11} is aryl;

R^{13} is cycloalkyl, or heterocycloalkyl;

R^{14} is alkyl, which is unsubstituted or substituted with R^{15}, OR^{15}, $N(R^{15})_2$, or CN;

each R^{15} is independently R^{17}, R^{18}, or R^{19};

R^{17} is heteroaryl;

R^{18} is cycloalkyl, or heterocycloalkyl;

R^{19} is alkyl;

wherein the moieties represented by R^{11}, R^{13} and R^{18} are unsubstituted or substituted with one or two or three or four of independently selected R^{21}, OR^{21}, $CO(O)R^{21}$;

each R^{21} is independently R^{25};

R^{25} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with R^{26}; and

each R^{26} is aryl.

In one embodiment of formula (III), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In one embodiment of formula (III), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In another embodiment of formula (III), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl. In another embodiment of formula (III), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; and R^8 is alkyl.

In one embodiment of formula (III), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is R^{10} or $C(O)NHR^{10}$. In one embodiment of formula (III), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is R^{10} or $C(O)NHR^{10}$. In another embodiment of formula (III), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is R^{10} or $C(O)NHR^{10}$. In another embodiment of formula (III), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is R^{10} or $C(O)NHR^{10}$.

In one embodiment of formula (III), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is R^{10}. In one embodiment of formula (III), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is R^{10}. In another embodiment of formula (III), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is R^{10}. In another embodiment of formula (III), Y is pyridinyl;

wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is R^{10}.

In one embodiment of formula (III), Y is aryl; wherein the aryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is $C(O)NHR^{10}$. In one embodiment of formula (III), Y is phenyl; wherein the phenyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is $C(O)NHR^{10}$. In another embodiment of formula (III), Y is heteroaryl; wherein the heteroaryl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is $C(O)NHR^{10}$. In another embodiment of formula (III), Y is pyridinyl; wherein the pyridinyl is substituted with $NR^7SO_2R^8$; R^7 is alkyl; R^8 is alkyl; R^1 is OR^{10}; and R^3 is $C(O)NHR^{10}$.

Pharmaceutical Compositions, Combination Therapies, Methods of Treatment, and Administration

Another embodiment comprises pharmaceutical compositions comprising a compound having Formula (I) and an excipient.

Still another embodiment comprises methods of treating cancer in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating diseases during which focal adhesion kinase is expressed, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I).

Still another embodiment pertains to methods of treating disease in a patient during which focal adhesion kinase and anaphastic lymphoma kinase (ALK) are expressed, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said compositions

comprising an excipient and a therapeutically effective amount of the compound having Formula (I).

Still another embodiment pertains to methods of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating diseases during which focal adhesion kinase and anaphastic lymphoma kinase (ALK) are expressed, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating disease in a patient during which focal adhesion kinase and anaphastic lymphoma kinase (ALK) are expressed, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to compositions for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic

leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Metabolites of compounds having Formula (I), produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases associated with focal adhesion kinase and anaphastic lymphoma kinase (ALK).

Certain precursor compounds which may be metabolized in vitro or in vivo to form compounds having Formula (I) may also have utility for treating diseases associated with expression of focal adhesion kinase and anaphastic lymphoma kinase (ALK).

Compounds having Formula (I) may exist as acid addition salts, basic addition salts or zwitterions. Salts of the compounds are prepared during isolation or following purification of the compounds. Acid addition salts of the compounds are those derived from the reaction of the compounds with an acid. For example, the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsufonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, para-toluenesulfonate, and undecanoate salts of the compounds and prodrugs thereof are contemplated as being embraced by this invention. Basic addition salts of the compounds are those derived from the reaction of the compounds with the hydroxide, carbonate or bicarbonate of cations such as lithium, sodium, potassium, calcium, and magnesium.

The compounds having Formula (I) may be administered, for example, bucally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperitoneally intrasternally, intravenously, subcutaneously), rectally, topically, transdermally or vaginally.

Therapeutically effective amounts of compounds having Formula (I) depend on the recipient of the treatment, the disorder being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered. The amount of a compound of this invention having Formula (I) used to make a composition to be administered daily to a patient in a single dose or in divided doses is from about 0.03 to about 200 mg/kg body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

Compounds having Formula (I) may be administered with or without an excipient. Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

Excipients for preparation of compositions comprising a compound having Formula (I) to be administered orally in solid dosage form include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and

mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered ophthalmically or orally in liquid dosage forms include, for example, 1,3-butylene glycol, castor oil, corn oil, cottonseed oil, ethanol, fatty acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered osmotically include, for example, chlorofluorohydrocarbons, ethanol, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered parenterally include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered rectally or vaginally include, for example, cocoa butter, polyethylene glycol, wax and mixtures thereof.

Compounds having Formula (I) are expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNA's, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteosome

inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, etinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiqutin ligase inhibitors, and the like, and in combination with one or more of these agents .

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B.

SiRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH_3-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/ or the 3'-ends of a given strand.

Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy chain DVD

polypeptide, a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, CLORETAZINE® (laromustine, VNP 40101M), cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, TREANDA® (bendamustine), treosulfan, rofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

Antimetabolites include ALIMTA® (pemetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA® (capecitabine), carmofur, LEUSTAT® (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-β -D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethnylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR® (gemcitabine), hydroxyurea, ALKERAN®(melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

Antivirals include ritonavir, hydroxychloroquine and the like.

Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, Aurora A-specific kinase inhibitors, Aurora B-specific kinase inhibitors and pan-Aurora kinase inhibitors and the like.

Bcl-2 protein inhibitors include AT-101 ((-)gossypol), GENASENSE® (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) (ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263), GX-070 (obatoclax) and the like.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (imatinib) and the like.

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

COX-2 inhibitors include ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX® (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX® (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl-1H-pyrrole), MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) and the like.

EGFR inhibitors include ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX® (cetuximab), HR3, IgA antibodies, IRESSA® (gefitinib), TARCEVA® (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB® (lapatinib) and the like.

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), HERCEPTIN® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (2C4, petuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecfic antibodies, mAB AR-209, mAB 2B-1 and the like.

Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB® (human

recombinant antibody to HSP-90), NCS-683664, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

Inhibitors of inhibitors of apoptosis proteins include HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

Antibody drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, SGN-75 and the like

Activators of death receptor pathway include TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR4 and DR5) such as Apomab, conatumumab, ETR2-ST01, GDC0145, (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

Kinesin inhibitors include Eg5 inhibitors such as AZD4877, ARRY-520; CENPE inhibitors such as GSK923295A and the like.

JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCB018424 and the like.

MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, Torin 1 and the like.

Non-steroidal anti-inflammatory drugs include AMIGESIC® (salsalate), DOLOBID® (diflunisal), MOTRIN® (ibuprofen), ORUDIS® (ketoprofen), RELAFEN® (nabumetone), FELDENE® (piroxicam), ibuprofen cream, ALEVE® (naproxen) and NAPROSYN® (naproxen), VOLTAREN® (diclofenac), INDOCIN® (indomethacin), CLINORIL® (sulindac), TOLECTIN® (tolmetin), LODINE® (etodolac), TORADOL® (ketorolac), DAYPRO® (oxaprozin) and the like.

PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

Platinum chemotherapeutics include cisplatin, ELOXATIN® (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN® (carboplatin), satraplatin, picoplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

Phosphoinositide-3 kinase (PI3K) inhibitors include wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

VEGFR inhibitors include AVASTIN® (bevacizumab), ABT-869, AEE-788, ANGIOZYME™ (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, CO.) and Chiron, (Emeryville, CA)) , axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pegaptamib), NEXAVAR® (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), VEGF trap, ZACTIMA™ (vandetanib, ZD-6474) and the like.

Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE® (bleomycin), daunorubicin, CAELYX® or MYOCET® (liposomal doxorubicin), elsamitrucin, epirbucin, glarbuicin, ZAVEDOS® (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR® (valrubicin), zinostatin and the like.

Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR® (irinotecan hydrochloride), camptothecin, CARDIOXANE® (dexrazoxine), diflomotecan, edotecarin, ELLENCE® or PHARMORUBICIN® (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbucin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

Antibodies include AVASTIN® (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzimab, CD20 antibodies types I and II and the like.

Hormonal therapies include ARIMIDEX® (anastrozole), AROMASIN® (exemestane), arzoxifene, CASODEX® (bicalutamide), CETROTIDE® (cetrorelix),

degarelix, deslorelin, DESOPAN® (trilostane), dexamethasone, DROGENIL® (flutamide), EVISTA® (raloxifene), AFEMA™ (fadrozole), FARESTON® (toremifene), FASLODEX® (fulvestrant), FEMARA® (letrozole), formestane, glucocorticoids, HECTOROL® (doxercalciferol), RENAGEL® (sevelamer carbonate), lasofoxifene, leuprolide acetate, MEGACE® (megesterol), MIFEPREX® (mifepristone), NILANDRON™ (nilutamide), NOLVADEX® (tamoxifen citrate), PLENAXIS™ (abarelix), prednisone, PROPECIA® (finasteride), rilostane, SUPREFACT® (buserelin), TRELSTAR® (luteinizing hormone releasing hormone (LHRH)), VANTAS® (Histrelin implant), VETORYL® (trilostane or modrastane), ZOLADEX® (fosrelin, goserelin) and the like.

Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN® (aliretinoin), ATRAGEN® (liposomal tretinoin), TARGRETIN® (bexarotene), LGD-1550 and the like.

PARP inhibitors include ABT-888, olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

Proteasome inhibitors include VELCADE® (bortezomib), MG132, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE® (interferon gamma-1b) or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE®,(IFN-α), BAM-002 (oxidized glutathione), BEROMUN® (tasonermin), BEXXAR® (tositumomab), CAMPATH® (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE® (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab, molgramostim, MYLOTARG™ (gemtuzumab ozogamicin), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pemtumomab (Y-muHMFG1), PROVENGE® (sipuleucel-T), sargaramostim, sizofilan, teceleukin, THERACYS® (Bacillus Calmette-Guerin),

ubenimex, VIRULIZIN® (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodecaoxide (TCDO)), PROLEUKIN® (aldesleukin), ZADAXIN® (thymalfasin), ZENAPAX® (daclizumab), ZEVALIN® (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA® (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR® (gemcitabine), TOMUDEX® (ratitrexed), TROXATYL™ (triacetyluridine troxacitabine) and the like.

Purine analogs include LANVIS® (thioguanine) and PURI-NETHOL® (mercaptopurine).

Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilone, XRP-9881 (larotaxel), vinflunine, ZK-EPO (synthetic epothilone) and the like.

Ubiqutin ligase inhibitors include MDM2 inhibitors, such as nutlins, NEDD8 inhibitors such as MLN4924 and the like.

Compounds of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy and the like.

Additionally, compounds having Formula (I) may be combined with other chemotherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN® (Ad5CMV-p53 vaccine), ALTOCOR® or MEVACOR® (lovastatin), AMPLIGEN® (poly I:poly C12U, a synthetic RNA), APTOSYN® (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), AVAGE® (tazarotene), AVE-8062 (combreastatin derivative) BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CEAVAC® (cancer vaccine), CELEUK® (celmoleukin),

CEPLENE® (histamine dihydrochloride), CERVARIX® (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CYPAT™ (cyproterone acetate), combrestatin A4P, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor) or TransMID-107R™ (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, EVIZON™ (squalamine lactate), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906 (epithilone B), GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), GASTRIMMUNE®, GENASENSE®, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon-α, interferon-γ, JUNOVAN™ or MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT®(AE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), ONCOVAX® (IL-2 Vaccine), ORATHECIN™ (rubitecan), OSIDEM® (antibody-based cell drug), OVAREX® MAb (murine monoclonal antibody), paclitaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REVLIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN® (bexarotene), TAXOPREXIN® (DHA-paclitaxel), TELCYTA® (canfosfamide, TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFERADE™ (adenovector: DNA carrier containing the gene for tumor necrosis factor-α), TRACLEER® or ZAVESCA® (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX® (arsenic trioxide), VIRULIZIN®, ukrain (derivative of

alkaloids from the greater celandine plant), vitaxin (anti-alphavbeta3 antibody), XCYTRIN® (motexafin gadolinium), XINLAY™ (atrasentan), XYOTAX™ (paclitaxel poliglumex), YONDELIS® (trabectedin), ZD-6126, ZINECARD® (dexrazoxane), ZOMETA® (zolendronic acid), zorubicin and the like.

Data

Procedure used to determine FAK Activity

Focal adhesion kinase (recombinant human FAK fragment, amino acids 411-686; Millipore cat. no. 14-720) activity was measured using the HTRF assay format (Cisbio HTRF KinEASE-TK kit, cat. no. 62K0PEB). The assay was run in a 20 ul volume, in 384 well plates (Corning 384-well, white, low-volume NSB plate, cat. no. 3673). Reaction conditions consisted of 4 nM FAK, 50 μM ATP, and 0.2 μM TK substrate-biotin in a buffer containing 50 mM Tris pH 7.5, 10 mM magnesium chloride, 2 mM manganese chloride, 2.5 mM dithiothreitol, 100 uM sodium orthovanadate, and 0.01 percent bovine serum albumin (BSA). Compound IC50s were measured in 8 point dilution curves using 3-fold dilutions beginning at a maximum compound concentration of 10 or 1 uM, and resulting in a final DMSO concentration in the assay of no more than 5 percent. The reaction was carried out for 1 hour at room temperature, and terminated with 10 μl/well Stop Buffer, consisting of 20 mM HEPES, 240 mM potassium fluoride, 0.05 percent BSA, 0.005 percent Tween 20, 0.025 uM TK-StreptXL665, and 1xTK-Ab-Cryptate. After a 1.25 hour incubation, the fluorescence was measured on a Perkin Elmer Envision plate reader at 320 nm excitation/620 nm and 665 nm emissions. The ratio of 665/620 was used to calculate specific signal for each well. IC50s were calculated using the standard 4-parameter curve fit model. Results are shown in Table 1.

Table 1

FAK Activity

Example	HTRF_FAK Human - IC50 (μM)	Example	HTRF_FAK Human - IC50 (μM)
1	0.0446	45	0.436
2	0.0496	46	0.453

3	0.0506	47	0.466
4	0.057	48	0.471
5	0.0581	49	0.472
6	0.0599	50	0.534
7	0.0609	51	0.559
8	0.0645	52	0.567
9	0.0704	53	0.574
10	0.0723	54	0.579
11	0.0764	55	0.62
12	0.0782	56	0.717
13	0.0798	57	0.718
14	0.151	58	0.744
15	0.0901	59	0.985
16	0.0912	60	1.1
17	0.0934	61	1.53
18	0.0988	62	1.74
19	0.107	63	1.26
20	0.108	64	2.18
21	0.115	65	2.28
22	0.137	66	1.24
23	0.159	67	5.79
24	0.164	68	1.56
25	0.175	69	12.65
26	0.183	70	3.83

27	0.19	71	5.92
28	0.192	72	14.23
29	0.209	73	32.31
30	0.213	74	3.44
31	0.231	75	0.237
32	0.252	76	8.23
33	0.26	77	0.363
34	0.263	78	0.392
35	0.269	79	0.567
36	0.275	80	0.939
37	0.281	81	1.07
38	0.284	82	1.1
39	0.292	83	1.23
40	0.305	84	1.37
41	0.386	85	1.82
42	0.39	86	2.5
43	0.4	87	3.29
44	0.421	88	5.61

Procedure used to determine ALK Activity

Assays were performed in a total volume of 40 μL in black 384-well plates using 3 nM ALK (Millipore) and 50 mM ATP in assay buffer (50 mM Hepes/NaOH, pH 7.4, 10 mM $MgCl_2$,2 mM $MnCl_2$,0.01% BSA,100 μM sodium orthovanadate, with 1 mM DTT added before use). Compounds are diluted in 10% DMSO/buffer and the final concentration of DMSO was 2.5%. The reaction was started initialized by addition of substrate (0.5 μM biotin LCK-peptide, biotin-Ahx-GAEEEIYAAFFA-COOH).

After 1 hour, the wells are quenched by addition of a 50 μL solution of streptavidin-allophycocyanin (SA-APC) and Europium-cryptate PT66 monoclonal antibody in 40 mM Hepes/NaOH, pH 7.4, 480 mM potassium fluoride, 66 mM EDTA with 0.1% BSA and 0.008% Tween-20. Plates are read between 1 and 3 hours after addition of the detection reagents. IC50s were calculated from the plate data using a sigmoidal fit of the concentration/inhibition response curves with the Assay Explorer software. Results are shown in Table 2.

Table 2

ALK Activity

Example	HTRF_ALK Human - IC50 (μM)	Example	HTRF_ALK Human - IC50 (μM)
1	3.2149	45	3.1183
2	3.7447	46	10.0000
3	2.4295	47	6.6251
4	1.8350	48	7.2396
5	nd	49	6.8016
6	0.9151	50	9.5603
7	4.5287	51	8.0179
8	nd	52	4.0886
9	nd	53	4.5628
10	4.3661	54	1.8771
11	nd	55	6.2478
12	3.7521	56	10.0000
13	1.4249	57	6.0630
14	nd	58	6.9988
15	nd	59	7.1164

16	9.1940	60	nd
17	5.3743	61	5.6471
18	5.2113	62	6.0269
19	nd	63	6.5736
20	1.7169	64	nd
21	3.4476	65	1.8936
22	nd	66	10.0000
23	5.6936	67	nd
24	7.4022	68	10.0000
25	5.5495	69	nd
26	3.7666	70	10.0000
27	10.0000	71	10.0000
28	5.7700	72	nd
29	6.6056	73	10.0000
30	5.7592	74	nd
31	5.1025	75	6.3575
32	1.2252	76	1.5982
33	6.3872	77	10.0000
34	5.9329	78	10.0000
35	nd	79	nd
36	3.6148	80	10.0000
37	2.2780	81	10.0000
38	7.3199	82	10.0000
39	nd	83	10.0000

40	nd	84	10.0000
41	8.7575	85	nd
42	4.5047	86	10.0000
43	3.6530	87	6.8617
44	5.7766	88	10.0000

nd = not determined

Therefore, compounds of the present invention assessed by the above-described assay were found to have FAK and ALK inhibiting activity.

