SULFONYL AMIDE DERIVATIVES FOR THE TREATMENT OF ABNORMAL CELL GROWTH

Background of the Invention

This invention relates to novel sulfonyl amide derivatives that are useful in the treatment of abnormal cell growth, such as cancer, in mammals. This invention also relates to a method of using such compounds in the treatment of abnormal cell growth in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e., a gene which, on activation, leads to the formation of malignant tumor cells). Many oncogenes encode proteins that are aberrant tyrosine kinases capable of causing cell transformation. Alternatively, the overexpression of a normal proto-oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

Receptor tyrosine kinases are enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion which functions as a kinase to phosphorylate specific tyrosine residues in proteins and hence to influence cell proliferation. Other receptor tyrosine kinases include c-erbB-2, c-met, tie-2, PDGFr, FGFr, and VEGFR. It is known that such kinases are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. It has also been shown that epidermal growth factor receptor (EGFR), which possesses tyrosine kinase activity, is mutated and/or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid tumors.

Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, erbstatin, a tyrosine kinase inhibitor, selectively attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma that expresses epidermal growth factor receptor tyrosine kinase (EGFR) but is without effect on the growth of another carcinoma that does not express the EGF receptor. Thus, selective inhibitors of certain receptor tyrosine kinases, are useful in the treatment of abnormal cell growth, in

particular cancer, in mammals. In addition to receptor tyrosine kinases, selective inhibitors of certain non-receptor tyrosine kinases, such as FAK (focal adhesion kinase), lck, src, abl or serine/threonine kinases (e.g., cyclin dependent kinases), are useful in the treatment of abnormal cell growth, in particular cancer, in mammals. FAK is also known as the Protein-Tyrosine Kinase 2, PTK2.

Convincing evidence suggests that FAK, a cytoplasmic, non-receptor tyrosine kinase, plays an essential role in cell-matrix signal transduction pathways (Clark and Brugge 1995, Science 268: 233-239) and its aberrant activation is associated with an increase in the metastatic potential of tumors (Owens et al. 1995, Cancer Research 55: 2752-2755). FAK was originally identified as a 125 kDa protein highly tyrosine-phosphorylated in cells transformed by v-Src. FAK was subsequently found to be a tyrosine kinase that localizes to focal adhesions, which are contact points between cultured cells and their underlying substratum and sites of intense tyrosine phosphorylation. FAK is phosphorylated and, thus, activated in response to extracellular matrix (ECM)-binding to integrins. Recently, 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. 1996, Cell Growth and Diff. 7: 413-418). In addition to being expressed in most tissue types, FAK is found at elevated levels in most human cancers, particularly in highly invasive metastases.

Various compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties. Five European patent publications, namely EP 0 566 226 A1 (published October 20, 1993), EP 0 602 851 A1 (published June 22, 1994), EP 0 635 507 A1 (published January 25, 1995), EP 0 635 498 A1 (published January 25, 1995), and EP 0 520 722 A1 (published December 30, 1992), refer to certain bicyclic derivatives, in particular quinazoline derivatives, as possessing anti-cancer properties that result from their tyrosine kinase inhibitory properties.

Also, World Patent Application WO 92/20642 (published November 26, 1992), refers to certain bis-mono and bicyclic aryl and heteroaryl compounds as tyrosine kinase inhibitors that are useful in inhibiting abnormal cell proliferation. World Patent Applications WO96/16960 (published June 6, 1996), WO 96/09294 (published March 6, 1996), WO 97/30034 (published August 21, 1997), WO 98/02434 (published January 22, 1998), WO 98/02437 (published January 22, 1998), and WO 98/02438 (published January 22, 1998), also refer to substituted bicyclic heteroaromatic derivatives as

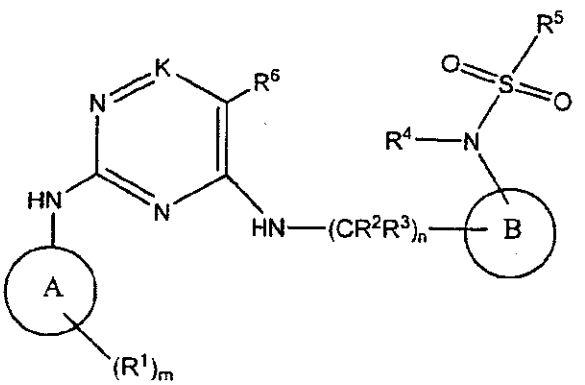
tyrosine kinase inhibitors that are useful for the same purpose. In addition, the following list of publications relate to bis-mono and bicyclic aryl and heteroaryl compounds that may optionally be used as tyrosine kinase inhibitors: WO 03/030909, WO 03/032997, US Patent Application Publication No. 2003/0181474, US Patent Application Publication No. 2003/0162802, US Patent No. 5,863,924, WO 03/078404, US Patent No. 4,507146, WO 99/41253, WO 01/72744, WO 02/48133, US Patent Application Publication No. 2002/156087, WO 02/102783, and WO 03/063794.

U.S. Patent Application Publication No. 20040220177 relates to a broad class of novel pyrimidine derivatives that are kinase inhibitors, and more specifically, inhibitors of FAK. Moreover, U.S. Patent No. 7,107,335 relates more specifically to a subset of pyrimidine derivatives, i.e., those bearing a 5-aminooxindole, which are tyrosine kinase inhibitors, and more particularly, FAK inhibitors. Compounds such as these are useful in the treatment of abnormal cell growth.

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, in mammals. The present invention provides novel sulfonyl amide derivatives that are kinase inhibitors and inhibitors of the non-receptor tyrosine kinase, FAK, Aurora (e.g., Aurora-1 and Aurora-2), Pyk, HgK, and are useful in the treatment of abnormal cell growth.

Summary of the Invention

The present invention provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof; wherein

A is a ring moiety selected from the group consisting of a:

(a) 4- to 7-membered carbocyclyl,

(b) 4- to 7-membered heterocyclyl,

(c) phenyl, and

(d) 5- to 6-membered heteroaryl ring,

wherein each of said 4- to 7-membered carbocyclyl and 4- to 7-membered heterocyclyl of said A group may optionally contain one or two olefinic bonds; and wherein one or two carbon ring atoms in each of said 4- to 7-membered carbocyclyl and 4- to 7-membered heterocyclic of said A group may independently optionally be replaced with one or two moieties independently selected from the group consisting of -C(O)-, -C(S)- and -C(=NR^4)-;

B is phenyl or a 5- to 6-membered heteroaryl;

K is CH, C(NH_2) or N;

each R^1 is independently selected from the group consisting of -H, halo, -CF_3, -CN, -NO_2, -NR^7R^8, -$NR^7C(NR^7R^8)(=CR^9)$, -$CR^7(NR^7R^8)(=NR^7)$, -$NR^7C(NR^7R^8)(=NR^7)$, -$NR^7C(O)R^9$, -$C(O)NR^7R^8$, -$C(O)R^9$, -$C(O)C(O)R^9$, -$C(O)OR^{10}$, -$OC(O)R^9$, -OR^{10}, -$OC(O)OR^{10}$, -$S(O)_jR^{11}$, -$S(O)(=NR^7)R^8$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^1 is optionally independently substituted by one to three R^{12} groups;

R^2 and R^3 are each independently selected from the group consisting of –H, -halo, -OR^{10}, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^2 and R^3 is optionally substituted by one to three R^{12} groups;

R^4 and R^5 are each independently selected from the group consisting of –H, -NR^7R^8, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and

-(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^4 and R^5 is optionally substituted by one to three R^{12} groups;