Table 3

FAK comparator data

Example	HTRF__FAK Human - IC50 (μM)
8	0.0645
11	0.0764
14	0.151
19	0.107
61	1.53
76	8.23

The data in table 3 shows the necessity of $NR^7SO_2R^8$, wherein R^7 and R^8 are alkyl, on FAK activity.

Involvement of FAK in cancer is described in Sieg et al, *J. Cell Science*, **1999**, 112, 2677-2691; Richardson A. and Parsons T., *Cell*, **1997**, 97, 221-231; and Xu et al, *Cell Growth Differ*. **1996**, 4, 413-418.

Involvement of ALK in cancer is described in Gascoyne et al, *Blood*, **2003**, 102, 2568-2573; Griffin et al, *Cancer Res.*, **1999**, 59, 2776-2780; and Lawrence et al, Am. *J. Pathol.*, **2000**, 157, 377-384).

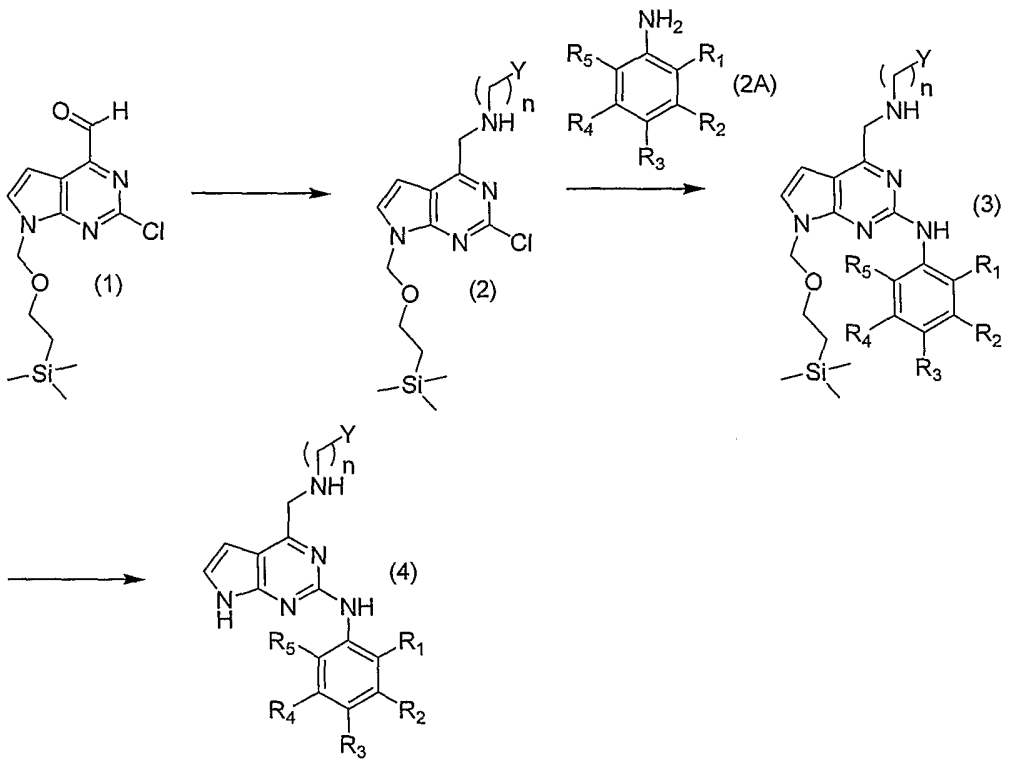
Schemes and Experimentals

The following abbreviations have the meanings indicated. ADDP means 1,1'-(azodicarbonyl)dipiperidine; AD-mix-β means a mixture of $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, and K_2SO_4; 9-BBN means 9-borabicyclo(3.3.1)nonane; Boc means tert-butoxycarbonyl; $(DHQD)_2PHAL$ means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL means diisobutylaluminum hydride; DIEA means diisopropylethylamine; DMAP means N,N-dimethylaminopyridine; DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means dimethylsulfoxide; dppb means 1,4-bis(diphenylphosphino)-butane; dppe means 1,2-bis(diphenylphosphino)ethane; dppf means 1,1'-bis(diphenylphosphino)ferrocene; dppm means 1,1-bis(diphenylphosphino)methane; EDAC·HCl means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Fmoc means fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N'N'N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; MP-BH_3 means macroporous triethylammonium methylpolystyrene cyanoborohydride; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP means N-methylpyrrolidine; PPh_3 means triphenylphosphine.

The following schemes are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. Compounds of this invention may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

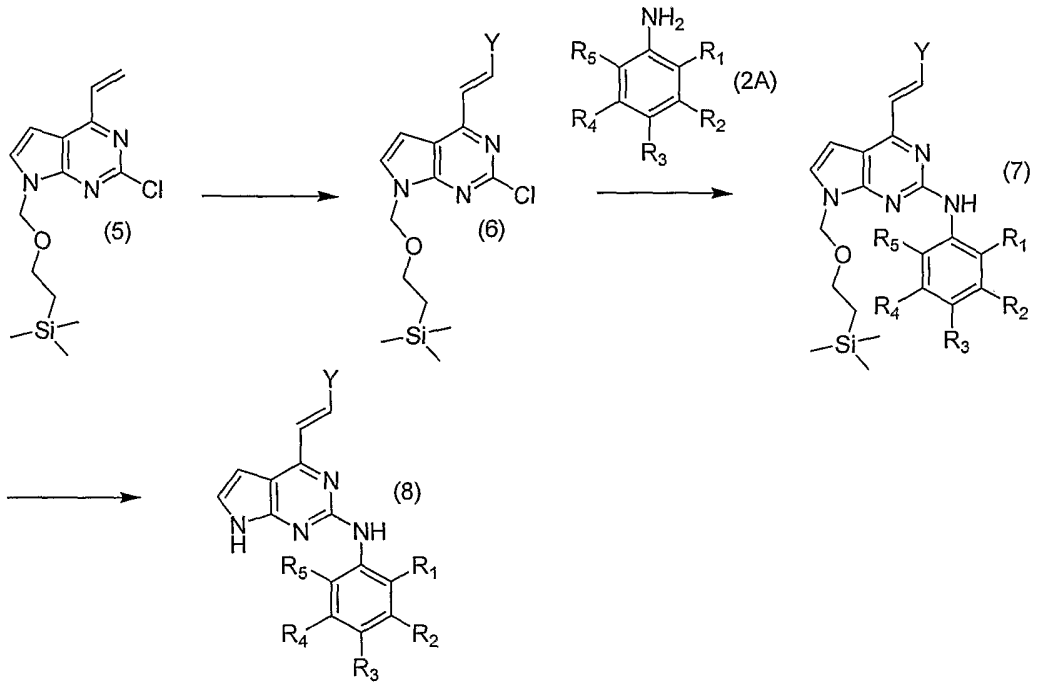
Schemes

Scheme 1



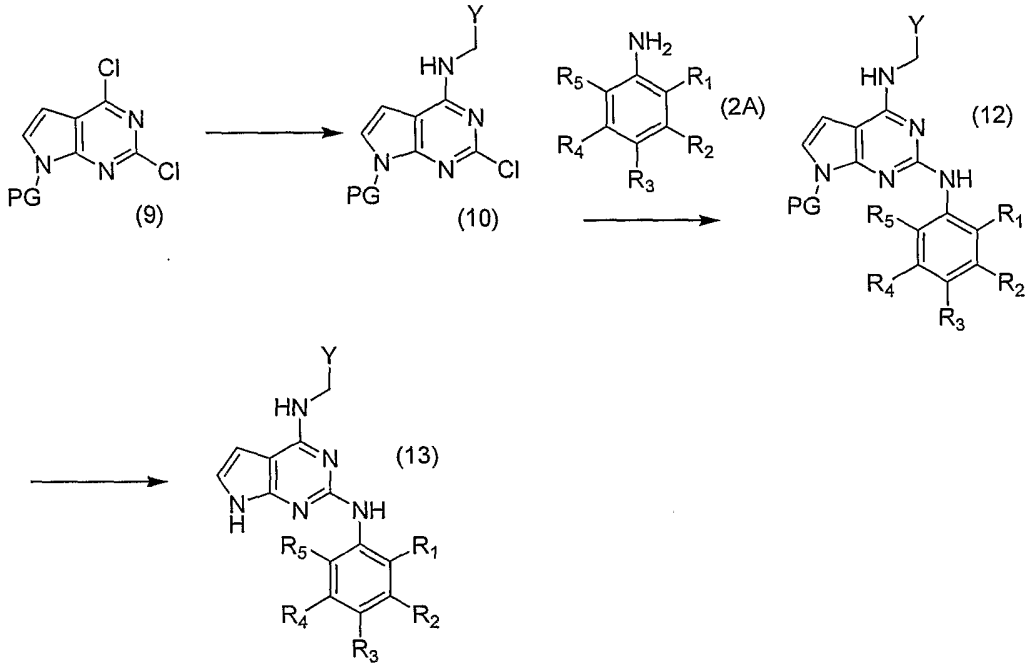
As shown in Scheme 1, compounds of formula (1) can be reacted with a compound of formula $NH_2(CH_2)_nY$, wherein n is 0 or 1 and Y is as described herein, and a reducing agent such as but not limited to sodium cyanoborohydride ($NaBH_3CN$) and sodium triacetoxyborohydride ($NaBH(OCOCH_3)_3$ to provide a compound of formula (2). Acetic acid may be used to facilitate the reaction, which is typically performed at room temperature in a solvent such as but not limited to dichloromethane, methanol, tetrahydrofuran, and the like, or mixtures thereof. Compounds of formula (3), wherein R^1, R^2, R^3, R^4, and R^5 are as described herein, can be prepared by reacting a compound of formula (2) with a compound of formula (2A), using Buchwald-Hartwig coupling conditions described herein, known to those skilled in the art, and readily available in the literature. Compounds of formula (3) can be reacted with tetrabutyl ammonium fluoride and ethylenediamine to provide compounds of formula (4), which are representative of the compounds of this invention. The reaction is typically performed in a solvent such as but not limited to tetrahydrofuran at an elevated temperature.

Scheme 2



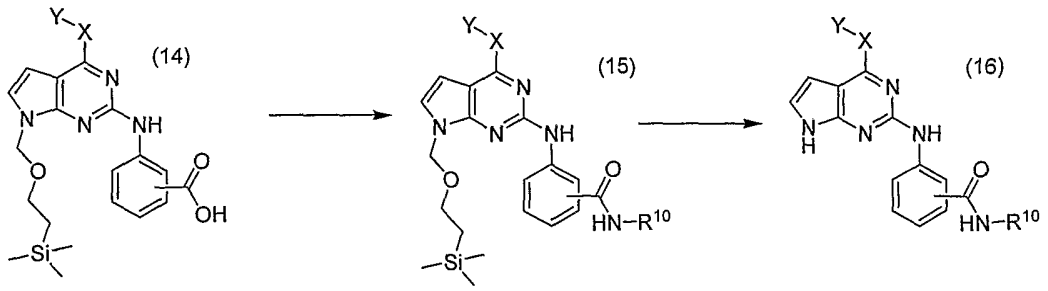
Compounds of formula (5) can be converted to compounds of formula (6) wherein Y is as described herein, using Heck coupling conditions described herein, known to those skilled in the art, and readily available in the literature. Compounds of formula (7), wherein R^1, R^2, R^3, R^4, and R^5 are as described herein, can be prepared by reacting a compound of formula (6) with a compound of formula (2A), using Buchwald-Hartwig coupling conditions described herein, known to those skilled in the art, and readily available in the literature. Compounds of formula (7) can be reacted with tetrabutyl ammonium fluoride and ethylenediamine to provide compounds of formula (8), which are representative of the compounds of this invention. The reaction is typically performed in a solvent such as but not limited to tetrahydrofuran at an elevated temperature.

Scheme 3



Compounds of formula (9), wherein PG is a suitable NH protecting group as described herein, can be reacted with compounds of formula Y-CH_2NH_2 in the presence of a base such as but not limited to *N,N*-diisopropylethylamine to provide compounds of formula (11). The reaction is typically performed in a solvent such as but not limited to 1,4-dioxane at an elevated temperature. Compounds of formula (12), wherein R^1, R^2, R^3, R^4, and R^5 are as described herein, can be prepared by reacting a compound of formula (10) with a compound of formula (2A), using Buchwald-Hartwig coupling conditions described herein, known to those skilled in the art, and readily available in the literature. Removal of the protecting group, PG, from compounds of formula (12) using methods known to those skilled in the art, and readily available in the literature will provide compounds of formula (13) which are representative of the compounds of this invention.

Scheme 4



Compounds of formula (15), wherein X, Y, and R^{10} are as described herein, can be prepared by coupling compounds of formula (14) with compounds of formula NH_2R^{10}, using conditions described herein, known to those skilled in the art, and readily available in the literature. Compounds of formula (16), which are representative of the compounds of this invention, can be prepared by reacting compounds of formula (15) with tetrabutyl ammonium fluoride and ethylenediamine. The reaction is typically performed in a solvent such as but not limited to tetrahydrofuran at an elevated temperature.

Examples

The following examples are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. The exemplified compounds were named using ACD/ChemSketch Version 5.06 (05 June 2001, Advanced Chemistry Development Inc., Toronto, Ontario), or ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA). Intermediates were named using ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA).

Example 1

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(3-morpholin-4-ylpropyl)benzamide

Example 1A

2-amino-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one

To a stirred solution of N,N-dimethylformamide (600 ml) and water (100 ml) at room temperature was added 2,6-diaminopyrimidin-4-ol (50 g, 0.39 mol) and sodium acetate (32.55 g, 0.39 mol). After the mixture became homogeneous, 50% aqueous α-chloroacetaldehyde (61.9 g, 0.39 mol) was added all at once, and the reaction mixture

was stirred further for 1 day. After evaporation of the solvent under vacuum, the residue was triturated with 50 ml of water, cooled to 0°C, and filtered. The resulting solid was purified using silica gel column chromatography (20% methanol in $CHCl_2$) to afford title compound. MS(ESI) *m/z* 151.7 $(M+H)^+$.

Example 1B

4-chloro-7H-pyrrolo[2,3-d]pyrimidin-2-amine

A suspension of Example 1A (25 g, 0.16 mol) in $POCl_3$ (250 ml) was heated under reflux for 3 hours. After cooling to room temperature, excess of $POCl_3$ was removed under vacuum. Ice water (250 ml) was added and the resulting solid was filtered off. The pH of the filtrate was adjusted to pH = 2 with aqueous ammonia. After leaving the precipitate in an ice bath, the mixture was filtered off, and was washed with cold water (25 ml) and cold ether (25 ml) consecutively. The solid was dried under vacuum to give the title compound. MS (ESI) (+) *m/z* 169.7 $(M+H)^+$.

Example 1C

2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine

In a stirred solution of Example 1B (20 g, 0.12 mol) and 25% aqueous HCl (200 ml) at 0°C was added a mixture of $NaNO_2$ (12.32 g, 0.17mol) and water (15 ml) slowly. The mixture was stirred at 0°C for 15 minutes. Then the mixture was added to a stirred solution of CuCl (17.8 g, 0.17 mol) and water (15 ml) at 0°C. Then it was heated to 80°C for 2 hours. After cooling to room temperature, the pH was adjusted to 8.0 with concentrated NH_4OH, and the mixture was extracted with ethyl acetate. The organic layer was concentrated to provide the title compound. MS (ESI)(+) *m/z* 188.7 $(M+H)^+$.

Example 1D

2,4-Dichloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

To a suspension of NaH (1.54 g, 0.0384mol), in N,N-dimethylformamide (80 ml) at 0 °C was added a solution of Example 1C (6.0 g, 0.032 mol) in N,N-dimethylformamide (20 mL) followed by the addition of 2-trimethylsilylethyoxymethyl chloride (6.4 g, 0.0384 mol) and the reaction mixture was stirred at this temperature for 1

hour and warmed up to room temperature overnight. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the crude material was purified by chromatography on silica gel (0~50% ethyl acetate in hexane) to give the title compound. MS (ESI)(+) *m/z* 318.7 $(M+H)^+$.

Example 1E

N-(2-cyanophenyl)-N-methylmethanesulfonamide

A mixture of 2-fluorobenzonitrile (5.0 ml, 47.0 mmol), N-methylmethanesulfonamide (6.16 g, 56.4 mmol), and cesium carbonate (30.6 g, 94 mmol) in N,N-dimethylacetamide (75 ml) was stirred at room temperature for 2 days. The mixture was filtered and the filtrate was poured into ice water and stirred for 0.5 hour. The precipitate was collected by filtration, and dried in a vacuum oven to give the title compound. MS (ESI)(+) *m/z* 223.9 $(M+NH_3)^+$.

Example 1F

N-(2-(aminomethyl)phenyl)-N-methylmethanesulfonamide

To a mixture of Example 1E (3.13 g, 14.89 mmol) and 7M NH_3-methanol (150 ml) in a 250 mL pressure bottle was added Ra-Ni (6.26 g, 107 mmol) and the mixture stirred for 4 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and the filtrate was concentrated. The crude material was then dissolved in ethyl acetate and treated with 2N HCl in ether. The precipitate was filtered, and air-dried to give the title compound. MS (ESI)(+) *m/z* 214.9 $(M+H)^+$.

Example 1G

N-(2-((2-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)methyl)phenyl)-N-methylmethanesulfonamide

A suspension of Example 1D (4.6 g, 0.0145 mol), and Example 1F (3.7 g, 0.017 mol) in 1,2-dimethoxyethane (100 ml) was treated with diisopropylethylamine (10 ml, 0.058 mol). The reaction mixture was heated at reflux for 16 hours. The solvent was

removed and the residue was purified on silica gel (10~70% ethyl acetate in hexane) to give the title compound. MS (ESI)(+) *m/z* 496.7 $(M+H)^+$.

Example 1H

Ethyl 4-(4-(2-(N-methylmethylsulfonamido)benzylamino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzoate

In a 20 mL Biotage reaction vessel, a mixture of Example 1G (1.0 g, 2.02 mmol), ethyl 4-aminobenzoate and sodium *t*-butoxide (0.39 g, 4.04 mmol in toluene (5 ml) was degassed on a sonicator for 5 minutes. Then tris(dibenzylideneacetone)dipalladium(0) (0.19g, 0.202 mmol) and Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) (0.24 g, 0.404 mmol) was added and the mixture was evacuated and purged with nitrogen three times. The suspension was then heated at 110 °C for 16 hours. The solution was cooled, diluted with ethyl acetate and filtered through diatomaceous earth. The filtrate was concentrated and purified on silica gel (10~80% ethyl acetate in hexane) to give the title compound. MS (ESI)(+) *m/z* 625.7 $(M+H)^+$.