R^6 is selected from the group consisting of -halo, -NR^7R^8, -OR^{10}, -$C(O)R^9$, -CO_2R^{10}, -$CONR^7R^8$, -$S(O)_jR^{11}$, -$NR^7CONR^7R^8$, and -$NR^8SO_2R^{11}$, -NO_2, -CN, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_2-C_6)perfluorinated alkyl, -(C_2-C_6)perfluorinated alkenyl, -(C_3-C_6)perfluorinated alkynyl, -(C_3-C_7)cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, -(C_1-C_9)heteroaryl, -(C_6-C_{10})perfluorinated aryl, and -(C_1-C_9)perfluorinated heteroaryl; and wherein each of said -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl moieties of said R^6 is optionally substituted by one to three R^{12} groups;

R^7 and R^8 are each independently selected from the group consisting of -H, -OR^{10}, -$S(O)_jR^{11}$, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^7 and R^8 is optionally substituted by one to three R^{12} groups;

each R^9 is independently selected from the group consisting of -H, -halo, -$NR^{13}R^{14}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^9 is optionally substituted by one to three R^{12} groups;

each R^{10} is independently selected from the group consisting of -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{10} is optionally substituted by one to three R^{12} groups;

each R^{11} is independently selected from the group consisting of -H, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; land wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{11} is optionally substituted by one to three R^{12} groups;

each R^{12} is independently selected from the group consisting of -H, -OR^{13}, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$OC(O)OR^{13}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, -$NR^{13}C(NR^{13}R^{14})(=NR^{13})$, -$NR^{13}C(NR^{13}R^{14})(=N\text{-}C(O)R^{13})$, -$NR^{13}C(O)R^{14}$, -$NR^{13}S(O)_jR^{13}$, -$S(O)_jR^{13}$, -$CF_3$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_6$-$C_{10}$)bicycloalkyl, -($C_6$-$C_{10}$)bicycloalkenyl, -($C_2$-$C_9$)heterocycloalkyl, -($C_4$-$C_9$)heterocycloalkenyl, -($C_6$-$C_9$)heterobicycloalkyl, -($C_6$-$C_9$)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{12} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -$C(O)R^{15}$, -$C(O)NR^{15}R^{16}$, -$S(O)_jR^{15}$, and -$S(O)_jNR^{15}R^{16}$, -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{13} and R^{14} are each independently selected from the group consisting of –H, -$NR^{15}C(O)R^{16}$, -CF_3, -CN, -$S(O)_jR^{15}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-

C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{13} and R^{14} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{15} and R^{16} are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said $R^{15}$and R^{16} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

wherein one or two carbon ring atoms in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkenyl in said R^1-R^{14} groups may optionally and independently be replaced with -C(O)- or -C(S)-;

wherein two groups attached to the same tetravalent carbon atom in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkeny of said R^1 to R^{14} groups may optionally join to form a ring system selected from the group consisting of a -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl; and wherein

j is an integer from 0 to 2;

n is an integer from 1 to 3; and

m is an integer from 0 to 3.

In one embodiment, the invention relates to a compound of formula I wherein A is a 4- to 7-membered carbocyclyl; and wherein said carbocyclyl may additionally contain one or two olefinic bonds.

In another embodiment, the invention relates to a compound of formula I wherein A is a 4- to 7-membered carbocyclyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentendienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptenyl, and cycloheptadienyl.

In another embodiment, the invention relates to a compound of formula I wherein A is a 4- to 7-membered heterocyclyl; and wherein said 4- to 7-membered heterocyclyl may additionally contain one or two olefinic bonds.

In another embodiment, the invention relates to a compound of formula I wherein A is a 4- to 7-membered heterocyclyl selected from the group consisting of azetidinyl, oxetanyl, pyrrolidynyl, dihydropyrazolyl, tetrahydropyrazolyl, dihydrofuranyl, tetradydrofuranyl, dihydrothiophenyl, tetrahydrothiopenyl, dihydropyridinyl, tetrahydropyridinyl, piperidinyl, piperazinyl, pyranyl, dihydropyranyl, tetrahydropyranyl, thiopyrianyl, dihydrothiopyranyl, tetrahydrothiopyranyl, morpholinyl, dihydroazepinyl, tetrahydroazepinyl, dihyrooxepinyl, tetrahydrooxepinyl, oxepanyl, dihyrothiepinyl, tetrahydrothiepinyl and thiepanyl.

In another embodiment, the invention relates to a compound of formula I wherein A is a phenyl.

In another embodiment, the invention relates to a compound of formula I wherein A is a 5- to 6-membered heteroaryl.

In another embodiment, the invention relates to a compound of formula I wherein A is a 5- to 6-membered heteroaryl selected from the group consisting of furanyl, pyrrolyl, thiopenyl, thiazolyl, isothiazolyl, pyrazolyl, oxazoyl, isoxazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, oxadiazoyl, thiadiazoyl, and benzothiazole, benzooxazole.

In one embodiment, the invention relates to a compound of formula I wherein each R^1 is independently selected from the group consisting of -H, halo, $-CF_3$, -CN, $-NO_2$, $-NR^7R^8$, $-NR^7C(NR^7R^8)(=CR^9)$, $-CR^7(NR^7R^8)(=NR^7)$, $-NR^7C(NR^7R^8)(=NR^7)$, $-NR^7C(O)R^9$, $-C(O)NR^7R^8$, $-C(O)R^9$, $-C(O)C(O)R^9$, $-C(O)OR^{10}$, $-OC(O)R^9$, $-OR^{10}$, $-OC(O)OR^{10}$, $-S(O)_jR^{11}$, and $-S(O)(=NR^7)R^8$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-S(O)_jR^{11}$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-S(O)_jR^{11}$, and R^{11} is selected from the group consisting of -H, $-NR^{13}R^{14}$ and $-(C_1$-$C_6)$alkyl; and wherein said $-(C_1$-$C_6)$alkyl of said R^{11} is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)OR^{10}$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)OR^{10}$ and R^{10} is $-(C_1$-$C_6)$alkyl optionally substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$ and R^9 is selected from the group consisting of $-NR^{13}R^{14}$, $-(C_1$-$C_6)$alkyl and $-(C_3$-$C_{10})$cycloalkyl; wherein each of said $-(C_1$-$C_6)$alkyl, and $-(C_3$-$C_{10})$cycloalkyl of said R^9 group is optionally substituted by one to three R^{12} groups; and wherein two groups attached to the same tetravalent carbon atom of said $-(C_1$-$C_6)$alkyl and $-(C_3$-$C_{10})$cycloalkyl of said R^9 may optionally join to form a ring system selected from the group consisting of a $-(C_3$-$C_{10})$cycloalkyl, $-(C_5$-$C_{10})$cycloalkenyl, $-(C_2$-$C_9)$heterocycloalkyl, and $-(C_4$-$C_9)$heterocycloalkenyl.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$, and R^9 is $-(C_1$-$C_6)$alkyl optionally substituted by a group selected from the group consisting of $-NR^{13}R^{14}$, $-NR^{15}C(O)R^{16}$ and $-CF_3$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$, and R^9 is $-NR^{13}R^{14}$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$, R^9 is $-NR^{13}R^{14}$, and R^{13} and R^{14} are each independently selected from the group consisting of –H and $-(C_1$-$C_6)$alkyl; and wherein said $-(C_1$-$C_6)$alkyl of said R^{13} and R^{14} groups is optionally independently substituted with one to three groups selected from the group consisting of -halo, $-CF_3$, -CN, $-NO_2$, -OH, $-O((C_1$-$C_6)$alkyl), $-C(O)((C_1$-$C_6)$alkyl), $-(C_3$-$C_{10})$cycloalkyl, $-(C_2$-$C_9)$heterocycloalkyl, -SH, $-S((C_1$-$C_6)$alkyl), $-NH_2$, $-NH((C_1$-$C_6)$alkyl) and $-N((C_1$-$C_6)$alkyl)$_2$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$, R^9 is $-NR^{13}R^{14}$, and R^{13} and R^{14} are each independently selected from the group consisting –H and $-(C_1-C_6)$alkyl; wherein said $-(C_1-C_6)$alkyl of said R^{13} and R^{14} are each optionally independently substituted with one to three groups selected from the group consisting of $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of said $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl optional substituents of said $-(C_1-C_6)$alkyl of said R^{13} and R^{14} is optionally independently substituted by one to three groups selected from the group consisting of -halo, $-CF_3$, -CN, $-NO_2$, -OH, $-O((C_1-C_6)alkyl)$, $-C(O)((C_1-C_6)alkyl)$, $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, -SH, $-S((C_1-C_6)alkyl)$, $-NH_2$, $-NH((C_1-C_6)alkyl)$ and $-N((C_1-C_6)alkyl)_2$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$, R^9 is $-NR^{13}R^{14}$, and R^{13} and R^{14} are each independently selected from the group consisting of $-(C_3-C_{10})$cycloalkyl and $-(C_2-C_9)$heterocycloalkyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of said $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl of said R^{13} and R^{14} is optionally independently substituted by one to three groups independently selected from the group consisting of -halo, $-CF_3$, -CN, $-NO_2$, -OH, $-O((C_1-C_6)alkyl)$, $-C(O)((C_1-C_6)alkyl)$, $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, -SH, $-S((C_1-C_6)alkyl)$, $-NH_2$, $-NH((C_1-C_6)alkyl)$ and $-N((C_1-C_6)alkyl)_2$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$, and R^9 is selected from the group consisting of $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl and $-(C_6-C_9)$heterobicycloalkenyl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl and (C_4-C_9)heterocycloalkenyl moieties of said R^9 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)R^9$, and R^9 is selected from the group consisting of $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^9 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7R^8$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7R^8$, and R^7 and R^8 are each independently selected from the group consisting of -H, $-CF_3$ and $-S(O)_jR^{11}$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7R^8$, and R^7 and R^8 are each independently selected from the group consisting of $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl moieties of said R^7 and R^8 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$ and R^7 is selected from the group consisting of –H and $-(C_1-C_6)$alkyl; and wherein said $-(C_1-C_6)$alkyl of said R^7 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$ and R^7 is selected from the group consisting of –H and $-(C_1-C_6)$alkyl; and wherein said $-(C_1-C_6)$alkyl of said R^7 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$, and R^9 is selected from the group consisting of –H and $-S(O)_jR^{11}$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$, and R^9 is selected from the group consisting of –H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl; and wherein said $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl of said R^9 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$ and R^9 is $-(C_1-C_6)$alkyl; wherein said $-(C_1-C_6)$alkyl of said R^9 is optionally independently substituted by one to three R^{12} groups; and wherein two groups attached to the same tetravalent carbon atom of said $-(C_1-C_6)$alkyl of said R^9 may optionally join to form a ring system selected from the group consisting of a $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, and $-(C_4-C_9)$heterocycloalkenyl.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$ and R^9 is $-(C_1-C_6)$alkyl; and wherein said $-(C_1-C_6)$alkyl of said R^9 is