Example 1I

4-(4-(2-(N-methylmethylsulfonamido)benzylamino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzoic acid

A solution of Example 1H (3.8 g, 0.006 mol) in methanol (250 ml) was treated with 5N aqueous sodium hydroxide solution (30 ml) at room temperature overnight. The reaction mixture was diluted with water, and the pH was adjusted to 5 with 3N aqueous HCl. After removal of the methanol, the acid was dissolved in ethyl acetate and aqueous phase was extracted with ethyl acetate. The combined organic phases were concentrated to obtain the title compound. MS (ESI)(+) *m/z* 597.3 $(M+H)^+$.

Example 1J

4-(4-(2-(N-methylmethylsulfonamido)benzylamino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(3-morpholinopropyl)benzamide

To a solution of Example 1I (0.1g, 0.17 mmol)), 3-morpholinopropan-1-amine (0.34 mmol)) and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate

(017g, 0.34 mmol) in N,N-dimethylformamide (2 mL), *N,N*-diisopropylethylamine (0.12 ml, 0.67 mmol) was added. The mixture was stirred at room temperature for 2 hours. Saturated aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and filtered. The filtrate was concentrated to give the title compound. MS (ESI)(+) *m/z* 723.2 $(M+H)^+$.

Example 1K

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(3-morpholin-4-ylpropyl)benzamide

In a capped vial under nitrogen, a solution of Example 1J (61.4 mg, 0.085 mmol), tetrabutyl ammonium fluoride (5 equiv), and ethylenediamine (10 equiv) in tetrahydrofuran (2.5 ml) was heated at 80 °C overnight. After the removal of the solvent, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by HPLC (Waters 2545 Auto-purification system, x-Bridge C18 30 ′ 100 mm 5 mm column, 35-95% (NH_4HCO_3 10 ppm in water) in acetonitrile) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 (d, J = 8.54 Hz, 2 H) 7.63 (d, J = 8.85 Hz, 2 H) 7.54 (dd, J = 7.63, 1.53 Hz, 1 H) 7.22 - 7.47 (m, 3 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 4.90 (s, 2 H) 3.50 - 3.64 (m, 2 H) 3.26 (t, J = 7.02 Hz, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.26 - 2.42 (m, 8 H) 1.59 - 1.77 (m, 2 H). MS ESI(+) *m/z* 593.2 [M+H]+.

Example 2

N-cyclobutyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting cyclobutanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.75 - 7.85 (m, 2 H) 7.61 - 7.69 (m, 2 H) 7.49 - 7.58 (m, 1 H) 7.28 - 7.46 (m, 3 H) 6.87 (d, J = 3.66 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 4.84 (s, 2 H) 4.31 -

4.50 (m, 1 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.14 - 2.27 (m, 2 H) 1.95 - 2.13 (m, 2 H) 1.58 - 1.78 (m, 2 H). MS ESI(+) *m/z* 520.2 [M+H]+..

Example 3

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-morpholin-4-ylethyl)benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting 2-morpholinoethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 (d, J = 8.85 Hz, 2 H) 7.59 - 7.68 (m, 2 H) 7.54 (dd, J = 7.63, 1.53 Hz, 1 H) 7.28 - 7.46 (m, 3 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 4.83 (s, 2 H) 3.53 - 3.64 (m, 2 H) 3.37 (t, J = 6.87 Hz, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.38 - 2.49 (m, 8 H). MS ESI(+) *m/z* 579.2 $[M+H]^+$.

Example 4

N-[3-(1H-imidazol-1-yl)propyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting 3-(1H-imidazol-1-yl)propan-1-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.78 (d, J = 8.85 Hz, 2 H) 7.69 (s, 1 H) 7.61 - 7.67 (m, 2 H) 7.54 (dd, J = 7.63, 1.53 Hz, 1 H) 7.28 - 7.46 (m, 3 H) 7.22 (s, 1 H) 6.91 (s, 1 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 4.89 (s, 2 H) 4.02 (t, J = 6.87 Hz, 2 H) 3.19 - 3.29 (m, 5 H) 3.11 (s, 3 H) 1.87 - 2.01 (m, 2 H). MS ESI(+) *m/z* 574.2 $[M+H]^+$.

Example 5

N-methyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide

The title compound was prepared as described in Examples 1A-1H and 1K, except substituting 3,4,5-trimethoxyaniline for ethyl 4-aminobenzoate. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.36 (s, 1 H) 7.56 (dd, J = 7.35, 1.47 Hz, 1 H) 7.18 - 7.50 (m, 3

H) 7.02 (s, 2 H) 6.92 (s, 1 H) 6.57 (s, 1 H) 4.92 (s, 2 H) 3.67 (s, 6 H) 3.60 (s, 3 H) 3.19 (s, 3 H) 3.09 (s, 3 H). MS ESI(+) *m/z* 513.1 $[M+H]^+$.

Example 6

N-(2-methoxyethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting 2-methoxyethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 (d, J = 8.85 Hz, 2 H) 7.65 (d, J = 8.85 Hz, 2 H) 7.50 - 7.57 (m, 1 H) 7.27 - 7.47 (m, 3 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 4.89 (s, 2 H) 3.27 (s, 3 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.97 - 3.07 (m, 2 H) 1.66 - 1.85 (m, 2 H). MS ESI (+) *m/z* 524.2 $[M+H]^+$.

Example 7

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(4-methylpiperazin-1-yl)propyl]benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting 3-(4-methylpiperazin-1-yl)propan-1-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.37 (s, 1 H) 9.31 (s, 1 H) 8.33 (t, J = 5.26 Hz, 1 H) 8.13 (s, 1 H) 7.73 - 7.82 (m, 2 H) 7.67 (d, J = 8.78 Hz, 2 H) 7.55 (d, J = 7.37 Hz, 1 H) 7.27 - 7.48 (m, 3 H) 6.81 - 6.97 (m, 1 H) 6.53 (s, 1 H) 4.89 (s, 2 H) 3.42 (s, 4 H) 3.24 - 3.35 (m, 4 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.96 - 3.08 (m, 2 H) 2.93 (s, 2 H) 2.76 (s, 3 H) 1.68 - 1.97 (m, 2 H). MS ESI (+) *m/z* 606.2 $[M+H]^+$.

Example 8

N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide

Example 8A

4-(3-methoxy-4-nitrophenyl)morpholine

A solution of 4-fluoro-2-methoxy-1-nitrobenzene (7.12 g, 41.6 mmol) and morpholine (45 ml, 520 mmol) was heated at reflux for 3 hours. The reaction mixture was cooled and the precipitate was filtered, and washed with ether and hexane. The solid was then washed with a copious amount of water and dried in vacuum oven at 50 °C overnight to give the title compound. MS ESI (+) *m/z* 238.9 $[M+H]^+$.

Example 8B

2-methoxy-4-morpholinoaniline

A mixture of ammonium chloride (0.56 g, 10.49 mmol), iron (10.55 g, 189 mmol), and acetic acid (2.64 mL, 46.2 mmol) in water (100 ml) was stirred at 50°C for 30 minutes. Then a solution of 4-(3-methoxy-4-nitrophenyl)morpholine (5.0 g, 20.99 mmol) in N,N-dimethylformamide (50 ml) was added dropwise and the suspension was stirred for another 1 hour. The reaction mixture was cooled, and basified with ammonium hydroxide. The suspension was filtered through a diatomaceous earth pad and washed with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and then diluted with 100 mL of ethyl acetate, and treated with 2N HCl in ether. The salt was filtered and washed with hexane to give the title compound. MS ESI (+) *m/z* 208.9 $[M+H]^+$.

Example 8C

N-(3-cyanophenyl)methanesulfonamide

To a cold solution of 3-aminobenzonitrile (1.67 g, 14.14 mmol) in pyridine (30 ml) was added methanesulfonyl chloride (0.991 ml, 12.72 mmol) dropwise and the mixture was stirred at room temperature overnight. The solvent was removed and the residue was partitioned between 1N aqueous HCl and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated to give the title compound. MS ESI (-) *m/z* 194.9 $[M-H]^-$.

Example 8D

N-(3-cyanophenyl)-N-methylmethanesulfonamide

To a mixture of N-(3-cyanophenyl)methanesulfonamide (2.0 g, 10.19 mmol) and potassium carbonate (2.82 g, 20.38 mmol) in N,N-dimethylformamide (25 ml) was added iodomethane (0.91 ml, 11.21 mmol) and the reaction mixture was stirred at room temperature overnight. The suspension was diluted with ethyl acetate and filtered. The filtrate was washed with water, brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude material was triturated with hexane to give the title compound. MS ESI (-) *m/z* 208.8 $[M-H]^-$.

Example 8E

N-(3-(aminomethyl)phenyl)-N-methylmethanesulfonamide

In a 250 mL pressure bottle, a solution of Example 8D (3.13 g, 14.89 mmol) in 7M NH_3-methanol (100 ml) was treated with water-wet Ra-Ni (12.52 g, 213 mmol) and the mixture was stirred for 4 hours at 30 psi and room temperature. The suspension was filtered through a nylon membrane and the filtrate was concentrated. The crude material was dissolved in ethyl acetate and treated 2M HCl in ether. The precipitate was collected by filtration, and air-dried to give the title compound. MS ESI (+) *m/z* 214.9 $[M+H]^+$.

Example 8F

N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 1A-1H and 1K, except substituting Example 8E for Example 1F and Example 8B for ethyl 4-aminobenzoate. ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 11.04 (s, 1 H) 8.19 (d, J = 8.82 Hz, 1 H) 7.75 (t, J = 5.70 Hz, 1 H) 7.48 - 7.59 (m, 1 H) 7.39 - 7.45 (m, 1 H) 7.28 - 7.37 (m, 2 H) 6.93 (s, 1 H) 6.72 - 6.82 (m, 1 H) 6.61 (d, J = 2.57 Hz, 1 H) 6.44 (s, 1 H) 6.36 (dd, J = 8.64, 2.39 Hz, 1 H) 4.90 (s, 1 H) 4.64 (s, 1 H) 3.82 (s, 3 H) 3.68 - 3.79 (m, 4 H) 3.28 (s, 3 H) 3.12 (s, 3 H) 2.97 - 3.07 (m, 4 H). MS ESI (+) *m/z* 538.1 $[M+H]^+$.

Example 9

N-ethyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.72 - 7.90 (m, 2 H) 7.60 - 7.70 (m, 2 H) 7.51 - 7.59 (m, 1 H) 7.27 - 7.45 (m, 3 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.47 (s, 1 H) 4.89 (s, 2 H) 3.19 - 3.34 (m, 5 H) 3.12 (s, 3 H) 1.11 (t, J = 7.32 Hz, 3 H). MS ESI (+) *m/z* 494.2 $[M+H]^+$.

Example 10

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(tetrahydrofuran-2-ylmethyl)benzamide

The title compound was prepared as described in Examples 1A-1H and 1K, except substituting (tetrahydrofuran-2-yl)methanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.51 (s, 1 H) 9.45 (s, 1 H) 8.48 (s, 1 H) 8.20 - 8.36 (m, 1 H) 7.69 (s, 4 H) 7.56 (d, J = 7.70 Hz, 1 H) 7.25 - 7.44 (m, 3 H) 6.86 - 7.02 (m, 1 H) 6.58 (s, 1 H) 4.92 (s, 2 H) 3.90 - 4.01 (m, 1 H) 3.68 - 3.81 (m, 1 H) 3.55 - 3.68 (m, 1 H) 3.22 - 3.36 (m, 2 H) 3.19 (s, 3 H) 3.10 (s, 3 H) 1.42 - 2.01 (m, 4 H). MS ESI (+) *m/z* 550.2 $[M+H]^+$.

Example 11

N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]-3-methylphenyl}-N-methylmethanesulfonamide

Example 11A

N-(2-cyano-3-methylphenyl)-N-methylmethanesulfonamide

A mixture of 2-fluoro-6-methylbenzonitrile (1.00 g, 7.40 mmol), N-methylmethanesulfonamide (0.808 g, 7.40 mmol) and potassium carbonate (2.045 g, 14.80 mmol) in N,N-dimethylformamide (10 ml) was heated at 180°C for 16 hours. The suspension was cooled and poured into ice water, then extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified on silica gel (eluting with 10~70% ethyl acetate in hexane) to give the title compound. MS ESI (+) *m/z* 241.9 $[M+NH_4]^+$.

Example 11B

N-(2-(aminomethyl)-3-methylphenyl)-N-methylmethanesulfonamide

To a solution of Example 11A (0.5 g, 2.229 mmol) in 7M NH_3-methanol (40 ml) was added to Ra-Ni (1.0 g, 17.04 mmol) and the reaction mixture was stirred for 16 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and the filtrate was concentrated. The crude material was dissolved in ethyl acetate, then 2M HCl in ether was added. The precipitate was collected by filtration, and air-dried to give the title compound. MS ESI (+) *m/z* 228.9 $[M+H]^+$.

Example 11C

N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]-3-methylphenyl}-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 1A-1H and 1K, except substituting Example 11B for Example 1F and Example 8B for ethyl 4-aminobenzoate. ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 11.03 (s, 1 H) 8.38 (d, J = 8.82 Hz, 1 H) 7.20 - 7.61 (m, 3 H) 7.07 (s, 1 H) 6.95 (t, J = 4.41 Hz, 1 H) 6.69 - 6.81 (m, 1 H) 6.65 (d, J = 2.57 Hz, 1 H) 6.47 (dd, J = 8.82, 2.57 Hz, 1 H) 6.30 - 6.40 (m, 1 H) 4.94 (d, J = 13.60 Hz, 1 H) 4.55 (d, J = 8.82 Hz, 1 H) 3.87 (s, 3 H) 3.65 - 3.81 (m, 4 H) 3.23 (s, 3 H) 3.09 (s, 3 H) 3.00 - 3.07 (m, 4 H) 2.37 (s, 3 H). MS ESI (+) *m/z* 552.2 $[M+H]^+$.

Example 12

N-cyclopropyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting cyclopropanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.76 (d, *J* = 8.85 Hz, 2 H) 7.62 (d, *J* = 8.85 Hz, 2 H) 7.50 - 7.58 (m, 1 H) 7.26 - 7.47 (m, 3 H) 6.87 (d, *J* = 3.36 Hz, 1 H) 6.48 (d, *J* = 3.05 Hz, 1 H) 4.83 (s, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.99 - 3.07 (m, 1 H) 0.66 - 0.80 (m, 2 H) 0.51 - 0.59 (m, 2 H). MS ESI (+) *m/z* 506.2 $[M+H]^+$.

Example 13

3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(1-methylpiperidin-4-yl)benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 1-methylpiperidin-4-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.09 - 8.20 (m, 2 H) 7.68 (dd, J = 7.63, 1.53 Hz, 1 H) 7.45 - 7.62 (m, 3 H) 7.29 - 7.43 (m, 2 H) 7.00 (d, J = 3.36 Hz, 1 H) 6.62 (d, J = 3.05 Hz, 1 H) 5.06 (s, 2 H) 3.92 - 4.00 (m, 1 H) 3.37 (s, 3 H) 3.27 (s, 3 H) 3.07 (d, J = 10.99 Hz, 2 H) 2.46 (s, 3 H) 1.96 (d, J = 10.07 Hz, 2 H) 1.59 - 1.87 (m, 4 H). MS ESI (+) *m/z* 563.2 $[M+H]^+$.

Example 14

N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 1A-1H and 1K, except substituting Example 8B for ethyl 4-aminobenzoate. ^{1}H NMR (500 MHz, DMSO-d_6) d ppm 11.15 (s, 1 H) 8.01 (s, 2 H) 7.55 (d, J = 7.32 Hz, 1 H) 7.24 - 7.45 (m, 3 H) 6.83 (s, 1 H) 6.63 (d, J = 1.98 Hz, 1 H) 6.51 (s, 1 H) 6.38 (d, J = 7.78 Hz, 1 H) 4.92 (s, 1 H) 4.67 (s, 1 H) 3.82 - 3.82 (m, 3 H) 3.70 - 3.78 (m, 4 H) 3.25 (s, 3 H) 3.12 - 3.13 (m, 3 H) 3.05 (s, 4 H). MS ESI (+) *m/z* 538.2 $[M+H]^+$.

Example 15

N-cyclopentyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting cyclopentanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.74 - 7.88 (m, 2 H) 7.62 - 7.68 (m, 2 H) 7.54 (dd, J = 7.48, 1.68 Hz, 1 H) 7.27 - 7.46 (m, 3 H) 6.87 (d, J = 3.66 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 4.89 (s, 2 H) 4.07 - 4.35 (m, 1 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 1.82 - 1.93 (m, 2 H) 1.63 - 1.77 (m, 2 H) 1.40 - 1.64 (m, 4 H). MS ESI (+) *m/z* 534.2 $[M+H]^+$.

Example 16

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting 1-(3-aminopropyl)pyrrolidin-2-one for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 (d, J = 8.85 Hz, 2 H) 7.59 - 7.68 (m, 2 H) 7.51 - 7.58 (m, 1 H) 7.28 - 7.44 (m, 3 H) 6.87 (d, J = 3.66 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 4.89 (s, 2 H) 3.37 (t, J = 7.02 Hz, 2 H) 3.23 (s, 3 H) 3.17 - 3.28 (m, 4 H) 3.12 (s, 3 H) 2.25 (t, J = 8.09 Hz, 2 H) 1.87 - 2.03 (m, 2 H) 1.61 - 1.72 (m, 2 H). MS ESI (+) *m/z* 591.2 $[M+H]^+$.

Example 17

N-methyl-N-(2-{[(2-{[4-(morpholin-4-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide

The title compound was prepared as described in Examples 1A-1K, except substituting morpholine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.74 (d, J = 8.85 Hz, 2 H) 7.49 - 7.64 (m, 1 H) 7.28 - 7.49 (m, 3 H) 7.20 (d, J = 8.54 Hz, 2 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.49 (d, J = 3.36 Hz, 1 H) 4.87 (d, J = 4.88 Hz, 2 H) 3.60 (d, J = 4.27 Hz, 4 H) 3.50 (s, 4 H) 3.22 (s, 3 H) 3.12 (s, 3 H). MS ESI (+) *m/z* 536.2 $[M+H]^+$.