substituted by one to three R^{12} groups independently selected from the group consisting of $-OR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-OC(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}C(NR^{13}R^{14})(=NR^{13})$, $-NR^{13}C(NR^{13}R^{14})(=N-C(O)R^{13})$, $-NR^{13}C(O)R^{14}$, $-NR^{13}S(O)_jR^{13}$, $-S(O)_jR^{13}$, $-CF_3$, and $-CN$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$ and R^9 is $-(C_1-C_6)$alkyl, wherein said $-(C_1-C_6)$alkyl of said R^9 is substituted by one to three R^{12} groups independently selected from the group consisting of $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$ and R^9 is $-(C_1-C_6)$alkyl; wherein said $-(C_1-C_6)$alkyl of said R^9 is substituted by one to three R^{12} groups independently selected from the group consisting of $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl and $-(C_6-C_9)$heterobicycloalkenyl; and wherein each of the foregoing $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl and $-(C_6-C_9)$heterobicycloalkenyl of said R^{12} is optionally independently substituted by one to three groups independently selected from the group consisting of -halo, $-CF_3$, $-CN$, $-NO_2$, $-OH$, $-O((C_1-C_6)$alkyl), $-C(O)((C_1-C_6)$alkyl), $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, $-SH$, $-S((C_1-C_6)$alkyl), $-NH_2$, $-NH((C_1-C_6)$alkyl) and $-N((C_1-C_6)$alkyl$)_2$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-NR^7C(O)R^9$ and R^9 is $-(C_1-C_6)$alkyl; wherein said $-(C_1-C_6)$alkyl of said R^9 is substituted by one to three R^{12} groups independently selected from the group consisting of $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl of said R^{12} is optionally independently substituted by one to three groups selected from the group consisting of -halo, $-CF_3$, $-CN$, $-NO_2$, $-OH$, $-O((C_1-C_6)$alkyl), $-C(O)((C_1-C_6)$alkyl), $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, $-SH$, $-S((C_1-C_6)$alkyl), $-NH_2$, $-NH((C_1-C_6)$alkyl) and $-N((C_1-C_6)$alkyl$)_2$.

In another embodiment, the invention relates to a compound of formula I wherein each R^1 is independently selected from the group consisting of $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, and $-(C_2-C_6)$alkynyl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl moieties of said R^1 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is -(C_1-C_6)alkyl optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein each R^1 is -(C_1-C_6)alkyl is independently substituted with a group selected from the group consisting of R^{13}, $-S(O)_jR^{13}$, and $-NR^{13}S(O)_jR^{13}$.

In another embodiment, the invention relates to a compound of formula I wherein each R^1 is independently selected from the group consisting of -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkenyl; and wherein each of the foregoing -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl and -(C_4-C_9)heterocycloalkenyl moieties of said R^1 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is selected from the group consisting of -(C_2-C_9)heterocycloalkyl; and wherein said -(C_2-C_9)heterocycloalkyl of said R^1 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein each R^1 is independently selected from the group consisting of -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl of said R^1 moieties is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-S(O)_2NR^{13}R^{14}$.

In one embodiment, the invention relates to a compound of formula I wherein R^2 and R^3 are each independently selected from the group consisting of –H, -halo, and -OR^{10}.

In another embodiment, the invention relates to a compound of formula I wherein R^2 and R^3 are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl moieties of said R^2 and R^3 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^2 and R^3 are each independently selected from the group consisting of –H, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl; and wherein each of the foregoing -(C_3-C_{10})cycloalkyl, -(C_5-

C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl moieties of said R^2 and R^3 is optionally independently substituted by one to three R^{12} groups.

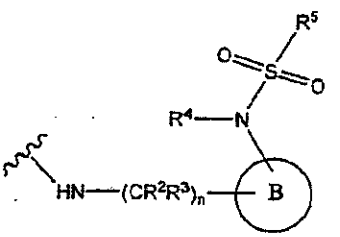
In another embodiment, the invention relates to a compound of formula I wherein R^2 and R^3 are each independently selected from the group consisting of –H, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^2 and R^3 is optionally independently substituted by one to three R^{12} groups.

In one embodiment, the invention relates to a compound of formula I wherein R^4 and R^5 are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl moieties of said R^4 and R^5 is optionally independently substituted by one to three R^{12} groups.

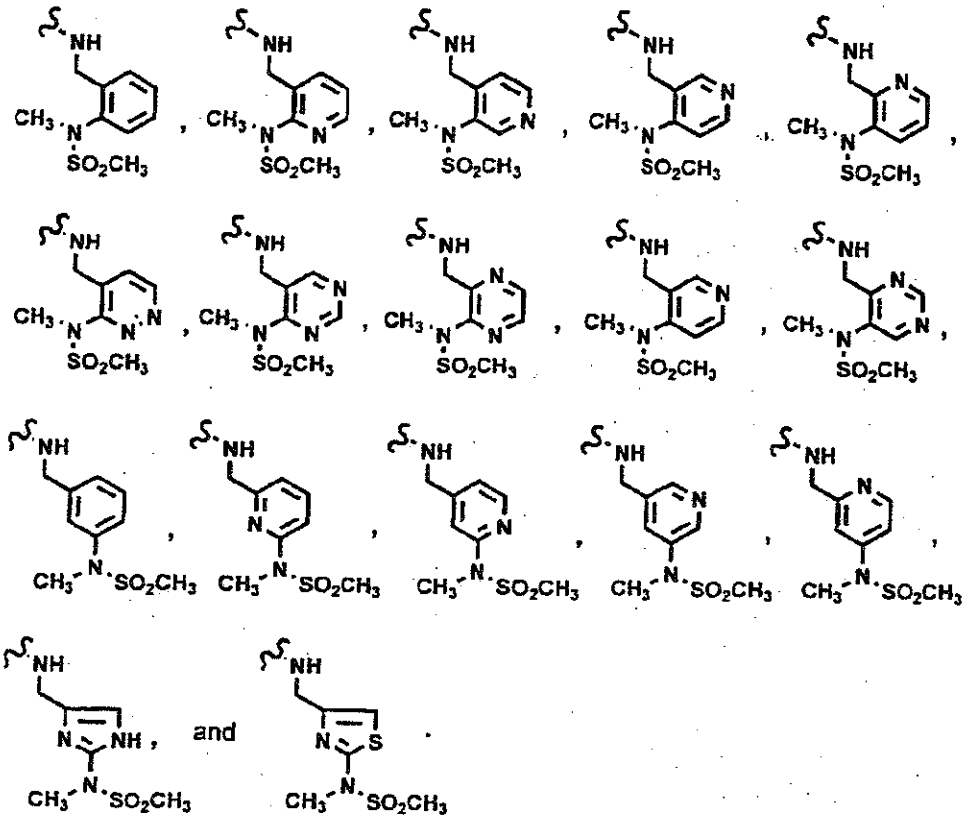
In another embodiment, the invention relates to a compound of formula I wherein R^4 and R^5 are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl and -(C_4-C_9)heterocycloalkenyl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl moieties of said R^4 and R^5 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^4 and R^5 are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^4 and R^5 is optionally independently substituted by one to three R^{12} groups.

In one embodiment, the invention relates to a compound of formula I wherein the moiety



represents a moiety selected from the group consisting of:



In one embodiment, the invention relates to a compound of formula I wherein R^6 is selected from the group consisting of $-NR^7R^8$, $-OR^{10}$, $-C(O)R^9$, $-CO_2R^{10}$, $-CONR^7R^8$, $-S(O)_jR^{11}$, $-NR^7CONR^7R^8$, $-NR^8SO_2R^{11}$-NO_2, –CN and $–CF_3$.

In another embodiment, the invention relates to a compound of formula I wherein R^6 is selected from the group consisting of $-CF_3$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_2-C_6)$perfluorinated alkyl, $-(C_2-C_6)$perfluorinated alkenyl, and $-(C_3-C_6)$perfluorinated alkynyl; and wherein each of said $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl moieties of said R^6 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^6 is $-CF_3$.

In another embodiment, the invention relates to a compound of formula I wherein R^6 is selected from the group consisting of $-(C_3-C_7)$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_5-C_{10})$bicycloalkenyl, $-(C_1-C_9)$heterocyclyl, $-(C_1-C_{10})$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, and $-(C_6-C_9)$heterobicycloalkenyl; and wherein each of said $-(C_3-C_7)$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl,

-(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, and -(C_6-C_9)heterobicycloalkenyl moieties of said R^6 is optionally independently substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula I wherein R^6 is selected from the group consisting of -(C_6-C_{10})aryl, -(C_1-C_9)heteroaryl, -(C_6-C_{10})perfluorinated aryl and -(C_1-C_9)perfluorinated heteroaryl; and wherein each of said -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^6 is optionally independently substituted by one to three R^{12} groups.

In one embodiment, the invention relates to a compound of formula I wherein K is CH.

In another embodiment, the invention relates to a compound of formula I wherein K is C(NH_2).

In another embodiment, the invention relates to a compound of formula I wherein K is N.

In one embodiment, the invention relates to a compound of formula I wherein m is 1.

In another embodiment, the invention relates to a compound of formula I wherein m is 0.

In one embodiment, the invention relates to a compound of formula I wherein n is 1.

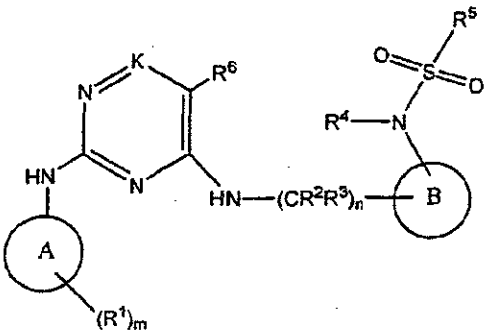
In another embodiment, the invention relates to a compound of formula I wherein n is 2.

In another embodiment, the invention relates to a compound of formula I wherein n is 3.

In one embodiment, the invention relates to a compound of formula I wherein K is CH, n is 1, and R_6 is $-CF_3$.

In one embodiment, the invention relates to a compound of formula I wherein K is CH, n is 2, and R_6 is $-CF_3$.

The present invention also provides a compound of formula Ia:



Ia

or a pharmaceutically acceptable salt thereof; wherein

A is phenyl;

B is phenyl or a 5- to 6-membered heteroaryl;

K is CH, $C(NH_2)$ or N;

each R^1 is independently selected from the group consisting of -H, halo, $-CF_3$, $-CN$, $-NO_2$, $-NR^7R^8$, $-NR^7C(NR^7R^8)(=CR^9)$, $-CR^7(NR^7R^8)(=NR^7)$, $-NR^7C(NR^7R^8)(=NR^7)$, $-NR^7C(O)R^9$, $-C(O)NR^7R^8$, $-C(O)R^9$, $-C(O)C(O)R^9$, $-C(O)OR^{10}$, $-OC(O)R^9$, $-OR^{10}$, $-OC(O)OR^{10}$, $-S(O)_jR^{11}$, $-S(O)(=NR^7)R^8$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_1-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^1 is optionally independently substituted by one to three R^{12} groups;

R^2 and R^3 are each independently selected from the group consisting of –H, -halo, $-OR^{10}$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^2 and R^3 is optionally substituted by one to three R^{12} groups;

R^4 and R^5 are each independently selected from the group consisting of –H, $-NR^7R^8$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl,

-(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^4 and R^5 is optionally substituted by one to three R^{12} groups;

R^6 is selected from the group consisting of -halo, $-NR^7R^8$, $-OR^{10}$, $-C(O)R^9$, $-CO_2R^{10}$, $-CONR^7R^8$, $-S(O)_jR^{11}$, $-NR^7CONR^7R^8$, and $-NR^8SO_2R^{11}$, $-NO_2$, -CN, $-CF_3$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_2-C_6)perfluorinated alkyl, -(C_2-C_6)perfluorinated alkenyl, -(C_3-C_6)perfluorinated alkynyl, -(C_3-C_7)cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, -(C_1-C_9)heteroaryl, -(C_6-C_{10})perfluorinated aryl, and -(C_1-C_9)perfluorinated heteroaryl; and wherein each of said -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl moieties of said R^6 is optionally substituted by one to three R^{12} groups;

R^7 and R^8 are each independently selected from the group consisting of -H, $-OR^{10}$, $-S(O)_jR^{11}$, $-NO_2$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^7 and R^8 is optionally substituted by one to three R^{12} groups;

each R^9 is independently selected from the group consisting of -H, -halo, $-NR^{13}R^{14}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^9 is optionally substituted by one to three R^{12} groups;

each R^{10} is independently selected from the group consisting of -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-