Example 18

N-methyl-N-(2-{[(2-{[4-(pyrrolidin-1-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide

The title compound was prepared as described in Examples 1A-1K, except substituting pyrrolidine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.73 (d, J = 8.85 Hz, 2 H) 7.54 (dd, J = 7.63, 1.53 Hz, 1 H) 7.27 - 7.45 (m, 5 H) 6.86 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 4.87 (d, J = 4.88 Hz, 2 H) 3.44 (t, J = 6.56 Hz, 4 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 1.76 - 1.94 (m, 4 H). MS ESI (+) *m/z* 520.2 $[M+H]^+$.

Example 19

N-ethyl-N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide

Example 19A

N-(2-(aminomethyl)phenyl)-N-ethylmethanesulfonamide

The title compound was prepared as described in Examples 8D-8E, except substituting iodoethane for iodomethane. MS ESI (+) *m/z* 228.9 $[M+H]^+$.

Example 19B

N-ethyl-N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide

The title compound was prepared as described in Examples 1A-1H and 1K, except substituting Example 19A for Example 1F and Example 8B for ethyl 4-aminobenzoate. ^{1}H NMR (300 MHz, DMSO-D_6) d ppm 9.12 (s, 1 H) 9.03 (s, 1 H) 7.55 (d, J = 6.62 Hz, 2 H) 7.30 - 7.50 (m, 6 H) 6.94 - 7.04 (m, 1 H) 6.57 - 6.79 (m, 2 H) 6.40 (s, 1 H) 3.82 (s, 3 H) 3.69 - 3.79 (m, 4 H) 3.09 (s, 3 H) 3.02 - 3.20 (m, 4 H) 1.00 (t, J = 7.17 Hz, 3 H). MS ESI (+) *m/z* 552.2 $[M+H]^+$.

Example 20

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-propylbenzamide

The title compound was prepared as described in Examples 1A-1K, except substituting propan-1-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-D_6) d ppm 11.50 (d, J = 6.29 Hz, 1 H) 9.42 (s, 1 H) 8.49 (s, 1 H) 8.17 - 8.26 (m, 1 H) 7.68 (s, 4 H) 7.57 (d, J = 7.70 Hz, 1 H) 7.25 - 7.46 (m, 3 H) 6.82 - 7.00 (m, 1 H) 6.58 (s, 1 H) 4.92 (s, 2 H) 3.19 (s, 3 H) 3.13 - 3.25 (m, 2 H) 3.10 (s, 3 H) 1.41 - 1.63 (m, 2 H) 0.87 (t, J = 7.43 Hz, 3 H). MS ESI (+) *m/z* 508.2 $[M+H]^+$.

Example 21

N-(2-furylmethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting furan-2-ylmethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.75 - 7.87 (m, 2 H) 7.67 (d, J = 8.85 Hz, 2 H) 7.50 - 7.57 (m, 2 H) 7.24 - 7.46 (m, 3 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.05 Hz, 1 H) 6.40 (dd, J = 3.20, 1.98 Hz, 1 H) 6.26 (d, J = 3.05 Hz, 1 H) 4.89 (s, 2 H) 4.44 (s, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H). MS ESI (+) *m/z* 546.2 $[M+H]^+$.

Example 22

N-{2-[({2-[(2-methoxy-4-piperazin-1-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide

Example 22A

benzyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate

The title compound was prepared as described in Examples 8A-8B, except substituting benzyl piperazine-1-carboxylate for morpholine. MS ESI (+) *m/z* 342.0 $[M+H]^+$.

Example 22B

Benzyl 4-(3-methoxy-4-(4-(2-(N-methylmethylsulfonamido)benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)phenyl)piperazine-1-carboxylate

The title compound was prepared as described in Examples 1A-1H and 1K except substituting 22A for ethyl 4-aminobenzoate. MS ESI (+) *m/z* 671.3 $[M+H]^+$.

Example 22C

N-{2-[({2-[(2-methoxy-4-piperazin-1-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide

A mixture of Example 22B (0.05 g, 0.075 mmol) and Pd/C (0.063 g, 0.060 mmol) in methanol (3.5 ml) was hydrogenated with a hydrogen balloon overnight. The suspension was filtered through diatomaceous earth and the filtrate was concentrated under vacuum to give the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 11.03 (s, 1 H) 8.16 (d, J = 8.82 Hz, 1 H) 7.74 (t, J = 6.07 Hz, 1 H) 7.49 - 7.63 (m, 1 H) 7.38 -

7.47 (m, 1 H) 7.22 - 7.37 (m, 2 H) 6.91 (s, 1 H) 6.72 - 6.83 (m, 1 H) 6.57 (d, J = 2.57 Hz, 1 H) 6.44 (s, 1 H) 6.34 (dd, J = 8.82, 2.57 Hz, 1 H) 4.91 (s, 1 H) 4.64 (s, 1 H) 3.81 (s, 3 H) 3.28 (s, 3 H) 3.12 (s, 3 H) 2.95 (dd, J = 6.25, 3.31 Hz, 4 H) 2.79 - 2.86 (m, 4 H). MS ESI (+) *m/z* 537.2 $[M+H]^+$.

Example 23

N-[3-(1H-imidazol-1-yl)propyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 3-(1H-imidazol-1-yl)propan-1-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.41 (t, *J* = 5.65 Hz, 1 H) 7.92 - 8.07 (m, 2 H) 7.72 (s, 1 H) 7.47 - 7.62 (m, 1 H) 7.29 - 7.46 (m, 3 H) 7.15 - 7.28 (m, 3 H) 6.93 (s, 1 H) 6.84 (d, *J* = 3.36 Hz, 1 H) 6.46 (d, *J* = 3.05 Hz, 1 H) 4.85 (d, *J* = 41.81 Hz, 2 H) 4.03 (t, *J* = 7.02 Hz, 2 H) 3.22 - 3.25 (m, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 1.85 - 2.12 (m, 2 H). MS ESI (+) *m/z* 574.2 $[M+H]^+$.

Example 24

3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(3-morpholin-4-ylpropyl)benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.83 - 8.04 (m, 2 H) 7.49 - 7.61 (m, 1 H) 7.29 - 7.45 (m, 3 H) 7.16 - 7.24 (m, 2 H) 6.84 (d, *J* = 3.36 Hz, 1 H) 6.46 (d, *J* = 3.36 Hz, 1 H) 4.85 (d, *J* = 42.42 Hz, 2 H) 3.57 (t, *J* = 4.58 Hz, 4 H) 3.27 (t, *J* = 7.02 Hz, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.37 (d, *J* = 7.32 Hz, 4 H) 1.63 - 1.85 (m, 2 H) 1.48 - 1.63 (m, 2 H). MS ESI (+) *m/z* 593.2 $[M+H]^+$.

Example 25

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(1-methylpiperidin-4-yl)benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting 1-methylpiperidin-4-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.78 - 7.87 (m, 2 H) 7.56 - 7.66 (m, 1 H) 7.35 - 7.54 (m, 3 H) 7.23 (d, J = 8.85 Hz, 2 H) 6.93 (d, J = 3.66 Hz, 1 H) 6.55 (d, J = 3.36 Hz, 1 H) 4.93 (s, 2 H) 3.55 (s, 4 H) 3.28 (s, 3 H) 3.18 (s, 3 H) 2.39 (s, 4 H) 2.26 (s, 3 H). MS ESI (+) *m/z* 549.2 $[M+H]^+$.

Example 26

3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(pyridin-3-ylmethyl)benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and pyridin-3-ylmethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.01 (t, J = 5.95 Hz, 1 H) 8.54 (s, 1 H) 8.45 (d, J = 3.97 Hz, 1 H) 7.95 - 8.13 (m, 2 H) 7.68 - 7.83 (m, 1 H) 7.52 (dd, J = 7.63, 1.53 Hz, 1 H) 7.16 - 7.45 (m, 6 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.85 (d, J = 40.59 Hz, 2 H) 4.48 (d, J = 5.80 Hz, 2 H) 3.21 (s, 3 H) 3.18 (s, 3 H). MS ESI (+) *m/z* 557.2 $[M+H]^+$.

Example 27

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(pyridin-3-ylmethyl)benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting pyridin-3-ylmethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.25 (s, 1 H) 9.02 (s, 1 H) 7.92 (d, J = 8.67 Hz, 2 H) 7.83 (t, J = 4.61 Hz, 1 H) 7.77 (d, J = 8.78 Hz, 2 H) 7.63 - 7.71 (m, 1 H) 7.55 (dd, J = 6.94, 2.17 Hz, 1 H) 7.41 - 7.52 (m, 3 H) 6.97 (d, J = 2.93 Hz, 1 H) 6.61 (s, 1 H) 5.02 (s, 2 H) 3.37 (s, 3 H) 3.25 (s, 3 H) 1.56 - 1.72 (m, 2 H) 1.39 - 1.52 (m, 2 H) 1.01 (t, J = 7.37 Hz, 3 H). MS ESI (+) *m/z* 551.2 $[M+H]^+$.

Example 28

N-[3-(dimethylamino)propyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting N, N-dimethylpropane-1,3-diamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 (d, J = 8.85 Hz, 2 H) 7.63 (d, J = 9.16 Hz, 2 H) 7.54 (dd, J = 7.63, 1.53 Hz, 1 H) 7.26 - 7.47 (m, 3 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.05 Hz, 1 H) 4.90 (s, 2 H) 3.23 - 3.32 (m, 2 H) 3.21 - 3.24 (m, 3 H) 3.07 - 3.16 (m, 3 H) 2.30 (t, J = 7.17 Hz, 2 H) 2.16 (s, 6 H) 1.59 - 1.70 (m, 2 H). MS ESI (+) *m/z* 551.2 $[M+H]^+$.

Example 29

N-[2-(dimethylamino)ethyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and N, N-dimethylethane-1,2-diamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.06 - 8.19 (m, 2 H) 7.68 (dd, J = 7.63, 1.53 Hz, 1 H) 7.45 - 7.63 (m, 3 H) 7.30 - 7.43 (m, 2 H) 6.99 (d, J = 3.66 Hz, 1 H) 6.62 (d, J = 3.05 Hz, 1 H) 5.02 (d, J = 41.20 Hz, 2 H) 3.51 (t, J = 6.71 Hz, 2 H) 3.37 (s, 3 H) 3.27 (s, 3 H) 2.62 (t, J = 6.71 Hz, 2 H) 2.38 (s, 6 H). MS ESI (+) *m/z* 537.2 $[M+H]^+$.

Example 30

N-[3-(dimethylamino)propyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and N, N-dimethylpropane-1,3-diamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.80 - 8.13 (m, 2 H) 7.52 (dd, J = 7.48, 1.37 Hz, 1 H) 7.29 - 7.47 (m, 3 H) 7.15 - 7.28 (m, 2 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.90 (s, 2 H) 3.26 (t, J = 7.02 Hz, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.45 (t, J = 7.32 Hz, 2 H) 2.28 (s, 6 H) 1.64 - 1.80 (m, 2 H). MS ESI (+) *m/z* 551.2 $[M+H]^+$.

Example 31

N,N-dimethyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting dimethylamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.72 (d, *J* = 8.54 Hz, 2 H) 7.54 (dd, *J* = 7.48, 1.37 Hz, 1 H) 7.31 - 7.44 (m, 3 H) 7.20 (d, *J* = 8.85 Hz, 2 H) 6.86 (d, *J* = 3.66 Hz, 1 H) 6.48 (d, *J* = 3.36 Hz, 1 H) 4.86 (s, 2 H) 3.22 (s, 3 H) 3.12 (s, 3 H) 2.96 (s, 6 H). MS ESI (+) *m/z* 494.2 $[M+H]^+$.

Example 32

benzyl 4-(3-methoxy-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}phenyl)piperazine-1-carboxylate

The title compound was prepared as described in Example 22B. ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 11.04 (s, 1 H) 8.19 (d, J = 8.82 Hz, 1 H) 7.75 (t, J = 6.07 Hz, 1 H) 7.49 - 7.59 (m, 1 H) 7.29 - 7.47 (m, 8 H) 6.94 (s, 1 H) 6.78 (dd, J = 3.31, 2.21 Hz, 1 H) 6.63 (d, J = 2.57 Hz, 1 H) 6.44 (d, J = 1.10 Hz, 1 H) 6.38 (dd, J = 8.82, 2.21 Hz, 1 H) 5.11 (s, 2 H) 4.90 (s, 1 H) 4.64 (s, 1 H) 3.82 (s, 3 H) 3.55 (s, 4 H) 3.28 (s, 3 H) 3.12 (s, 3 H) 2.95 - 3.08 (m, 4 H). MS ESI (+) *m/z* 671.3 $[M+H]^+$.

Example 33

N-cyclopentyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and cyclopentanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.25 (d, *J* = 7.32 Hz, 2 H) 8.03 (dd, *J* = 8.24, 1.83 Hz, 1 H) 7.99 (s, 1 H) 7.56 - 7.66 (m, 1 H) 7.35 - 7.52 (m, 3 H) 7.15 - 7.31 (m, 2 H) 6.90 (d, *J* = 3.36 Hz, 1 H) 6.52 (d, *J* = 3.05 Hz, 1 H) 4.91 (d, *J* = 45.78 Hz, 2 H) 3.28 (s, 3 H) 3.17 (s, 3 H) 1.87 - 2.05 (m, 2 H) 1.64 - 1.80 (m, 2 H) 1.34 - 1.65 (m, 4 H). MS ESI (+) *m/z* 534.2 $[M+H]^+$.

Example 34

N-cyclopropyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and cyclopropanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.90 - 8.01 (m, 2 H) 7.49 - 7.60 (m, 1 H) 7.28 - 7.45 (m, 3 H) 7.09 - 7.25 (m, 2 H) 6.84 (d, J = 3.36 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.85 (d, J = 42.11 Hz, 2 H) 3.22 (s, 3 H) 3.11 (s, 3 H) 2.75 - 2.91 (m, 1 H) 0.65 - 0.77 (m, 2 H) 0.50 - 0.61 (m, 2 H). MS ESI (+) *m/z* 506.2 $[M+H]^+$.

Example 35

N-ethyl-N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide

Example 35A

N-(3-cyanopyridin-2-yl)methanesulfonamide

To methanesulfonamide (2.57 g, 27.0 mmol) in N,N-dimethylformamide (60 ml) was added potassium tert-butoxide (3.03 g, 27.0 mmol). The mixture was stirred for 20 minutes at room temperature and 2-fluoronicotinonitrile (3.00 g, 24.6 mmol) was added. The resulting mixture was refluxed for 2 hours. The reaction was cooled and poured into water (200 ml), extracted with dichloromethane, washed with brine, dried ($MgSO_4$), filtered, and the solvent was evaporated. The resulting residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (10-85% ethyl acetate in hexane gradient), to yield the title compound. MS ESI(+) *m/z* 198.5 $[M+H]^+$.

Example 35B

N-(3-cyanopyridin-2-yl)-N-ethylmethanesulfonamide

To a suspension of Example 35A (0.57 g, 2.89 mmol) and potassium carbonate (0.799 g, 5.78 mmol) in N,N-dimethylformamide (10 ml) was added iodoethane (0.947 ml, 11.10 mmol) and the reaction mixture was stirred at room temperature for 18 hours. The reaction was diluted with ethyl acetate and filtered. The filtrate was washed with

brine, dried ($MgSO_4$), filtered, and the solvent was evaporated. The resulting residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (10-65% ethyl acetate in hexane gradient), to yield the title compound. MS ESI(+) *m/z* 226.5 $[M+H]^+$.

Example 35C

N-(3-(aminomethyl)pyridin-2-yl)-N-ethylmethanesulfonamide

To the mixture of Example 35B (0.321 g, 1.425 mmol) and 7M NH_3-methanol (20 ml) was added Ra-Ni, water-wet (1.605 g, 27.3 mmol). The mixture was shaken under 60 psi of hydrogen at room temperature for 43 hours. The reaction was filtered and the filtrate was concentrated to dryness to yield the title compound. MS ESI(+) *m/z* 230.5 $[M+H]^+$.

Example 35D

2-chloro-4-(methylthio)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

To a solution of Example 1D (3.08 g, 9.68 mmol) in anhydrous tetrahydrofuran (100 ml) was added sodium methanethiolate (0.882 g, 12.58 mmol) and the reaction mixture was stirred under nitrogen at room temperature for 18 hours. The solvent was evaporated and the resulting residue was diluted with CH_2Cl_2. The organic layer was washed with water, brine and dried ($MgSO_4$). The organic solution was filtered through a short silica pad and concentrated to yield the title compound. MS ESI(+) *m/z* 330.4 $[M+H]^+$.

Example 35E

N-(2-methoxy-4-morpholinophenyl)-4-(methylthio)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

In a 20 mL Biotage reaction vial, a mixture of Example 35D (1.5 g, 4.55 mmol), Example 8B (1.98 g, 7.05 mmol), and sodium tert-butoxide (1.092 g, 11.37 mmol) in toluene (16 ml) was degassed for 5 minutes. Tris(dibenzylideneacetone)dipalladium(0) (0.167 g, 0.182 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.316 g,

0.546 mmol) were added and the reaction mixture was purged with nitrogen. The suspension was heated at 110°C for 16 hours. The reaction was cooled, filtered through diatomaceous earth and the solvent was evaporated. The resulting residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (10-70% ethyl acetate in hexane gradient), to yield the title compound. MS ESI(+) *m/z* 502.5 $[M+H]^+$.

Example 35F

N-(2-methoxy-4-morpholinophenyl)-4-(methylsulfonyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

A solution of Example 35E (0.324g, 0.646 mmol) in tetrahydrofuran (1 5ml) at 0°C was treated drop wise over 15 minutes with a solution of potassium peroxymonosulfate (Oxone) (0.603 ml, 1.098 mmol) in water (10 ml). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was extracted into ethyl acetate, dried over sodium sulfate and filtered. The filtrate was concentrated to give the title compound. MS ESI(+) *m/z* 534.5 $[M+H]^+$.

Example 35G

N-ethyl-N-(3-((2-(2-methoxy-4-morpholinophenylamino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)methyl)pyridin-2-yl)methanesulfonamide

The mixture of Example 35F (0.200 g, 0.375 mmol), Example 35C (0.258 g, 1.124 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.324 ml, 1.874 mmol) in *t*-butanol (2 ml) was heated in a microwave (Biotage Initiator Microwave Synthesizer) at 170° for 70 minutes. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel, eluting with 9/1 mixture of ethyl acetate/hexane to give the title compound. MS ESI(+) *m/z* 683.3 $[M+H]^+$.

Example 35H

N-ethyl-N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide

In a capped vial under nitrogen, a solution of Example 35D (0.075 g, 0.110 mmol), tetrabutylammonium fluoride (0.549 ml, 0.549 mmol), and ethylenediamine (0.066g, 1.01 mmol) in tetrahydrofuran (2 ml) was heated at 80 °C for 18 hours. The solvent was evaporated and the residue was diluted with ethyl acetate. The organic solution was washed with water, brine, dried ($MgSO_4$) and filtered. The filtrate was concentrated and purified by reverse phase HPLC (Waters 2545 Auto-purification system, x-Bridge C18 30 ′ 100 mm 5 mm column, 35-95% (NH_4HCO_3 10 ppm in water) in acetonitrile) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.35 - 8.47 (m, 1 H) 7.23 - 7.31 (m, 2 H) 6.52 (m, 1 H) 3.80 - 3.94 (m, 6 H) 3.02 - 3.15 (m, 4 H) 2.37 - 2.51 (m, 2 H) 1.75 (s, 2 H) 1.38 - 1.46 (m, 2 H) 1.22 - 1.36 (m, 5 H) 1.14 (t, 3 H) 0.82 - 0.97 (m, 4 H). MS ESI(+) *m/z* 553.5 $[M+H]^+$.

Example 36

3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(4-methylpiperazin-1-yl)propyl]benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 3-(4-methylpiperazin-1-yl)propan-1-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.04 - 8.21 (m, 2 H) 7.67 (dd, J = 7.63, 1.53 Hz, 1 H) 7.58 (dd, J = 7.48, 1.98 Hz, 1 H) 7.44 - 7.56 (m, 4 H) 7.30 - 7.42 (m, 2 H) 6.91 - 7.10 (m, J = 3.36 Hz, 2 H) 6.61 (d, J = 3.36 Hz, 1 H) 5.01 (d, J = 43.95 Hz, 2 H) 3.42 (t, J = 6.87 Hz, 2 H) 3.37 (s, 3 H) 3.27 (s, 3 H) 2.39 - 2.62 (m, 10 H) 2.29 (s, 3 H) 1.77 - 1.96 (m, 2 H). MS ESI(+) *m/z* 606.2 $[M+H]^+$.

Example 37

3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-morpholin-4-ylethyl)benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 2-morpholinoethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.91 - 8.06 (m, 2 H) 7.49 - 7.60 (m, 1 H) 7.28 - 7.48 (m, 3 H) 7.14 - 7.27 (m, 2

H) 6.84 (d, J = 3.36 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.85 (d, J = 42.42 Hz, 2 H) 3.51 - 3.63 (m, 4 H) 3.37 (t, J = 6.87 Hz, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.46 (t, J = 7.02 Hz, 2 H) 2.39 - 2.43 (m, 4 H). MS ESI(+) *m/z* 579.2 $[M+H]^+$.

Example 38

N-cyclobutyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and cyclobutanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.52 (d, J = 7.63 Hz, 1 H) 7.87 - 8.05 (m, 2 H) 7.49 - 7.60 (m, 1 H) 7.28 - 7.47 (m, 3 H) 7.11 - 7.26 (m, 2 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.85 (d, J = 43.95 Hz, 2 H) 4.23 - 4.54 (m, 1 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.15 - 2.27 (m, 2 H) 1.94 - 2.13 (m, 2 H) 1.60 - 1.73 (m, 2 H). MS ESI(+) *m/z* 520.2 $[M+H]^+$.

Example 39

N-methyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting methanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.63 - 7.76 (m, 4 H) 7.51 - 7.62 (m, 1 H) 7.32 - 7.46 (m, 3 H) 6.95 (d, J = 3.36 Hz, 1 H) 6.58 (s, 1 H) 4.93 (s, 2 H) 3.19 (s, 3 H) 3.11 (s, 3 H) 2.77 (s, 3 H). MS ESI(+) *m/z* 480.2 $[M+H]^+$.

Example 40

N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide

Example 40A

N-(3-cyanopyridin-2-yl)-N-methylmethanesulfonamide

To the N-methylmethanesulfonamide (1.00 g, 9.17 mmol) in N,N-dimethylformamide (20 ml) was added potassium tert-butoxide (1.03 g, 9.17 mmol). The mixture was stirred for 20 minutes and 2-fluoronicotinonitrile (1.12 g, 9.17 mmol) was added. The resulting mixture was refluxed for 2 hours. The reaction was cooled and poured into water (100 ml), extracted with dichloromethane, washed with brine, dried ($MgSO_4$), filtered, and the solvent was evaporated. The resulting residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (10-85% ethyl acetate in hexane gradient), to yield the title compound. MS ESI(+) *m/z* 212.4 $[M+H]^+$.

Example 40B

N-(3-(aminomethyl)pyridin-2-yl)-N-methylmethanesulfonamide

To a mixture of Example 40A (1.0 g, 4.73 mmol) and 7M NH_3-methanol (20 ml) was added Ra-Ni, water-wet (5 g, 85 mmol). The mixture was shaken under 30 psi of hydrogen at room temperature for 75 minutes. The reaction was filtered and the filtrate was concentrated to dryness to yield the title compound. MS ESI(+) *m/z* 216.3 $[M+H]^+$.

Example 40C

N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 35D-35H, except substituting Example 40B for Example 35C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.60 - 8.77 (m, 1 H), 8.37 - 8.45 (m, 1 H), 8.02 (d, 1 H) 8.32 (d, 1 H), 7.20 - 7.32 (m, 1 H), 7.08 - 7.17 (m, 1 H), 6.60 - 6.74 (m, 1 H), 6.38 - 6.61 (m, 1 H), 6.17 - 6.27 (m, 1 H), 5.78 - 6.01 (m, 1 H), 4.90 - 5.08 (m, 1 H), 3.75 - 4.02 (m, 4 H), 3.26 - 3.41 (m, 3 H), 3.00 - 3.18 (m, 4 H), 2.24 - 2.52 (m, 1 H), 1.52 - 1.81 (m, 2 H), 1.19 - 1.49 (m, 2 H), 0.79 - 1.02 (m, 1 H). MS ESI(+) *m/z* 539.6 $[M+H]^+$.

Example 41

3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(tetrahydrofuran-2-ylmethyl)benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and (tetrahydrofuran-2-yl)methanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.93 - 8.04 (m, 2 H) 7.46 - 7.59 (m, 1 H) 7.26 - 7.46 (m, 3 H) 7.11 - 7.30 (m, 2 H) 6.85 (d, J = 3.66 Hz, 1 H) 6.47 (d, J = 3.05 Hz, 1 H) 4.90 (s, 2 H) 3.91 - 4.04 (m, 1 H) 3.74 - 3.82 (m, 1 H) 3.58 - 3.67 (m, 1 H) 3.24 - 3.40 (m, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 1.50 - 2.07 (m, 4 H). MS ESI (+) *m/z* 550.2 $[M+H]^+$.

Example 42

N-methyl-N-(2-{[(2-{[3-(pyrrolidin-1-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and pyrrolidine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.73 - 7.92 (m, 2 H) 7.52 (dd, J = 7.63, 1.53 Hz, 1 H) 7.26 - 7.47 (m, 3 H) 7.18 (t, J = 7.93 Hz, 1 H) 6.91 (d, J = 7.63 Hz, 1 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.81 (s, 2 H) 3.44 (t, J = 6.87 Hz, 2 H) 3.38 (t, J = 6.56 Hz, 2 H) 3.23 (s, 3 H) 3.11 (s, 3 H) 1.67 - 1.96 (m, 4 H). MS ESI (+) *m/z* 520.2 $[M+H]^+$.

Example 43

N-methyl-N-[2-({[2-({3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 1-methylpiperazine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.86 (dd, J = 8.24, 1.22 Hz, 1 H) 7.69 (s, 1 H) 7.53 (dd, J = 7.63, 1.53 Hz, 1 H) 7.27 - 7.46 (m, 3 H) 7.15 - 7.24 (m, 1 H) 6.84 (d, J = 3.36 Hz, 1 H) 6.78 (d, J = 7.63 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.88 (s, 2 H) 3.59 (s, 2 H) 3.28 - 3.37 (m, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.35 (m, 4 H) 2.18 (s, 3 H). MS ESI (+) *m/z* 549.2 $[M+H]^+$.

Example 44

N-ethyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and ethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.82 - 8.07 (m, 2 H) 7.52 (dd, J = 7.63, 1.53 Hz, 1 H) 7.28 - 7.46 (m, 3 H) 7.11 - 7.27 (m, 2 H) 6.84 (d, J = 3.36 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.90 (s, 2 H) 3.26 (q, J = 7.32 Hz, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 1.11 (t, J = 7.17 Hz, 3 H). MS ESI (+) *m/z* 494.2 $[M+H]^+$.

Example 45

N-methyl-N-(2-{[(2-{[3-(morpholin-4-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and morpholine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.79 - 7.92 (m, 1 H) 7.74 (s, 1 H) 7.49 - 7.57 (m, 1 H) 7.27 - 7.46 (m, 3 H) 7.20 (t, J = 7.93 Hz, 1 H) 6.84 (d, J = 3.36 Hz, 1 H) 6.81 (d, J = 7.63 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.88 (s, 2 H) 3.32 - 3.67 (m, 8 H) 3.23 (s, 3 H) 3.11 (s, 3 H). MS ESI (+) *m/z* 536.2 $[M+H]^+$.

Example 46

N-[2-(dimethylamino)ethyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting N, N-dimethylethane-1,2-diamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.76 (d, J = 8.85 Hz, 2 H) 7.66 - 7.74 (m, 4 H) 7.63 (d, J = 8.85 Hz, 2 H) 7.28 - 7.48 (m, 2 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.66 Hz, 1 H) 4.84 (s, 2 H) 4.08 - 4.24 (m, 2 H) 3.34 (t, J = 6.87 Hz, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.40 (t, J = 6.87 Hz, 2 H) 2.18 (s, 6 H). MS ESI (+) *m/z* 537.2 $[M+H]^+$.

Example 47

N-[3-(dimethylamino)propyl]-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and N^1, N^1, N^3-trimethylpropane-1,3-diamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.62 - 7.91 (m, 2 H) 7.47 - 7.59 (m, 1 H) 7.29 - 7.45 (m, 3 H) 7.18 (t, J = 7.93 Hz, 1 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.76 (s, 1 H) 6.46 (d, J = 3.05 Hz, 1 H) 4.62 - 5.06 (m, 2 H) 3.35 - 3.49 (m, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.17 (s, 3 H) 2.01 - 2.09 (m, 2 H) 1.97 (s, 6 H) 1.51 - 1.85 (m, 2 H). MS ESI (+) *m/z* 565.2 $[M+H]^+$.

Example 48

3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-propylbenzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and propan-1-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.89 - 8.06 (m, 2 H) 7.48 - 7.59 (m, 1 H) 7.27 - 7.48 (m, 3 H) 7.07 - 7.27 (m, 2 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.85 (d, J = 41.20 Hz, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.98 - 3.06 (m, 2 H) 1.44 - 1.62 (m, 2 H) 0.88 (t, J = 7.48 Hz, 3 H). MS ESI (+) *m/z* 508.2 $[M+H]^+$.

Example 49

3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 1-(3-aminopropyl)pyrrolidin-2-one for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.03 (s, 1 H) 7.91 - 7.99 (m, 1 H) 7.52 (dd, J = 7.48, 1.37 Hz, 1 H) 7.25 - 7.46 (m, 3 H) 7.13 - 7.27 (m, 2 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.46 (d, J = 3.36 Hz,

1 H) 4.80 (s, 2 H) 3.36 (t, J = 7.17 Hz, 2 H) 3.16 - 3.29 (m, 5 H) 3.11 (s, 3 H) 2.20 - 2.30 (m, 2 H) 1.88 - 2.06 (m, 2 H) 1.61 - 1.73 (m, 4 H). MS ESI (+) *m/z* 591.2 $[M+H]^+$.

Example 50

N-(2-furylmethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and furan-2-ylmethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (t, J = 5.80 Hz, 1 H) 7.88 - 8.15 (m, 2 H) 7.45 - 7.62 (m, 2 H) 7.10 - 7.46 (m, 5 H) 6.84 (dd, J = 3.36, 1.83 Hz, 1 H) 6.46 (s, 1 H) 6.35 - 6.44 (m, 1 H) 6.27 (s, 1 H) 4.80 (s, 2 H) 4.44 (d, J = 4.88 Hz, 2 H) 3.22 (s, 3 H) 3.12 (s, 3 H). MS ESI (+) *m/z* 546.2 $[M+H]^+$.

Example 51

N-(2-furylmethyl)-N-methyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting 1-(furan-2-yl)-N-methylmethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.71 - 7.82 (m, 2 H) 7.63 (d, J = 1.83 Hz, 1 H) 7.45 - 7.57 (m, 1 H) 7.30 - 7.45 (m, 3 H) 7.24 (d, J = 8.54 Hz, 2 H) 6.86 (d, J = 3.36 Hz, 1 H) 6.48 (d, J = 3.36 Hz, 1 H) 6.46 (dd, J = 3.36, 1.83 Hz, 1 H) 6.37 (d, J = 2.75 Hz, 1 H) 4.87 (s, 2 H) 4.56 (s, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.89 (s, 3 H). MS ESI (+) *m/z* 560.2 $[M+H]^+$.

Example 52

N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and methanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.92 - 8.04 (m, 2 H)

7.47 - 7.62 (m, 1 H) 7.28 - 7.45 (m, 3 H) 7.10 - 7.25 (m, 2 H) 6.84 (d, J = 3.36 Hz, 1 H) 6.46 (d, J = 3.05 Hz, 1 H) 4.80 (s, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.76 (s, 3 H). MS ESI (+) *m/z* 480.2 $[M+H]^+$.

Example 53

N,N-dimethyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and dimethylamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.81 (dd, J = 7.78, 1.68 Hz, 1 H) 7.72 - 7.76 (m, 1 H) 7.49 - 7.59 (m, 1 H) 7.24 - 7.47 (m, 3 H) 7.11 - 7.24 (m, 1 H) 6.84 (d, J = 3.36 Hz, 1 H) 6.79 (d, J = 7.93 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.82 (s, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.95 (s, 3 H) 2.91 (s, 3 H). MS ESI (+) *m/z* 494.2 $[M+H]^+$.

Example 54

N-(2-methoxyethyl)-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 2-methoxy-N-methylethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.83 (s, 1 H) 7.69 (s, 1 H) 7.43 - 7.59 (m, 1 H) 7.26 - 7.46 (m, 3 H) 7.17 (s, 1 H) 6.84 (d, J = 3.36 Hz, 1 H) 6.77 (d, J = 7.32 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.88 (s, 2 H) 3.75 (s, 3 H) 3.56 (s, 2 H) 3.40 (s, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.94 (s, 3 H). MS ESI (+) *m/z* 538.2 $[M+H]^+$.

Example 55

N-(2-furylmethyl)-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 1-(furan-2-yl)-N-

methylmethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 - 7.95 (m, 2 H) 7.67 (s, 1 H) 7.61 (s, 1 H) 7.56 (s, 1 H) 7.50 - 7.56 (m, 1 H) 7.28 - 7.45 (m, 3 H) 7.19 (t, J = 7.78 Hz, 1 H) 6.84 (d, J = 3.36 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 6.31 - 6.45 (m, 1 H) 4.82 (s, 2 H) 4.63 (s, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 2.87 (s, 3 H). MS ESI (+) *m/z* 560.2 $[M+H]^+$.

Example 56

N-(2-methoxyethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 2-methoxyethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.93 - 8.06 (m, 2 H) 7.48 - 7.61 (m, 1 H) 7.28 - 7.47 (m, 3 H) 7.10 - 7.26 (m, 2 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.90 (s, 2 H) 3.35 - 3.55 (m, 4 H) 3.26 (s, 3 H) 3.21 (s, 3 H) 3.11 (s, 3 H). MS ESI (+) *m/z* 524.2 $[M+H]^+$.

Example 57

N-methyl-N-[2-({[2-({4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide

The title compound was prepared as described in Examples 1A-1K, except substituting 1-methylpiperazine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 (d, J = 8.54 Hz, 2 H) 7.65 (d, J = 8.85 Hz, 2 H) 7.51 - 7.58 (m, 1 H) 7.29 - 7.46 (m, 3 H) 6.87 (d, J = 3.66 Hz, 1 H) 6.48 (d, J = 3.05 Hz, 1 H) 4.84 (s, 2 H) 3.23 (s, 3 H) 3.16 - 3.31 (m, 1 H) 3.12 (s, 3 H) 2.76 - 2.87 (m, 4 H) 2.22 (s, 3 H) 1.95 - 2.15 (m, 4 H). MS ESI (+) *m/z* 563.2 $[M+H]^+$.

Example 58

N-isopropyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and propan-2-amine for 3-

morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.88 - 8.04 (m, 2 H) 7.51 - 7.64 (m, 1 H) 7.25 - 7.46 (m, 4 H) 7.21 (t, J = 8.24 Hz, 1 H) 6.87 (d, J = 3.36 Hz, 1 H) 6.50 (d, J = 3.05 Hz, 1 H) 4.86 (d, J = 47.30 Hz, 2 H) 3.98 - 4.14 (m, 1 H) 3.20 (s, 3 H) 3.11 (s, 3 H) 1.15 (d, J = 6.41 Hz, 6 H). MS ESI (+) *m/z* 508.2 $[M+H]^+$.