C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{10} is optionally substituted by one to three R^{12} groups;

each R^{11} is independently selected from the group consisting of -H, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; land wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{11} is optionally substituted by one to three R^{12} groups;

each R^{12} is independently selected from the group consisting of -H, -OR^{13}, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$OC(O)OR^{13}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, -$NR^{13}C(NR^{13}R^{14})(=NR^{13})$, -$NR^{13}C(NR^{13}R^{14})(=N\text{-}C(O)R^{13})$, -$NR^{13}C(O)R^{14}$, -$NR^{13}S(O)_jR^{13}$, -$S(O)_jR^{13}$, -$CF_3$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_6$-$C_{10}$)bicycloalkyl, -($C_6$-$C_{10}$)bicycloalkenyl, -($C_2$-$C_9$)heterocycloalkyl, -($C_4$-$C_9$)heterocycloalkenyl, -($C_6$-$C_9$)heterobicycloalkyl, -($C_6$-$C_9$)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{12} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -$C(O)R^{15}$, -$C(O)NR^{15}R^{16}$, -$S(O)_jR^{15}$, and -$S(O)_jNR^{15}R^{16}$, -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{13} and R^{14} are each independently selected from the group consisting of –H, -$NR^{15}C(O)R^{16}$, -CF_3, -CN, -$S(O)_jR^{15}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the

foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{13} and R^{14} is optionally independently substituted by one to three groups selected from the group consisting of -halo, $-CF_3$, -CN, $-NO_2$, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), $-NH_2$, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{15} and R^{16} are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said $R^{15}$and R^{16} is optionally independently substituted by one to three groups selected from the group consisting of -halo, $-CF_3$, -CN, $-NO_2$, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), $-NH_2$, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

wherein one or two carbon ring atoms in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkenyl in said R^1-R^{14} groups may optionally and independently be replaced with -C(O)- or -C(S)-;

wherein two groups attached to the same tetravalent carbon atom in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkeny of said R^1 to R^{14} groups may optionally join to form a ring system selected from the group consisting of a -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl; and wherein

j is an integer from 0 to 2;

n is an integer from 1 to 3; and

m is an integer from 0 to 3.

In another embodiment, the invention relates to a compound of formula Ia wherein at least one R^1 is $-C(O)OR^{10}$.

In another embodiment, the invention relates to a compound of formula Ia wherein at least one R^1 is $-C(O)OR^{10}$ and R^{10} is $-(C_1-C_6)$alkyl optionally substituted by one to three R^{12} groups.

In another embodiment, the invention relates to a compound of formula Ia wherein at least one R^1 is $-C(O)R^9$.

In another embodiment, the invention relates to a compound of formula Ia wherein at least one R^1 is $-C(O)R^9$ and R^9 is selected from the group consisting of $-NR^{13}R^{14}$, $-(C_1-C_6)$alkyl and $-(C_3-C_{10})$cycloalkyl; wherein each of said $-(C_1-C_6)$alkyl, and $-(C_3-C_{10})$cycloalkyl of said R^9 group is optionally substituted by one to three R^{12} groups; and wherein two groups attached to the same tetravalent carbon atom of said $-(C_1-C_6)$alkyl and $-(C_3-C_{10})$cycloalkyl of said R^9 may optionally join to form a ring system selected from the group consisting of a $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, and $-(C_4-C_9)$heterocycloalkenyl.

In another embodiment, the invention relates to a compound of formula Ia wherein at least one R^1 is $-C(O)R^9$ and R^9 is $-(C_1-C_6)$alkyl optionally substituted by a group selected from the group consisting of $-NR^{13}R^{14}$, $-NR^{15}C(O)R^{16}$ and $-CF_3$.

In another embodiment, the invention relates to a compound of formula Ia wherein at least one R^1 is $-C(O)R^9$ and R^9 is $-NR^{13}R^{14}$.

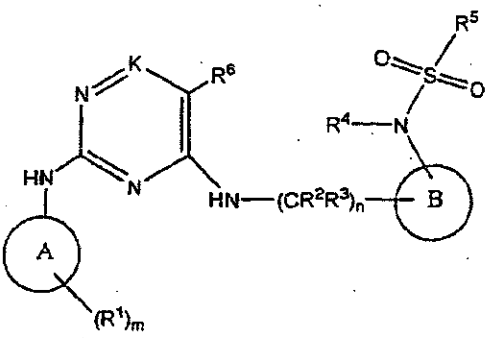
In another embodiment, the invention relates to a compound of formula Ia wherein at least one R^1 is $-C(O)R^9$, R^9 is $-NR^{13}R^{14}$, and R^{13} and R^{14} are each independently selected from the group consisting of –H and $-(C_1-C_6)$alkyl; and wherein said $-(C_1-C_6)$alkyl of said R^{13} and R^{14} groups is optionally independently substituted with one to three groups selected from the group consisting of -halo, $-CF_3$, -CN, $-NO_2$, -OH, $-O((C_1-C_6)$alkyl), $-C(O)((C_1-C_6)$alkyl), $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, -SH, $-S((C_1-C_6)$alkyl), $-NH_2$, $-NH((C_1-C_6)$alkyl) and $-N((C_1-C_6)\text{alkyl})_2$.

In another embodiment, the invention relates to a compound of formula Ia wherein at least one R^1 is $-C(O)R^9$, R^9 is $-NR^{13}R^{14}$, and R^{13} and R^{14} are each independently selected from the group consisting –H and $-(C_1-C_6)$alkyl; wherein said $-(C_1-C_6)$alkyl of said R^{13} and R^{14} are each optionally independently substituted with one to three groups selected from the group consisting of $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of said $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl optional

substituents of said -(C_1-C_6)alkyl of said R^{13} and R^{14} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$.

In another embodiment, the invention relates to a compound of formula Ia wherein m is 1.

The present invention also provides a compound of formula Ib:



Ib

or a pharmaceutically acceptable salt thereof; wherein

A is phenyl;

B is phenyl or a 5- to 6-membered heteroaryl;

K is CH, C(NH_2) or N;

at least one R^1 is -(C_1-C_6)alkyl optionally independently substituted by one to three R^{12} groups;

R^2 and R^3 are each independently selected from the group consisting of –H, -halo, -OR^{10}, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^2 and R^3 is optionally substituted by one to three R^{12} groups;

R^4 and R^5 are each independently selected from the group consisting of –H, -NR^7R^8, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-

C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^4 and R^5 is optionally substituted by one to three R^{12} groups;

R^6 is selected from the group consisting of -halo, $-NR^7R^8$, $-OR^{10}$, $-C(O)R^9$, $-CO_2R^{10}$, $-CONR^7R^8$, $-S(O)_jR^{11}$, $-NR^7CONR^7R^8$, and $-NR^8SO_2R^{11}$, $-NO_2$, -CN, $-CF_3$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_2-C_6)perfluorinated alkyl, -(C_2-C_6)perfluorinated alkenyl, -(C_3-C_6)perfluorinated alkynyl, -(C_3-C_7)cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, -(C_1-C_9)heteroaryl, -(C_6-C_{10})perfluorinated aryl, and -(C_1-C_9)perfluorinated heteroaryl; and wherein each of said -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl moieties of said R^6 is optionally substituted by one to three R^{12} groups;

R^7 and R^8 are each independently selected from the group consisting of -H, $-OR^{10}$, $-S(O)_jR^{11}$, $-NO_2$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^7 and R^8 is optionally substituted by one to three R^{12} groups;

each R^9 is independently selected from the group consisting of -H, -halo, $-NR^{13}R^{14}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^9 is optionally substituted by one to three R^{12} groups;

each R^{10} is independently selected from the group consisting of -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-