Example 59

N-(2-cyanoethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting ethyl 3-aminobenzoate for ethyl 4-aminobenzoate and 3-aminopropanenitrile for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.95 - 8.09 (m, 2 H) 7.48 - 7.61 (m, 1 H) 7.28 - 7.45 (m, 3 H) 7.14 - 7.26 (m, 2 H) 6.84 (d, J = 3.66 Hz, 1 H) 6.46 (d, J = 3.36 Hz, 1 H) 4.80 (s, 2 H) 3.48 (t, J = 6.56 Hz, 2 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 2.75 (t, J = 6.41 Hz, 2 H). MS ESI (+) *m/z* 519.2 $[M+H]^+$.

Example 60

N-{2-[({2-[(4-methoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 1A-1H and 1K, except substituting 4-methoxyaniline for ethyl 4-aminobenzoate. ^{1}H NMR (500 MHz, $CDOD_3$) δ ppm 7.54 (d, J = 7.91 Hz, 1 H) 7.32 - 7.48 (m, 5 H) 7.02 (d, J = 3.75 Hz, 1 H) 6.88 (d, J = 8.32 Hz, 2 H) 6.62 (d, J = 3.75 Hz, 1 H) 5.51 (s, 2 H) 3.78 (s, 3 H) 3.18 (s, 3 H) 3.05 (s, 3 H). MS ESI (+) *m/z* 453.1 $[M+H]^+$.

Example 61

N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide

Example 61A

N-(2-cyanophenyl)methanesulfonamide

A mixture of 2-fluorobenzonitrile (5.0 g, 41.3 mmol), methanesulfonamide (3.93 g, 41.3 mmol) and potassium carbonate (11.41 g, 83 mmol) in 1-methyl-2-pyrrolidinone (8.0 ml) was heated at 180°C for 16 hours. The mixture was cooled and poured into ice water, then extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified on silica gel (10~70% ethyl acetate in hexane) to give the title compound. MS ESI (+) *m/z* 227.8 $[M+NH_4]^+$.

Example 61B

N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide

The title compound was prepared as described in Examples 8E-8F, except substituting Example 61A for Example 8D. ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 11.10 (s, 1 H) 10.63 (s, 1 H) 8.06 (d, J = 8.82 Hz, 1 H) 7.92 (t, J = 6.25 Hz, 1 H) 7.35 - 7.46 (m, 2 H) 7.26 - 7.35 (m, 1 H) 7.15 - 7.26 (m, 2 H) 6.71 - 6.81 (m, 1 H) 6.62 (d, J = 2.21 Hz, 1 H) 6.43 (dd, J = 8.82, 2.57 Hz, 1 H) 6.39 (dd, J = 3.31, 1.84 Hz, 1 H) 4.65 (d, J = 6.25 Hz, 2 H) 3.82 (s, 3 H) 3.67 - 3.79 (m, 4 H) 3.08 (s, 3 H) 2.92 - 3.14 (m, 4 H). MS ESI (+) *m/z* 524.1 $[M+H]^+$.

Example 62

N-isopropyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting propan-2-amine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.64 - 7.79 (m, 4 H) 7.55 (dd, *J* = 7.48, 1.37 Hz, 1 H) 7.27 - 7.46 (m, 3 H) 6.91 (d, *J* = 3.36 Hz, 1 H) 6.52 (s, 1 H) 4.91 (s, 2 H) 4.02 - 4.11 (m, 1 H) 3.21 (s, 3 H) 3.11 (s, 3 H) 1.16 (d, *J* = 6.71 Hz, 6 H). MS ESI (+) *m/z* 508.2 $[M+H]^+$.

Example 63

2-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-methylbenzamide

Example 63A

N-(3-bromopyridin-2-yl)methanesulfonamide

To methanesulfonamide (8.5 g, 89 mmol) in 80 ml of N,N-dimethylformamide was added potassium tert-butoxide (9.5 g, 84.8 mmol). The mixture was stirred for 20 minutes and 3-bromo-2-fluoropyridine (10.0 g, 57 mmol) was added. The resulting mixture was refluxed for 2 hours. The mixture was poured into water and extracted with dichloromethane, washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The crude residue was put through a plug of silica (0~50% ethyl acetate in petroleum ether) to yield the title compound. MS ESI(+) *m/z* 251.7 $[M+H]^+$.

Example 63B

N-(3-bromopyridin-2-yl)-N-ethylmethanesulfonamide

To a solution of the Example 63A (4.7 g, 18.8 mmol) in N,N-dimethylformamide (50 ml) was added NaH (0.9g, 22 mmol) and the mixture was stirred at room temperature for 20 minutes. Iodoethane (1.81 ml, 22 mmol) was added and the mixture was heated at 50°C overnight. After cooling to room temperature, the mixture was concentrated, and the residue was put through a plug of silica (0~50%) ethyl acetate in petroleum ether) to yield the title compound. MS ESI(+) *m/z* 279.7 $[M+H]^+$.

Example 63C

2-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-4-vinyl-7H-pyrrolo[2,3-d]pyrimidine

To the solution of Example 1D (5.0 g, 15.7 mmol) in tetrahydrofuran (150 ml) under nitrogen was added bis(triphenylphosphine)palladium(II) dichloride (0.6 g, 0.85 mmol) followed by the addition of tributyl(vinyl)stannane (7.2 g, 22.7 mmol). The mixture was refluxed for 6 hours. The reaction was monitored by LC/MS. After the starting material was consumed, saturated ammonium chloride solution was added. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (0~50% ethyl acetate in petroleum ether) to yield the title compound. MS ESI(+) *m/z* 310.7 $[M+H]^+$.

Example 63D

(E)-N-(3-(2-(2-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)vinyl)pyridin-2-yl)-N-ethylmethanesulfonamide

A mixture of Example 63C (0.98 g, 32 mmol), Example 63B (6.14 g, 22 mmol), palladium(II) acetate (0.15 g, 0.66 mmol), tetrabutylammonium bromide (1.1g, 34mmol), and sodium bicarbonate (1.1g, 13 mmol) in dry N,N-dimethylformamide (10 ml) was heated at 90°C for 18 hours. The mixture was cooled, filtered through diatomaceous earth, washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (0~70% ethyl acetate in petroleum ether) to yield the title compound. MS ESI(+) *m/z* 509.7 $[M+H]^+$.

Example 63E

(E)-2-(4-(2-(2-(N-ethylmethylsulfonamido)pyridin-3-yl)vinyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

In a 20 mL Biotage reaction vessel, a mixture of Example 63D (0.5g, 1.13mmol, ethyl anthranilate (0.28 g, 1.69 mmol), and Cs_2CO_3 (1.11g, 3.4 mmol) in dioxane (5 ml) was degassed on a sonicator for 5 minutes. Then tris(dibenzylideneacetone)dipalladium(0) (0.104 g, 0.11 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.13 g, 0.22 mmol) were added and the vessel was evacuated and purged with nitrogen for three times. The suspension was then heated at 105 °C for 16 hours. The solution was cooled, diluted with ethyl acetate and filtered through diatomaceous earth. The filtrate was concentrated and purified on silica gel (10~80% ethyl acetate in hexane) to give the ester. A mixture of the ester (0.15 g, 0.23 mmol) in 20 ml methylamine solution (33 wt. % in absolute ethanol) was stirred at 45°C overnight. The solution was concentrated. The residue was purified on silica gel (10~80% ethyl acetate in hexane) to give the title compound. MS ESI(+) *m/z* 622.4 $[M+H]^+$.

Example 63F

(E)-2-(4-(2-(2-(N-ethylmethylsulfonamido)pyridin-3-yl)vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

In a capped vial under nitrogen, a solution of Example 63E (0.15 g, 0.24 mmol), tetrabutyl ammonium fluoride (1.35 ml, 1.35mmol), and ethylenediamine (0.17 ml, 2.7 mmol) in tetrahydrofuran (2.5 ml) was heated at 80 °C overnight. After the removal of the solvent, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The crude product was purified by reverse phase HPLC purification (Waters 2545 Auto-purification system, x-Bridge C18 30 ′ 100 mm 5 mm column, 35-95% (NH_4HCO_3 10 ppm in water) in acetonitrile) to yield the title compound. ^{1}H NMR (500MHz, DMSO-d_6) δppm : 11.65(s, 1H), 11.05(s,1H), 8.83(d,1H), 8.61(s,1H), 8.27(d,1H), 7.89(d,1H), 7.66(d,1H), 7.43(t,1H), 7.20(d,1H), 7.08(t,1H), 6.94(t,1H), 6.52(d,1H), 4.00-4.13(m,2H), 2.80(t,3H),1.23(t,6H). MS ESI(+) *m/z* 622.4 $[M+H]^+$.

Example 64

N-{6-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide

Example 64A

N-(6-(aminomethyl)pyridin-2-yl)-N-methylmethanesulfonamide

To methanesulfonamide (1.870 g, 19.66 mmol) in N,N-dimethylformamide (40 ml) was added potassium tert-butoxide (2.206 g, 19.66 mmol). The mixture was stirred for 20 minutes and 2-cyano-6-fluoropyridine (2.0 g, 16.38 mmol) was added. The resulting mixture was refluxed for 3.5 hours. It was poured into water and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. To the crude residue in a 250 ml pressure bottle was added 7M NH3-methanol (40 ml) and Ra-Ni, water-wet (6.80 g, 116 mmol) and the mixture was stirred for 4 hours at 30 psi at room temperature. The mixture was filtered through a nylon membrane and concentrated to give the title compound. MS ESI(+) *m/z* 216.4 $[M+H]^+$.

Example 64B

N-{6-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 35D-35H, except substituting Example 64A for Example 35C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.34 (d, 1 H), 7.72 (d, 1 H), 7.17 (t, 1 H), 6.67 - 6.77 (m, 1 H), 6.45 - 6.62 (m, 1 H), 6.25 - 6.39 (m, 1 H), 5.84 - 6.03 (m, 1 H), 4.94 (d, 1 H), 3.80 - 4.00 (m, 4 H), 3.30 - 3.55 (m, 3 H), 2.99 - 3.22 (m, 4 H), 2.99 - 3.22 (m, 4 H), 1.59 - 1.86 (m, 2 H), 1.14 - 1.41 (m, 4 H), 0.70 - 1.02 (m, 3 H). MS ESI(+) *m/z* 539.7 $[M+H]^+$.

Example 65

2-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzoic acid

Example 65A

N-(3-bromopyridin-2-yl)-N-methylmethanesulfonamide

To N-methylmethanesulfonamide (4.6 g, 42 mmol) in 50 ml of N,N-dimethylformamide was added potassium tert-butoxide (4.7g, 41 mmol). The mixture was stirred for 20 minutes and 3-bromo-2-fluoropyridine (5.0g, 28 mmol) was added. The resulting mixture was refluxed for 2 hours. It was poured into water, extracted with dichloromethane, washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The crude residue was put through a plug of silica (0~50% ethyl acetate in petroleum ether) to yield the title compound. MS ESI(+) *m/z* 265.7 $[M+H]^+$.

Example 65B

2-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzoic acid

The title compound was prepared as described in Examples 63C-63F, except substituting Example 65A for Example 63B and the ethyl anthranilate was saponified with LiOH prior to the SEM deprotection to yield the title compound. ^{1}H NMR(500MHz, DMSO-d_6) δ ppm 11.73(s, 1H), 11.51(s,1H), 8.97(d,1H), 8.28(t,1H), 7.99(d,1H), 7.90(d,1H), 7.49(t,1H), 7.24(d,1H), 7.08-7.10(m,1H), 6.92(t,1H), 6.55 (d,1H), 3.41(s,3H), 3.28(s,3H). MS ESI(+) *m/z* 465.7 $[M+H]^+$.

Example 66

2-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzoic acid

The title compound was prepared as described in Examples 63C-63F, except the ethyl anthranilate 63E was saponified with LiOH prior to the SEM deprotection to yield the title compound. ^{1}H NMR(500MHz, DMSO-d_6) δ ppm 11.92(s, 1H), 11.77(s, 1H), 9.02(d, 1H), 8.36(d,1H), 8.08(d,1H), 7.98(d,1H), 7.53(t,1,H), 7.30(s,1H), 7.14-7.17(m,1H), 6.97(t,1H), 6.60(s,1H), 4.09-4.23(m,2H), 2.58(s,3H), 1.30(t,3H). MS ESI(+) *m/z* 479.7 $[M+H]^+$.

Example 67

N-(cyclopropylmethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 1A-1K, except substituting cyclopropylmethanamine for 3-morpholinopropan-1-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.78 (d, J = 8.85 Hz, 2 H) 7.65 (d, J = 8.85 Hz, 2 H) 7.52 - 7.56 (m, 1 H) 7.24 - 7.47 (m, 3 H) 6.87 (d, J = 3.66 Hz, 1 H) 6.48 (d, J = 3.05 Hz, 1 H) 4.84 (s, 2 H) 3.23 (s, 3 H) 3.12 (s, 3 H) 3.07 - 3.15 (m, 2 H) 1.31 - 1.43 (m, 1 H) 0.36 - 0.52 (m, 2 H) 0.17 - 0.31 (m, 2 H). MS ESI (+) *m/z* 520.2 $[M+H]^+$.

Example 68

N-ethyl-N-[3-((E)-2-{2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}vinyl)pyridin-2-yl]methanesulfonamide

The title compound was prepared as described in Examples 63C-63F, except substituting Example 8E for the ethyl anthranilate to yield the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.19(s, 1H), 8.21(t,2H), 7.61(d,1H), 7.19(s,1H), 6.88-6.91(m,1H), 6.70(s,1H), 6.48(t,2H), 6.31(s,1H), 4.19-4.22(m,1H), 4.09-4.13(m,2H), 3.84(s,3H), 3.81(t,4H), 3.53-3.58(m,1H), 3.33-3.37(m,3H), 3.05(s,4H), 1.29(t,3H). MS ESI(+) *m/z* 550.7 $[M+H]^+$.

Example 69

N-[3-((E)-2-{2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}vinyl)pyridin-2-yl]-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 63C-63F, except substituting Example 65A for Example 63B and Example 8B for the ethyl anthranilate to yield the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.01(d, 1H), 8.24-8.25(t, 1H), 8.08(s, 1H), 7.70(s, 1H), 6.98-7.01(m,1H), 6.91(s,1H), 6.62(s,1H), 6.47(t,2H), 4.15-4.19(m,1H), 3.88-3.93(m,1H), 3.80-3.82(m,7H), 3.38(s,3H), 3.32-3.35(m,1H), 3.23(d,1H). MS ESI(+) *m/z* 536.7 $[M+H]^+$.

Example 70

N-methyl-2-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 63C-63F, except substituting Example 65A for Example 63B to yield the title compound. ^{1}H NMR(500MHz, DMSO-d_6) δ ppm 11.06(s,1H), 8.83(d,1H), 8.63(d,1H), 8.27-8.29(m,1H), 7.87(d,1H), 7.65-7.67(m,1H), 7.41-7.45(m,1H), 7.21-7.22(m,1H), 7.07-7.10(m,1H), 6.93-6.96(m,1H), 6.51-6.52(m,1H), 3.36(s,H), 3.28(s,3H), 2.80(d,3H). MS ESI(+) *m/z* 478.7 $[M+H]^+$.

Example 71

4-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-methoxyethyl)benzamide

The title compound was prepared as described in Examples 63C-63F, except substituting 4-amino-N-(2-methoxyethyl)benzamide for the ethyl anthranilate to yield the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.07(s, 1H), 8.22(d, 1H), 7.65-7.70(m,3H), 7.60(d,1H), 7.52(s,1H), 6.89-6.92(m,2H), 6.51(t, 1H), 6.40(s, 1H), 4.09-4.17(m,3H), 3.58-3.63(m,3H), 3.51(t, 2H), 3.33(t,5H), 1.29(t, 3H). MS ESI(+) *m/z* 536.7 $[M+H]^+$.

Example 72

N-(2-methoxyethyl)-4-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide

The title compound was prepared as described in Examples 63C-63F, except substituting Example 65A for Example 63B and 4-amino-N-(2-methoxyethyl)benzamide for ethyl anthranilate. t ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.69(s, 1H), 8.23(d, 1H), 7.67-7.72(m,4H), 7.61(d,1H), 6.98(s,1H), 6.98(s,1H), 6.91-6.94(m,1H), 6.43-6.46(m,2H), 4.19-4.23(m,1H), 3.58-3.61(m,2H), 3.51 (t,2H), 3.38(s,6H), 3.33(s,3H). MS ESI(+) *m/z* 522.7 $[M+H]^+$.

Example 73

N-methyl-N-(2-{[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]methyl}phenyl)methanesulfonamide

Example 73A

2-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbaldehyde

To a solution of Example 63C (4.0 g, 12.9 mmol) in 128 ml dioxane/water (3/1) was added 2,6-lutidine (4 ml), osmium tetroxide (0.0657 g, 0.258 mmol) and $NaIO_4$ (11.2 g, 52.3 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ and extracted into dichloromethane. It was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (0~50% ethyl acetate in petroleum ether) to yield the title compound. MS ESI(+) *m/z* 312.7 $[M+H]^+$.

Example 73B

N-(2-(((2-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)methylamino)methyl)phenyl)-N-methylmethanesulfonamide

To a mixture of Example 73A (0.2g, 0.64 mmol), Example 1F (0.32 g, 1.28 mmol) in 15 ml dry dichloromethane and 1.5 ml acetic acid was added after 5 minutes of stirring, $NaBH_3CN$ (0.3 g, 4.7 mmol). The suspension was stirred at room temperature. After 3.5 hours, saturated ammonium chloride solution was added and the mixture stirred

for 5 minutes. The mixture was extracted into dichloromethane, washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (10~60% ethyl acetate in petroleum ether) to yield the title compound. MS ESI(+) *m/z* 511.3 $[M+H]^+$.