C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{10} is optionally substituted by one to three R^{12} groups;

each R^{11} is independently selected from the group consisting of -H, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; land wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{11} is optionally substituted by one to three R^{12} groups;

each R^{12} is independently selected from the group consisting of -H, -OR^{13}, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$OC(O)OR^{13}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, -$NR^{13}C(NR^{13}R^{14})(=NR^{13})$, -$NR^{13}C(NR^{13}R^{14})(=N\text{-}C(O)R^{13})$, -$NR^{13}C(O)R^{14}$, -$NR^{13}S(O)_jR^{13}$, -$S(O)_jR^{13}$, -$CF_3$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_6$-$C_{10}$)bicycloalkyl, -($C_6$-$C_{10}$)bicycloalkenyl, -($C_2$-$C_9$)heterocycloalkyl, -($C_4$-$C_9$)heterocycloalkenyl, -($C_6$-$C_9$)heterobicycloalkyl, -($C_6$-$C_9$)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{12} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -$C(O)R^{15}$, -$C(O)NR^{15}R^{16}$, -$S(O)_jR^{15}$, and -$S(O)_jNR^{15}R^{16}$, -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{13} and R^{14} are each independently selected from the group consisting of –H, -$NR^{15}C(O)R^{16}$, -CF_3, -CN, -$S(O)_jR^{15}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-

C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{13} and R^{14} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{15} and R^{16} are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said $R^{15}$and R^{16} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

wherein one or two carbon ring atoms in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkenyl in said R^1-R^{14} groups may optionally and independently be replaced with -C(O)- or -C(S)-;

wherein two groups attached to the same tetravalent carbon atom in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkeny of said R^1 to R^{14} groups may optionally join to form a ring system selected from the group consisting of a -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl; and wherein

j is an integer from 0 to 2;

n is an integer from 1 to 3; and

m is an integer from 0 to 3.

In another embodiment, the invention relates to a compound of formula Ia or 1b wherein R^2 and R^3 are each independently selected from the group consisting of –H, -halo, and $-OR^{10}$.

In another embodiment, the invention relates to a compound of formula Ia or 1b wherein R^4 and R^5 are each independently selected from the group consisting of –H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, and $-(C_2-C_6)$alkynyl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl moieties of said R^4 and R^5 is optionally independently substituted by one to three R^{12} groups.

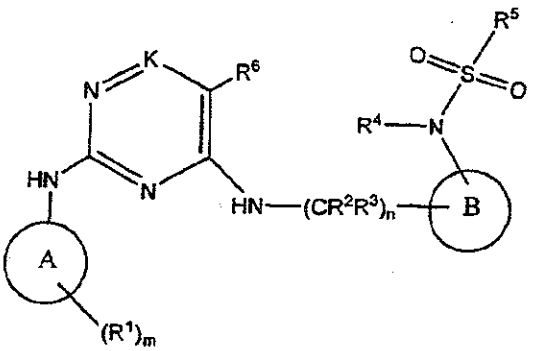
In another embodiment, the invention relates to a compound of formula Ia or 1b wherein R^6 is $-CF_3$.

In another embodiment, the invention relates to a compound of formula Ia or 1b wherein K is CH.

In another embodiment, the invention relates to a compound of formula Ia or 1b wherein m is 1.

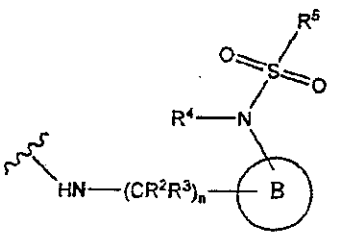
In another embodiment, the invention relates to a compound of formula Ia or 1b wherein n is 1.

The present invention provides a compound of formula Ic:

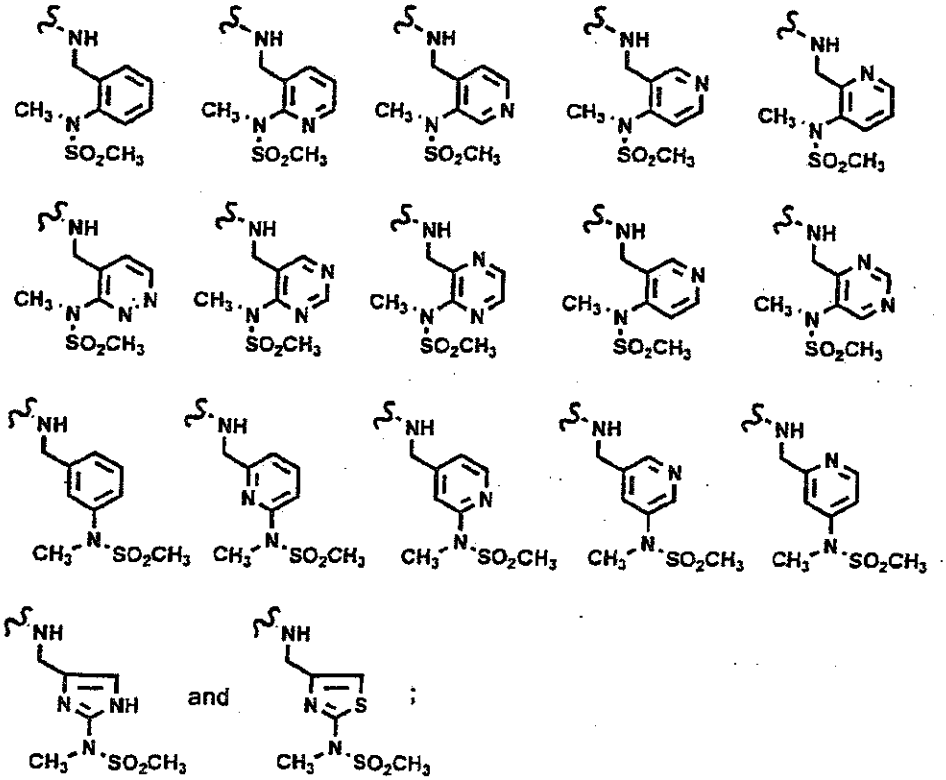


Ic

or a pharmaceutically acceptable salt thereof; wherein the moiety



represents a moiety selected from the group consisting of:



A is a ring moiety selected from the group consisting of a:

(a) 4- to 7-membered carbocyclyl,

(b) 4- to 7-membered heterocyclyl,

(c) phenyl, and

(d) 5- to 6-membered heteroaryl ring,

wherein each of said 4- to 7-membered carbocyclyl and 4- to 7-membered heterocyclyl of said A group may optionally contain one or two olefinic bonds; and wherein one or two carbon ring atoms in each of said 4- to 7-membered carbocyclyl and 4- to 7-membered heterocyclic of said A group may independently optionally be replaced with one or two moieties independently selected from the group consisting of -C(O)-, -C(S)- and -C(=NR^4)-;

K is CH, $C(NH_2)$ or N;

each R^1 is independently selected from the group consisting of -H, halo, $-CF_3$, -CN, $-NO_2$, $-NR^7R^8$, $-NR^7C(NR^7R^8)(=CR^9)$, $-CR^7(NR^7R^8)(=NR^7)$, $-NR^7C(NR^7R^8)(=NR^7)$,

$-NR^7C(O)R^9$, $-C(O)NR^7R^8$, $-C(O)R^9$, $-C(O)C(O)R^9$, $-C(O)OR^{10}$, $-OC(O)R^9$, $-OR^{10}$, $-OC(O)OR^{10}$, $-S(O)_jR^{11}$, $-S(O)(=NR^7)R^8$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^1 is optionally independently substituted by one to three R^{12} groups;

R^6 is selected from the group consisting of -halo, $-NR^7R^8$, $-OR^{10}$, $-C(O)R^9$, $-CO_2R^{10}$, $-CONR^7R^8$, $-S(O)_jR^{11}$, $-NR^7CONR^7R^8$, and $-NR^8SO_2R^{11}$, $-NO_2$, -CN, $-CF_3$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_2-C_6)$perfluorinated alkyl, $-(C_2-C_6)$perfluorinated alkenyl, $-(C_3-C_6)$perfluorinated alkynyl, $-(C_3-C_7)$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_1-C_9)$heterocyclyl, $-(C_1-C_{10})$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl, $-(C_6-C_{10})$aryl, $-(C_1-C_9)$heteroaryl, $-(C_6-C_{10})$perfluorinated aryl, and $-(C_1-C_9)$perfluorinated heteroaryl; and wherein each of said $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_7)$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_1-C_9)$heterocyclyl, $-(C_1-C_{10})$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl moieties of said R^6 is optionally substituted by one to three R^{12} groups;

R^7 and R^8 are each independently selected from the group consisting of -H, $-OR^{10}$, $-S(O)_jR^{11}$, $-NO_2$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^7 and R^8 is optionally substituted by one to three R^{12} groups;

each R^9 is independently selected from the group consisting of -H, -halo, $-NR^{13}R^{14}$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl -

(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^9 is optionally substituted by one to three R^{12} groups;

each R^{10} is independently selected from the group consisting of -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{10} is optionally substituted by one to three R^{12} groups;

each R^{11} is independently selected from the group consisting of -H, -$NR^{13}R^{14}$, -$C(O)R^{13}$, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; land wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{11} is optionally substituted by one to three R^{12} groups;

each R^{12} is independently selected from the group consisting of -H, -OR^{13}, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$OC(O)OR^{13}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, -$NR^{13}C(NR^{13}R^{14})(=NR^{13})$, -$NR^{13}C(NR^{13}R^{14})(=N\text{-}C(O)R^{13})$, -$NR^{13}C(O)R^{14}$, -$NR^{13}S(O)_jR^{13}$, -$S(O)_jR^{13}$, -$CF_3$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_6$-$C_{10}$)bicycloalkyl, -($C_6$-$C_{10}$)bicycloalkenyl, -($C_2$-$C_9$)heterocycloalkyl, -($C_4$-$C_9$)heterocycloalkenyl, -($C_6$-$C_9$)heterobicycloalkyl, -($C_6$-$C_9$)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{12} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -$C(O)R^{15}$, -$C(O)NR^{15}R^{16}$, -$S(O)_jR^{15}$, and -$S(O)_jNR^{15}R^{16}$, -(C_3-

C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{13} and R^{14} are each independently selected from the group consisting of –H, -$NR^{15}C(O)R^{16}$, -CF_3, -CN, -$S(O)_iR^{15}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{13} and R^{14} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{15} and R^{16} are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said $R^{15}$and R^{16} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

wherein one or two carbon ring atoms in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkenyl in said $R^1$and R^6-R^{14} groups may optionally and independently be replaced with -C(O)- or -C(S)-;

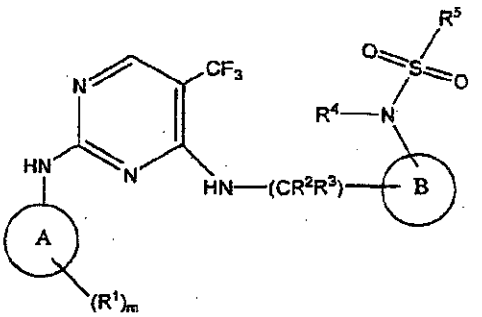
wherein two groups attached to the same tetravalent carbon atom in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-

C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkenyl of said $R^1$and R^6-R^{14} groups may optionally join to form a ring system selected from the group consisting of a -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl; and wherein

j is an integer from 0 to 2; and

m is an integer from 0 to 3.

The present invention also provides a compound of formula Id:



Id

or a pharmaceutically acceptable salt thereof; wherein

A is phenyl or a 5- to 6-membered heteroaryl;

B is selected from the group consisting of phenyl, pyridyl, pyrimidinyl and pyrazinyl;

each R^1 is independently selected from the group consisting of -H, halo, -CF_3, -CN, -C(O)NR^7R^8, -C(O)R^9, -OR^{10}, and -(C_1-C_6)alkyl; and wherein the -(C_1-C_6)alkyl moiety of said R^1 is optionally independently substituted by one to three R^{12} groups;

R^2 and R^3 are each independently selected from the group consisting of –H and -(C_1-C_6)alkyl;

R^4 and R^5 are each independently selected from the group consisting of –H and -(C_1-C_6)alkyl;

R^7 and R^8 are each independently selected from the group consisting of -H, -OR^{10}, -S(O)$_j R^{11}$, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and

-(C_1-C_9)heteroaryl moieties of said R^7 and R^8 is optionally substituted by one to three R^{12} groups;

each R^9 is independently selected from the group consisting of -H, -halo, $-NR^{13}R^{14}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^9 is optionally substituted by one to three R^{12} groups;

each R^{10} is independently selected from the group consisting of -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{10} is optionally substituted by one to three R^{12} groups;

each R^{11} is independently selected from the group consisting of -H, $-NR^{13}R^{14}$, $-C(O)R^{13}$, $-CF_3$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; land wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^{11} is optionally substituted by one to three R^{12} groups;

each R^{12} is independently selected from the group consisting of -H, $-OR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-OC(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}C(NR^{13}R^{14})(=NR^{13})$, $-NR^{13}C(NR^{13}R^{14})(=N-C(O)R^{13})$, $-NR^{13}C(O)R^{14}$, $-NR^{13}S(O)_jR^{13}$, $-S(O)_jR^{13}$, $-CF_3$, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-

C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{12} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)R^{15}, -C(O)$NR^{15}R^{16}$, -S(O)$_j R^{15}$, and -S(O)$_j NR^{15}R^{16}$, -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{13} and R^{14} are each independently selected from the group consisting of –H, -NR^{15}C(O)R^{16}, -CF_3, -CN, -S(O)$_j R^{15}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{13} and R^{14} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

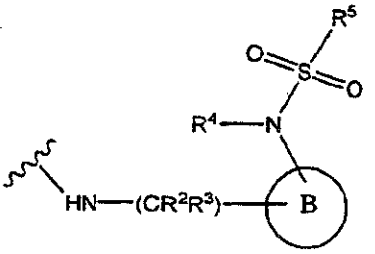
R^{15} and R^{16} are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said $R^{15}$and R^{16} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

j is an integer from 0 to 2; and

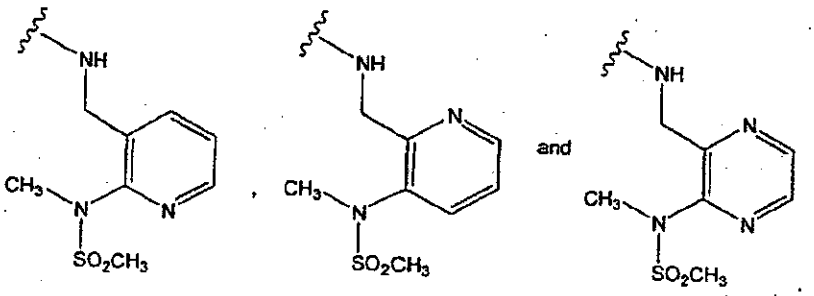
m is an integer from 1 to 3.

In another embodiment, the invention relates to a compound of formula Id wherein A is a phenyl.

In another embodiment, the invention relates to a compound of formula Id wherein the moiety



represents a moiety selected from the group consisting of:

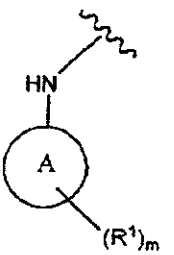


In another embodiment, the invention relates to a compound of formula Id wherein R^1 is $-C(O)NR^7R^8$ and R^7 and R^8 are each independently selected from the group consisting –H and $-(C_1-C_6)$alkyl.