Example 73C

N-methyl-N-(2-(((2-(3,4,5-trimethoxyphenylamino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)methylamino)methyl)phenyl)methanesulfonamide

The title compound was prepared as described in Examples 63E, except substituting 3,4,5-trimethoxyaniline for ethyl anthranilate. MS ESI(+) *m/z* 657.9.3 $[M+H]^+$

Example 73D

In a capped vial under nitrogen, a solution of Example 73C (0.06 g, 0.09 mmol), tetrabutyl ammonium fluoride (0.045 ml, 0.045 mmol), and ethylenediamine (0.061 ml, 0.91 mmol) in tetrahydrofuran (2.5 ml) was heated at 80 °C overnight. After the removal of the solvent, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The crude product was purified by reverse phase HPLC purification (Waters 2545 auto-purification system, x-Bridge C18 30 ′ 100 mm 5 mm column, 35-95% (NH_4HCO_3 10 ppm in water) in acetonitrile) to yield the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δppm 8.25 (s, 1 H), 7.60-7.688 (m, 4 H), 7.41 (m, 2 H), 7.30 (m, 1 H), 7.01 (s, 2 H), 6.87 (d, 1 H), 6.47 (d, 1 H), 4.34 (s, 1 H), 4.22 (s,1 H), 3.85 (s, 7 H), 3.29 (s, 3 H), 3.03 (s, 3 H), 2.06 (s, 3 H). MS ESI(+) *m/z* 527.3 [M+H]+.

Example 74

N-[2-({[2-({3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide

Example 74A

2,4-dichloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine

Example 1C (0.792 g, 4.21 mmol) was dissolved in N,N-dimethylformamide (15 ml) and 4-methylbenzene-1-sulfonyl chloride (0.803 g, 4.21 mmol) was added. The mixture was stirred at room temperature for 15 minutes then 4-methylbenzene-1-sulfonyl chloride (0.803 g, 4.21 mmol) was added. The mixture was stirred for 2 hours then diluted with 75 ml of ethyl acetate and washed with 50 ml of 2N aqueous HCl. The organic phase was dried over anhydrous Na_2SO_4, filtered, and absorbed on silica gel. The crude material was purified by flash chromatography on silica gel, eluting with a 0 – 50% ethyl acetate / hexanes gradient to yield the title compound. MS ESI(+) *m/z* 341.7 $[M+H]^+$.

Example 74B

N-(2-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)methyl)phenyl)-N-methylmethanesulfonamide

Example 74A (0.871g, 2.55 mmol), Example 1F (0.702g, 2.80 mmol), and N-ethyl-N-isopropylpropan-2-amine (1.33ml, 7.64 mmol) were combined in 25 ml of 1,4-dioxane. The mixture was heated at reflux for 1 hour then allowed to cool. The mixture was diluted with 50 ml of 2 N aqueous HCl and extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were dried over Na_2SO_4, filtered, and absorbed on 5 g of silica gel. The crude material was purified by flash chromatography on silica gel, eluting with a 0 – 100% ethyl acetate / hexanes gradient to yield the title compound. MS ESI(+) *m/z* 520.0 $[M+H]^+$.

Example 74C

methyl 2-methoxy-4-(4-(2-(N-methylmethylsulfonamido)benzylamino)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzoate

Example 74B (0.20 g, 0.385 mmol) and methyl 4-amino-2-methoxybenzoate (0.077 g, 0.423 mmol) were processed as described in Example 1H to provide the title compound. MS ESI(+) *m/z* 665.1 $[M+H]^+$.

Example 74D

methyl 2-methoxy-4-(4-(2-(N-methylmethylsulfonamido)benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzoate

Example 74C (92.3 mg, 0.139 mmol) was dissolved in methanol (3 ml) and tetrahydrofuran (2 ml) and cesium carbonate (136 mg, 0.417 mmol) was added. The resulting mixture was heated *via* microwave (Biotage Initiator Microwave Synthesizer) at 105°C for 10 minutes. After cooling, the crude material was purified by flash chromatography on silica gel, eluting with a 0 – 100% ethyl acetate / hexanes gradient to yield the title compound. MS ESI(+) *m/z* 511.1 $[M+H]^+$.

Example 74E

2-methoxy-4-(4-(2-(N-methylmethylsulfonamido)benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzoic acid

Example 74D (0.053g, 0.104 mmol) was dissolved in 6 ml of 1,4-dioxane and 1 ml of 2.5 M aqueous NaOH was added. The mixture was heated at 80°C for 1 hour then allowed to cool. The mixture was acidified with 5 ml of 2 N aqueous HCl and extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was removed under vacuum to provide the title compound which was used without further purification. MS ESI(+) 497.0 $[M+H]^+$.

Example 74F

N-[2-({[2-({3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide

Example 74E (0.044g, 0.088 mmol), 1-methylpiperazine (0.011 ml, 0.099 mmol), O-benzotriazole-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (0.042 g, 0.131 mmol), and N,N-diisopropylethylamine (0.046 ml, 0.263 mmol) were combined in 3 ml of 1,2-dichloroethane and stirred at room temperature for 16 hours. The mixture was applied directly to a SF15-12g Analogix silica gel cartridge and eluted with 0-10% NH_4OH in acetonitrile to provide the title compound. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 11.06 (s, 1 H), 8.84 (s, 1 H), 7.87 (t, 1 H), 7.73 (d, 1 H), 7.44 (s, 1 H), 7.33 - 7.39 (m, 2 H), 7.22 - 7.32 (m, 2 H), 6.94 (d, 1 H), 6.82 (dd, 1 H), 6.45 (dd, 1 H), 4.75 (d, 2 H),

3.67 (s, 3 H), 3.43 - 3.64 (m, 3 H), 3.22 - 3.43 (m, 3 H), 3.18 (s, 3 H), 3.14 (s, 2 H), 2.89 (s, 3 H), 2.17 (s, 3 H). MS ESI(+) 579.2 $[M+H]^+$.

Example 75

N-(2-{[(2-{[2-methoxy-4-(piperidin-4-yloxy)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)-N-methylmethanesulfonamide

Example 75A

tert-butyl 4-(3-methoxy-4-nitrophenoxy)piperidine-1-carboxylate

tert-Butyl 4-hydroxypiperidine-1-carboxylate (2.51g, 12.49 mmol) was dissolved in 25 ml of N,N-dimethylformamide and 60% wt. sodium hydride in mineral oil (0.50g, 12.49 mmol) was added. The mixture was stirred at room temperature for 15 minutes then 4-fluoro-2-methoxy-1-nitrobenzene (2.14g, 12.49 mmol) was added. The mixture was stirred at room temperature for 3 hours then diluted with 50 ml of ethyl acetate. The mixture was washed with 50 ml of saturated aqueous ammonium chloride and 50 ml of water. The organic phase was dried over Na_2SO_4, filtered, and absorbed on 5 g of silica gel. The crude material was purified by flash chromatography on silica gel, eluting with a 0 – 50% ethyl acetate / hexanes gradient to yield the title compound. LC/MS (AA+) *m/z* 253.1$[M-Boc+H]^+$.

Example 75B

tert-butyl 4-(4-amino-3-methoxyphenoxy)piperidine-1-carboxylate

Example 75A (3.30g, 9.36 mmol) was suspended in a mixture of 20 ml of ethanol and 40 ml of 1 N aqueous HCl and zinc powder (3.06g, 46.8 mmol) was added. The mixture was stirred at room temperature for 4 hours then neutralized by the addition of solid sodium bicarbonate. The mixture was extracted with ethyl acetate (2 x 50 ml) and the combined organic extracts were dried over Na_2SO_4, filtered, and absorbed on 5 g of silica gel. The crude material was purified by flash chromatography on silica gel, eluting with a 0 – 50% ethyl acetate / hexanes gradient to yield the title compound. MS DCI(+) *m/z* 323.2 $[M+H]^+$.

Example 75C

tert-butyl 4-(3-methoxy-4-(4-(2-(N-methylmethylsulfonamido)benzylamino)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)phenoxy)piperidine-1-carboxylate

Example 74A (0.290 g, 0.558 mmol) and Example 75B (0.198 g, 0.614 mmol) were processed as described in Example 1H to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.20 (t, 1 H), 8.15 (d, 1 H), 7.89 (d, 2 H), 7.29 - 7.43 (m, 5 H), 7.18 - 7.29 (m, 3 H), 6.74 (d, 1 H), 6.65 (d, 1 H), 6.61 (d, 1 H), 4.61 (d, 2 H), 4.51 - 4.59 (m, 1 H), 3.82 (s, 3 H), 3.62 - 3.72 (m, 2 H), 3.14 - 3.26 (m, 5 H), 2.88 (s, 3 H), 2.32 (s, 3 H), 1.85 - 1.95 (m, 2 H), 1.47 - 1.58 (m, 2 H), 1.40 (s, 9 H).

Example 75D

N-(2-{[(2-{[2-methoxy-4-(piperidin-4-yloxy)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)-N-methylmethanesulfonamide

Example 75C (0.068 g, 0.084 mmol) and cesium carbonate (0.082 g, 0.252 mmol) were combined in 3 ml of methanol in a 10 ml microwave reaction vessel. The mixture was heated at 105°C for 15 minutes *via* microwave (Biotage Initiator Microwave Synthesizer). The mixture was diluted with 10 ml of ethyl acetate and washed with 5 ml of water. The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resulting residue was dissolved in 5 ml of dichloromethane and 2 ml of trifluoroacetic acid was added. The mixture was stirred at room temperature for 1 hour. The mixture was diluted with 20 ml of ethyl acetate and washed with saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude material was purified by preparative HPLC on a Phenomenex Luna C8(2) 5 um 100Å AXIA column (30mm × 75mm). A gradient of acetonitrile (A) and 10 mM ammonium acetate in water (B) was used, at a flow rate of 50 ml/min (0-0.5 min 10% A, 0.5-7.0 min linear gradient 10-95% A, 7.0-10.0 min 95% A, 10.0-12.0 min linear gradient 95-10% A). 5 mL of 2 M HCl in diethyl ether was added to the product and the solvent was evaporated to provide the title compound as the HCl salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.90 (s, 1 H), 7.38 (s, 1 H), 7.28 (s, 1 H), 7.20 - 7.26 (m, 2 H), 7.16 - 7.19 (m, 2 H), 7.10 - 7.16 (m, 1 H), 7.08 (s, 1 H), 6.95 (s, 1 H), 6.67 (s, 1 H), 6.58 (d, 1 H), 4.66 (s, 2 H), 3.81 (s, 3 H), 3.18 - 3.20 (m, 3 H), 3.15

(s, 3 H), 2.99 - 3.11 (m, 2 H), 2.91 (s, 2 H), 2.29 (s, 3 H), 2.04 - 2.15 (m, 2 H), 1.77 - 1.90 (m, 2 H). MS ESI(+) *m/z* 552.2 $[M+H]^+$.

Example 76

N^4-benzyl-N^2-(2-methoxy-4-morpholin-4-ylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

Example 76A

N^4-benzyl-N^2-(2-methoxy-4-morpholinophenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

A mixture of Example 35F (250 mg, 0.47 mmol), benzylamine (0.26 mL, 2.34 mmol), and diisopropylethyl amine (0.41 mL, 2.34 mmol) in t-butanol (3.9 mL) was heated in the microwave (Biotage Initiator Microwave Synthesizer) at 170°C for 1 hour. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel, eluting with a 0 – 50% ethyl acetate / hexanes gradient with 1% methanol additive to yield the title compound. MS ESI(+) *m/z* 561.6 $[M+H]^+$.

Example 76B

N^4-benzyl-N^2-(2-methoxy-4-morpholin-4-ylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

The title compound was prepared as described in Examples 1K, except substituting Example 76A for Example 1J. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.00 (s, 1 H), 8.25 (d, 1 H), 7.80 (t, 1 H), 7.39 – 7.29 (m, 4 H), 7.22 (m, 1 H), 6.96 (s, 1 H), 6.76 (dt, 1 H), 6.62 (d, 1 H), 6.45 – 1.98 (m, 2 H), 3.84 (s, 3 H), 3.72 (t, 4 H), 3.04 (t, 4H). MS ESI(+) *m/z* 431.3 $[M+H]^+$.

Example 77

N-methyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide

Example 77A

N-(2-nitrophenyl)methanesulfonamide

To methanesulfonamide (20.0 g, 211 mmol) in N,N-dimethylformamide (300 ml) was added potassium tert-butoxide (23.6 g, 211 mmol). The mixture was stirred for 15 minutes. 2-Fluoronitrobenzene (29.7, 211 mmol) was added and the mixture was heated to reflux for 5 hours. The reaction mixture was concentrated and partitioned between water and dichloromethane. The organics were dried ($MgSO_4$), filtered, concentrated and purified by recrystallization from ethanol to yield the title compound. MS ESI(+) *m/z* 217.3 $[M+H]^+$.

Example 77B

N-methyl-N-(2-nitrophenyl)methanesulfonamide

To a solution of Example 77A (2.95 g, 13.6 mmol) in N,N-dimethylformamide (40 mL) was added NaH (0.65 g, 27.2 mmol) and the mixture stirred at room temperature for 20 minutes. Methyl Iodide (2.9 g, 20.4 mmol) was added and the mixture was heated at 30°C overnight. The reaction was cooled and the solvent was evaporated to yield the title compound. MS ESI(+) *m/z* 231.2 $[M+H]^+$.

Example 77C

N-(2-aminophenyl)-N-methylmethanesulfonamide

A solution of Example 77B (4.0 g, 17.4 mmol) in methanol (100 ml) was hydrogenated at atmospheric temperature and pressure using 5% Pd/C (0.61 g) as catalyst. The Pd/C was removed by filtration and the mixture was concentrated. Recrystallization from ethanol gave the title compound. MS ESI(+) *m/z* 201.1 $[M+H]^+$.

Example 77D

N-methyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide

The title compound was prepared as described in Examples 73B-73D, except substituting Example 77C for Example 1F. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.18(d, 1H), 7.10(s, 2H), 7.03(t, 1H), 7.10(d, 1H), 6.66(d, 1H), 6.57(t, 1H), 6.50(d, 1H), 4.48(d, 2H), 3.76(d, 6H), 3.63(s, 3H), 3.11(s, 3H), 2.96(s, 3H). MS ESI(+) *m/z* 513.2 $[M+H]^+$.

Example 78

N-ethyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide

Example 78A

N-(2-aminophenyl)-N-ethylmethanesulfonamide

The title compound was prepared as described in Examples 77A-77C, except substituting ethyl iodide for methyl iodide. MS ESI(+) *m/z* 215.3 $[M+H]^+$.

Example 78B

N-ethyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide

The title compound was prepared as described in Examples 73B-73D, except substituting Example 78A for Example 1F. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.15(d, 1H), 7.12(s, 3H), 7.08(t, 1H), 6.92(d, 1H), 6.71(d, 1H), 6.59(t, 1H), 6.51(d, 1H), 4.48(dd, 2H), 3.77(s, 6H), 3.65 (s, 3H), 3.50(m, 1H), 2.95(s, 3H), 1.00 (t, 1H). MS ESI(+) *m/z* 527.2 $[M+H]^+$.

Example 79

4-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-(2-methoxyethyl)benzamide

Example 79A

N-(3-aminopyridin-2-yl)-N-ethylmethanesulfonamide

The title compound was prepared as described in Examples 77A-77C, except substituting 2-chloro-3-nitropyridine for 2-fluoronitrobenzene and ethyl iodide for methyl iodide. MS ESI(+) *m/z* 216.7 $[M+H]^+$.

Example 79B

The title compound was prepared as described in Examples 73B-73D, except substituting Example 79A for Example 1F and 4-amino-N-(2-methoxyethyl)benzamide for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.80 (d, 2H), 7.69 (d, 3H), 7.09 (s, 2H), 6.98 (s, 1H), 6.57 (s, 1H), 4.54 (s, 2H), 3.62 (s, 2H), 3.47 (s, 4H), 3.30 (s, 3H), 3.05 (s, 3H), 0.96 (t, 3H). MS ESI(+) *m/z* 539.7 $[M+H]^+$.

Example 80

2-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-methylbenzamide

The title compound was prepared as described in Examples 73B-73D, except substituting Example 79A for Example 1F and 2-amino-N-methylbenzamide for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.80 (s, 1H), 10.58 (s, 1H), 8.74 (s,1H), 7.78 (d, 1H), 7.50 (d,1H), 7.42 (s, 1H), 7.28 (s, 1H),7.06 (d, 1H), 6.98 (d, 1H), 6.92 (s, 1H), 6.57 (s, 1H), 6.50 (s, 1H), 5.61 (s, 1H), 4.52 (d, 2H), 3.72 (d, 2H), 3.15 (s, 3H), 3.01 (d, 3H), 1.12 (t, 3H). MS ESI(+) *m/z* 495.7 $[M+H]^+$.

Example 81

N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide

Example 81A

N-(2-aminophenyl)methanesulfonamide

The title compound was prepared as described in Example 77C, except substituting 77A for 77B. MS ESI(+) *m/z* 187.3 $[M+H]^+$.

Example 81B

The title compound was prepared as described in Examples 73B-73D, except substituting Example 81A for Example 1F. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.14(s, 1H), 7.94(s, 1H), 7.14(d, 1H), 6.98(m, 2H), 6.69(d, 1H), 6.57(m, 1H), 6.53(t, 1H), 5.87(s, 1H), 4.52(d, 2H) , 3.71(s, 6H), 3.56(s, 3H), 2.92(s, 3H). MS ESI(+) *m/z* 499.0 $[M+H]^+$.

Example 82

N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 73B-73D, except substituting Example 77C for Example 1F and Example 8B for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 10.80 (s, 1H), 10.58 (s,1H), 8.74 (s, 1H), 7.78 (d,1H), 7.50 (d, 1H), 7.42 (s,1H), 7.28 (s,1H), 7.06 (d,1H), 6.98 (d, 1H), 6.92 (s,1H), 6.57 (s, 1H), 6.50 (s, 1H), 5.61 (s, 1H), 4.52 (d, 2H), 3.72 (d, 2H), 3.15 (s, 3H), 3.01 (d, 3H), 1.12 (t, 3H). MS ESI(+) *m/z* 495.7 $[M+H]^+$.

Example 83

2-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzoic acid

Example 83A

N-(3-aminopyridin-2-yl)-N-methylmethanesulfonamide

The title compound was prepared as described in Examples 77A-77C, except substituting 2-chloro-3-nitropyridine for 2-fluoronitrobenzene. MS ESI(+) *m/z* 202.7 $[M+H]^+$.

Example 83B

2-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzoic acid

The title compound was prepared as described in Examples 73B-73D, except substituting Example 83A for Example 1F and 2-aminobenzoic acid for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.88 (d, 1H), 7.95 (d, 1H), 7.61 (d, 1H), 7.37 (t, 1H), 6.98-7.03 (m, 3H), 6.81 (t, 1H), 6.58 (d, 1H), 4.59 (s, 2H), 3.15 (s, 3H), 3.10 (s, 3H). MS ESI(+) *m/z* 468.7 $[M+H]^+$.