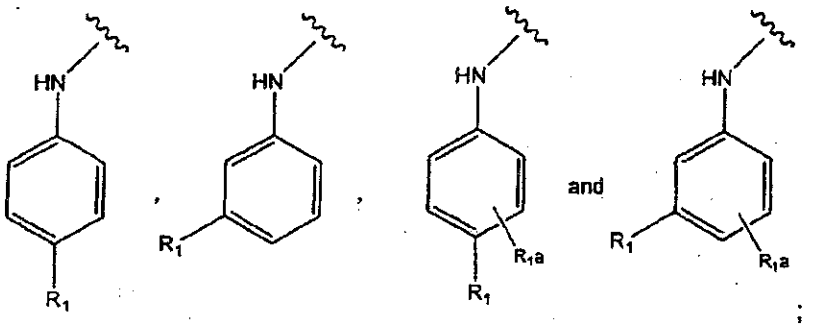
In another embodiment, the invention relates to a compound of formula Id wherein R^1 is $-OR^{10}$ and R^{10} is $-(C_1-C_6)$alkyl.

In another embodiment, the invention relates to a compound of formula Id wherein each R^1 is independently selected from the group consisting of -H, fluoro, chloro, $-CF_3$, -CN, methyl, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)NHCH_2CH_3$, $-C(O)N(CH_3)_2$, and $-OCH_3$.

In another embodiment, the invention relates to a compound of formula Id wherein the moiety



represents a moiety selected from the group consisting of:



;

R1 is –C(O)NH2 or –C(O)NHCH3; and

R1a is selected from the group consisting of fluoro, chloro, methyl and –OCH3.

In another embodiment, the invention relates to a compound of formula Id wherein R^2 and R^3 are –H.

In another embodiment, the invention relates to a compound of formula Id wherein R^4 and R^5 are methyl.

In another embodiment, the invention relates to a compound of formula Id wherein m is 1 or 2.

In another embodiment, the invention relates to a compound of formula I wherein each R^1 is independently selected from the group consisting of -H, fluoro, chloro, $-CF_3$, -CN, $-(C_1-C_6)$alkyl, $-C(O)NR^7R^8$, and $-OR^{10}$.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is $-C(O)NR^7R^8$ and R^7 and R^8 are each independently selected from the group consisting –H and $-(C_1-C_6)$alkyl.

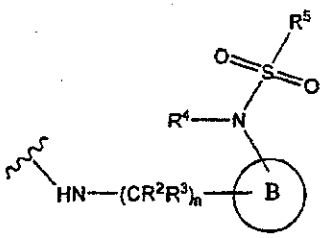
In another embodiment, the invention relates to a compound of formula I wherein R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of –H and $-(C_1-C_6)$alkyl.

In another embodiment, the invention relates to a compound of formula I wherein R^2 and R^3 are –H.

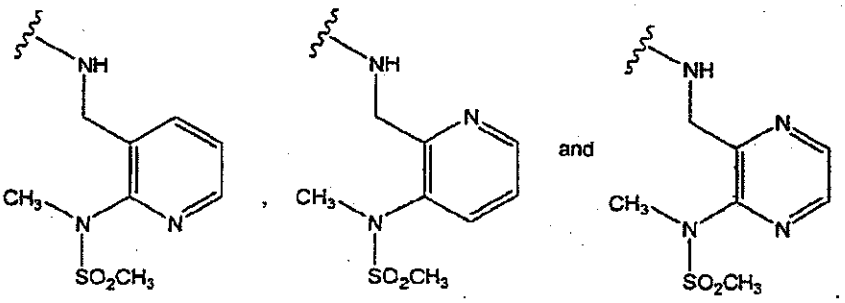
In another embodiment, the invention relates to a compound of formula I wherein R^4 and R^5 are methyl.

In another embodiment, the invention relates to a compound of formula I wherein R^6 is $-CF_3$, K is CH, m is 1 or 2, and n is 1.

In another embodiment, the invention relates to a compound of formula I wherein the moiety



represents a moiety selected from the group consisting of:



In another embodiment, the invention relates to a compound of formula **I, Ia, Ib, Ic or Id** wherein R^{12} further includes halo.

In another embodiment, the invention relates to a compound of formula **I, Ia or Ib** wherein R^4 is selected from the group consisting of –H, $-NR^7R^8$, $-OR^{10}$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl; wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^4 is optionally substituted by one to three R^{12} groups; and wherein R^4 is not –H when B is a 5- to 6-membered heteroaryl; and R^5 is selected from the group consisting of $-NR^7R^8$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^5 is optionally substituted by one to three R^{12} groups;

In one embodiment, the invention also relates to the compounds described as Compounds **1-415** in Examples **1-415** in the Examples section of the subject application, and pharmaceutically acceptable salts thereof.

Non-limiting examples of compounds representing the scope of this invention include:

4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide;

3-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

4-methoxy-3-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

3-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

2-fluoro-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

2-fluoro-4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide;

2-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

2-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

2-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

3-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

3-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

3-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

2-chloro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

2-chloro-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

2-chloro-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

3-fluoro-N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

2-fluoro-N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

N,2-dimethyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

N,3-dimethyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; and

N,3-dimethyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; or a pharmaceutically acceptable salt thereof.

Non-limiting examples of compounds representing the scope of this invention also include:

(R)-N-(3-((2-(4-(1-aminoethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide;

N-(3-((2-(4-(aminomethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide;

N-[4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzyl]acetamide;

N-(3-((2-(4-(hydroxymethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide;

N-(3-((2-(4-(chloromethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide;

N-(3-((2-(4-((1,3-dihydroxypropan-2-ylamino)methyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide;

tert-butyl 3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoate;

3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoic acid;

N-cyclopropyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

N-(3-((2-(4-(1-hydroxyethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide;

2-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

3-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; and

N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; or a pharmaceutically acceptable salt thereof.

Non-limiting examples of compounds representing the scope of this invention also include:

2-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

3-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; and

N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; or a pharmaceutically acceptable salt thereof.

Non-limiting examples of compounds representing the scope of this invention also include:

2-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide formate;

3-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide formate; and

N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride.

As used herein, the term "alkyl," as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, secondary-butyl, tertiary-butyl); optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl,

-(C_1-C_6)alkoxy, -(C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl. The phrase "each of said alkyl" as used herein refers to any of the preceding alkyl moieties within a group such alkoxy, alkenyl or alkylamino. Preferred alkyls include (C_1-C_6)alkyl, more preferred are (C_1-C_4)alkyl, and most preferred are methyl and ethyl.

As used herein, the term "halogen" or "halo' includes fluoro, chloro, bromo or iodo or fluoride, chloride, bromide or iodide.

As used herein, the term "alkenyl" means straight or branched chain unsaturated radicals of 2 to 6 carbon atoms, including, but not limited to ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, -(C_1-C_6)alkoxy, -(C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl.

As used herein, the term "alkynyl" means straight or branched hydrocarbon chain radicals having one triple bond including, but not limited to, ethynyl, propynyl, butynyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, -(C_1-C_6)alkoxy, -(C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl.

As used herein, the term "carbonyl" or "C(O)" (as used in phrases such as alkylcarbonyl, alkyl-C(O)- or alkoxycarbonyl) refers to the joinder of the >C=O moiety to a second moiety such as an alkyl or amino group (i.e. an amido group). Alkoxycarbonylamino (i.e. alkoxy-C(O)-NH-) refers to an alkyl carbamate group. The carbonyl group is also equivalently defined herein as C(O). Alkylcarbonylamino refers to groups such as acetamide.

As used herein, the term "cycloalkyl" refers to a mono-carbocyclic ring (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl,); optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, -(C_1-C_6)alkoxy, -(C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl. Cycloalkyls include -(C_3-C_{10})cycloalkyl.

As used herein, the term "cycloalkenyl" refers to a cycloalkyl as defined above and further containing 1 or 2 double bonds (e.g., cyclopentenyl, cyclohexenyl). Cycloalkenyls include -(C_5-C_{10})cycloalkenyl.

The term "4- to 7-membered carbocyclyl" refers to a non-aromatic ring containing 4 to 7 carbon ring atoms, optionally containing 1 or 2 double bonds, and optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro,

trifluoromethyl, -(C_1-C