Example 84

N-(2-methoxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]phenyl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

The title compound was prepared as described in Examples 73B-73D, except substituting Example 77C for Example 1F and 4-amino-N-(2-methoxyethyl)benzamide for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 11.64 (s,1H), 10.35 (s,1H), 8.80 (d,1H), 8.06 (d, 1H), 7.83 (d, 1H), 7.42 (t, 1H), 7.10 (t, 1H), 7.10 (t, 1H), 7.05 (s, 2H), 6.90 (t, 1H), 6.60 (s, 1H), 5.74 (s, 1H), 4.67 (s, 2H), 3.73 (d, 2H), 3.12 (s, 3H), 2.98 (t, 4H), 1.04 (t, 3H). MS ESI(+) *m/z* 482.7 $[M+H]^+$.

Example 85

N-(2-methoxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

The title compound was prepared as described in Examples 73B-73D, except substituting Example 83A for Example 1F and 4-amino-N-(2-methoxyethyl)benzamide for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.79 (d, 2H), 7.68 (d, 2H), 7.63 (s, 1H), 7.05 (d, 2H), 6.99 (d, 1H), 6.56 (d, 1H), 4.57 (s, 2H), 3.47 (s, 4H), 3.30 (s, 4H), 3.13 (s, 3H), 3.10 (s, 3H), 2.06 (s, 3H). MS ESI(+) m/z 525.7 [M+H]+.

Example 86

2-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzoic acid

The title compound was prepared as described in Examples 73B-73D, except substituting Example 79A for Example 1F and 2-aminobenzoic acid for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.64 (s, 1H), 10.35 (s, 1H), 8.80 (d,1H), 8.06 (d, 1H), 7.83 (d, 1H), 7.42 (t, 1H), 7.10 (t, 1H), 7.05 (s, 2H), 6.90 (t, 1H), 6.60 (s, 1H), 5.74 (s, 1H), 4.67 (s, 2H), 3.73 (d, 2H), 3.12 (s, 3H), 2.98 (t, 4H), 1.04 (t, 3H). MS ESI(+) *m/z* 482.7 $[M+H]^+$.

Example 87

N-ethyl-N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide

The title compound was prepared as described in Examples 73B-73D, except substituting Example 78A for Example 1F and Example 8B for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, $CDCL_3$) δ ppm 8.66(d, 1H), 7.46(d, 1H), 7.37(d, 1H), 7.32(t, 1H), 7.10(t, 1H), 6.94(d,1H), 6.85(t, 1H), 6.62(d, 1H), 6.48-6.52(m, 2H), 4.57(s, 2H), 2.81(s,6H). MS ESI(+) *m/z* 482.7 $[M+H]^+$.

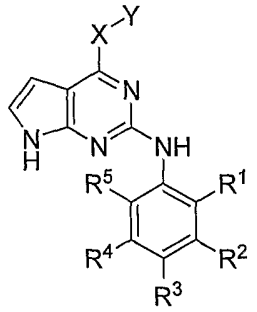
Example 88

4-({4-[({2-[ethyl(methylsulfonyl)amino]phenyl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-(2-methoxyethyl)benzamide

The title compound was prepared as described in Examples 73B-73D, except substituting Example 78A for Example 1F and 4-amino-N-(2-methoxyethyl)benzamide for 3,4,5-trimethoxyaniline. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.91 (d, 1H), 8.03 (d, 1H), 7.48 (d, 1H), 7.39 (t, 1H), 7.20 (t, 1H), 7.03 (d, 1H), 6.89 (t, 1H), 6.73 (d, 1H), 6.60 (q, 2H), 4.68 (s, 2H), 2.92 (s, 3H). MS ESI(+) *m/z* 417.7 $[M+H]^+$.

WHAT IS CLAIMED IS:

1. A compound having Formula (I)



(I);

or a therapeutically acceptable salt thereof, wherein

X is CH_2NH, CH_2NHCH_2, $CH_2C(R^6)_2$, CH_2CHR^6, CHR^6CH_2, $C(R^6)_2CH_2$, CH_2CH_2, CH=CH, $CH=CR_6$, $CR_6=CH$, or $NHCH_2$,

Y is aryl or heteroaryl; wherein the aryl or heteroaryl is substituted with $NR^7SO_2R^8$; wherein the aryl or heteroaryl is optionally further substituted with one or more R^9;

each R^6 is independently alkyl;

R^7 is hydrogen or alkyl;

R^8 is alkyl;

R^1, R^2, R^3, R^4, R^5, and R^9 are independently selected from the group consisting of hydrogen, R^{10}, OR^{10}, SR^{10}, $S(O)R^{10}$, SO_2R^{10}, $C(O)R^{10}$, $CO(O)R^{10}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, NH_2, NHR^{10}, $N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHS(O)_2R^{10}$, $NR^{10}S(O)_2R^{10}$, $NHC(O)OR^{10}$, $NR^{10}C(O)OR^{10}$, $NHC(O)NH_2$, $NHC(O)NHR^{10}$, $NHC(O)N(R^{10})_2$, $NR^{10}C(O)NHR^{10}$, $NR^{10}C(O)N(R^{10})_2$, $C(O)NH_2$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, C(O)NHOH, $C(O)NHOR^{10}$, $C(O)NHSO_2R^{10}$, $C(O)NR^{10}SO_2R^{10}$, SO_2NH_2, SO_2NHR^{10}, $SO_2N(R^{10})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{10}$, $C(N)N(R^{10})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{10} is independently R^{11}, R^{12}, R^{13}, or R^{14};

R^{11} is aryl;

R^{12} is heteroaryl;

R^{13} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{14} is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{15}, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $C(O)R^{15}$, $CO(O)R^{15}$, $OC(O)R^{15}$, $OC(O)OR^{15}$, NH_2, NHR^{15}, $N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHS(O)_2R^{15}$, $NR^{15}S(O)_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)NHR^{15}$, $NR^{15}C(O)N(R^{15})_2$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, C(O)NHOH, $C(O)NHOR^{15}$, $C(O)NHSO_2R^{15}$, $C(O)NR^{15}SO_2R^{15}$, SO_2NH_2, SO_2NHR^{15}, $SO_2N(R^{15})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{15}$, $C(N)N(R^{15})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{15} is independently R^{16}, R^{17}, R^{18}, or R^{19};

R^{16} is aryl;

R^{17} is heteroaryl;

R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{19} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{20}, OR^{20}, SR^{20}, $S(O)R^{20}$, SO_2R^{20}, $C(O)R^{20}$, $CO(O)R^{20}$, $OC(O)R^{20}$, $OC(O)OR^{20}$, NH_2, NHR^{20}, $N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{20}C(O)R^{20}$, $NHS(O)_2R^{20}$, $NR^{20}S(O)_2R^{20}$, $NHC(O)OR^{20}$, $NR^{20}C(O)OR^{20}$, $NHC(O)NH_2$, $NHC(O)NHR^{20}$, $NHC(O)N(R^{20})_2$, $NR^{20}C(O)NHR^{20}$, $NR^{20}C(O)N(R^{20})_2$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, C(O)NHOH, $C(O)NHOR^{20}$, $C(O)NHSO_2R^{20}$, $C(O)NR^{20}SO_2R^{20}$, SO_2NH_2, SO_2NHR^{20}, $SO_2N(R^{20})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{20}$, $C(N)N(R^{20})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I substituents;

each R^{20} is independently alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

wherein the moieties represented by R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, and R^{18} are unsubstituted or substituted with one or two or three or four of independently selected R^{21}, OR^{21}, SR^{21}, $S(O)R^{21}$, SO_2R^{21}, $C(O)R^{21}$, $CO(O)R^{21}$, $OC(O)R^{21}$, $OC(O)OR^{21}$, NH_2, NHR^{21}, $N(R^{21})_2$, $NHC(O)R^{21}$, $NR^{21}C(O)R^{21}$, $NHS(O)_2R^{21}$, $NR^{21}S(O)_2R^{21}$, $NHC(O)OR^{21}$, $NR^{21}C(O)OR^{21}$, $NHC(O)NH_2$, $NHC(O)NHR^{21}$, $NHC(O)N(R^{21})_2$, $NR^{21}C(O)NHR^{21}$, $NR^{21}C(O)N(R^{21})_2$, $C(O)NH_2$, $C(O)NHR^{21}$, $C(O)N(R^{21})_2$, C(O)NHOH, $C(O)NHOR^{21}$, $C(O)NHSO_2R^{21}$, $C(O)NR^{21}SO_2R^{21}$, SO_2NH_2, SO_2NHR^{21}, $SO_2N(R^{21})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{21}$, $C(N)N(R^{21})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{21} is independently R^{22}, R^{23}, R^{24}, or R^{25};

R^{22} is aryl;

R^{23} is heteroaryl;

R^{24} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

R^{25} is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{26}, OR^{26}, SR^{26}, $S(O)R^{26}$, SO_2R^{26}, $C(O)R^{26}$, $CO(O)R^{26}$, $OC(O)R^{26}$, $OC(O)OR^{26}$, NH_2, NHR^{26}, $N(R^{26})_2$, $NHC(O)R^{26}$, $NR^{26}C(O)R^{26}$, $NHS(O)_2R^{26}$, $NR^{26}S(O)_2R^{26}$, $NHC(O)OR^{26}$, $NR^{26}C(O)OR^{26}$, $NHC(O)NH_2$, $NHC(O)NHR^{26}$, $NHC(O)N(R^{26})_2$, $NR^{26}C(O)NHR^{26}$, $NR^{26}C(O)N(R^{26})_2$, $C(O)NH_2$, $C(O)NHR^{26}$, $C(O)N(R^{26})_2$, C(O)NHOH, $C(O)NHOR^{26}$, $C(O)NHSO_2R^{26}$, $C(O)NR^{26}SO_2R^{26}$, SO_2NH_2, SO_2NHR^{26}, $SO_2N(R^{26})_2$, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{26}$, $C(N)N(R^{26})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I;

each R^{26} is independently alkyl, alkenyl, alkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; and

the moieties represented by R^{22}, R^{23}, and R^{24} are unsubstituted or substituted with one or two or three or four of independently selected NH_2, $C(O)NH_2$, C(O)NHOH,

SO_2NH_2, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br, or I.

2. A compound having Formula (I) wherein
X is $NHCH_2$.

3. A compound having Formula (I) wherein
X is $NHCH_2$; and
Y is aryl wherein the aryl is substituted with $NR^7SO_2R^8$.

4. A compound having Formula (I) wherein
X is $NHCH_2$; and
Y is heteroaryl wherein the heteroaryl is substituted with $NR^7SO_2R^8$.

5. A compound having Formula (I) wherein
X is $NHCH_2$;
Y is aryl wherein the aryl is substituted with $NR^7SO_2R^8$;
R^7 is alkyl; and
R^8 is alkyl.

6. A compound having Formula (I) wherein
X is $NHCH_2$;
Y is heteroaryl wherein the heteroaryl is substituted with $NR^7SO_2R^8$;
R^7 is alkyl; and
R^8 is alkyl.

7. A compound having Formula (I) wherein
X is $NHCH_2$;
Y is aryl wherein the aryl is substituted with $NR^7SO_2R^8$;
R^7 is alkyl;
R^8 is alkyl;

R^1, R^2, R^4, and R^5, are hydrogen; and
R^3 is $C(O)NHR^{10}$.

8. A compound having Formula (I) wherein
X is $NHCH_2$;
Y is aryl wherein the aryl is substituted with $NR^7SO_2R^8$;
R^7 is alkyl;
R^8 is alkyl;
R^1, R^3, R^4, and R^5, are hydrogen; and
R^2 is $C(O)NHR^{10}$.

9. A compound having Formula (I) wherein
X is $NHCH_2$;
Y is aryl wherein the aryl is substituted with $NR^7SO_2R^8$;
R^7 is alkyl;
R^8 is alkyl;
R^2, R^4, and R^5 are hydrogen;
R^1 is OR^{10}; and
R^3 is R^{10} or $C(O)NHR^{10}$.

10. A compound of claim 1, wherein the compound is chosen from:
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(3-morpholin-4-ylpropyl)benzamide;
N-cyclobutyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-morpholin-4-ylethyl)benzamide;
N-[3-(1H-imidazol-1-yl)propyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;

N-methyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide;
N-(2-methoxyethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(4-methylpiperazin-1-yl)propyl]benzamide;
N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide;
N-ethyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(tetrahydrofuran-2-ylmethyl)benzamide;
N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]-3-methylphenyl}-N-methylmethanesulfonamide;
N-cyclopropyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(1-methylpiperidin-4-yl)benzamide;
N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide;
N-cyclopentyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide;
N-methyl-N-(2-{[(2-{[4-(morpholin-4-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide;
N-methyl-N-(2-{[(2-{[4-(pyrrolidin-1-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide;
N-ethyl-N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide;

4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-propylbenzamide;
N-(2-furylmethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-{2-[({2-[(2-methoxy-4-piperazin-1-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide;
N-[3-(1H-imidazol-1-yl)propyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(3-morpholin-4-ylpropyl)benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(1-methylpiperidin-4-yl)benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(pyridin-3-ylmethyl)benzamide;
4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(pyridin-3-ylmethyl)benzamide;
N-[3-(dimethylamino)propyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-[2-(dimethylamino)ethyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-[3-(dimethylamino)propyl]-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N,N-dimethyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
benzyl 4-(3-methoxy-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}phenyl)piperazine-1-carboxylate;
N-cyclopentyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-cyclopropyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;

N-ethyl-N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(4-methylpiperazin-1-yl)propyl]benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-morpholin-4-ylethyl)benzamide;
N-cyclobutyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-{3-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(tetrahydrofuran-2-ylmethyl)benzamide;
N-methyl-N-(2-{[(2-{[3-(pyrrolidin-1-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide;
N-methyl-N-[2-({[2-({3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide;
N-ethyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-N-(2-{[(2-{[3-(morpholin-4-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)methanesulfonamide;
N-[2-(dimethylamino)ethyl]-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-[3-(dimethylamino)propyl]-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-propylbenzamide;
3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide;

N-(2-furylmethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-furylmethyl)-N-methyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N,N-dimethyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-methoxyethyl)-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-furylmethyl)-N-methyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-methoxyethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-methyl-N-[2-({[2-({4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide;
N-isopropyl-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-(2-cyanoethyl)-3-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
N-{2-[({2-[(4-methoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide;
N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]phenyl}methanesulfonamide;
N-isopropyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;
2-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-methylbenzamide;
N-{6-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide;

2-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzoic acid;

2-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzoic acid;

N-(cyclopropylmethyl)-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;

N-ethyl-N-[3-((E)-2-{2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}vinyl)pyridin-2-yl]methanesulfonamide;

N-[3-((E)-2-{2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}vinyl)pyridin-2-yl]-N-methylmethanesulfonamide;

N-methyl-2-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;

4-{[4-((E)-2-{2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}-N-(2-methoxyethyl)benzamide;

N-(2-methoxyethyl)-4-{[4-((E)-2-{2-[methyl(methylsulfonyl)amino]pyridin-3-yl}vinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]amino}benzamide;

N-methyl-N-(2-{[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]methyl}phenyl)methanesulfonamide;

N-[2-({[2-({3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide;

N-(2-{[(2-{[2-methoxy-4-(piperidin-4-yloxy)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]methyl}phenyl)-N-methylmethanesulfonamide;

N^4-benzyl-N^2-(2-methoxy-4-morpholin-4-ylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine;

N-methyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide;

N-ethyl-N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide;

4-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-(2-methoxyethyl)benzamide;

2-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-methylbenzamide;
N-{2-[({2-[(3,4,5-trimethoxyphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide;
N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}-N-methylmethanesulfonamide;
2-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzoic acid;
N-(2-methoxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]phenyl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;
N-(2-methoxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;
2-({4-[({2-[ethyl(methylsulfonyl)amino]pyridin-3-yl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzoic acid;
N-ethyl-N-{2-[({2-[(2-methoxy-4-morpholin-4-ylphenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methyl)amino]phenyl}methanesulfonamide;
4-({4-[({2-[ethyl(methylsulfonyl)amino]phenyl}amino)methyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-N-(2-methoxyethyl)benzamide; and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

11. A composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of a compound of claim 1.

12. A method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer,

esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound of claim 1.

13. A method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of claim 1 and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2010/001578

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI, EPODOC, CNPAT, Chinese patent full text search system, Chinese medical patent search system, CNKI, Google CA: ABBOTT, pyrrolo [2,3-d] pyrimidin?, pyrrolo+ nW pyrimidin+, cancer, tumo?r, FAK, focal adhesion kinase, ALK, anaphastic lymphoma kinase, STN structure query

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/055674 A1 (TARGEGEN INC.) 30 Apr. 2009 (30.04.2009) see claims 24, 25, 34	1-13
A	WO 2010/090764 A1 (SUPERGEN, INC.) 12 Aug. 2010 (12.08.2010) see claims 35, 38-40	1-13
A	WO 2010/007114 A2 (BOEHRINGER INGELHEM INTERNATIONAL GMBH) 21 Jan. 2010 (21.01.2010) see page 1 line 10-20, page 169 strcture IV-24 to page 170 struture IV-27	1-13
A	WO 2010/045451 A1 (GLAXOSMITHKLINE LLC) 22 Apr. 2010 (22.04.2010) see claims 35, 38-40	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 July 2011 (05.07.2011)	**21 Jul. 2011 (21.07.2011)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer WANG Jingjing Telephone No. (86-10)62411133

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2010/001578

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12, 13
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 12 and 13 claim the method of treating cancers, which is an unsearchable subject matter defined by PCT R39.1(iv). However, the search has been carried out and based on the use of the compound in manufacturing the medicament for treating corresponding diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2010/001578

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO 2009/055674 A1	30.04.2009	None	
WO 2010/090764 A1	12.08.2010	US 2010204221 A1	12.08.2010
WO 2010/007114 A2	21.01.2010	WO 2010/007114 A3	11.03.2010
WO 2010/045451 A1	22.04.2010	None	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2010/001578

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/04 (2006.01)i

A61K 31/519 (2006.01)i

A61P 35/00 (2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC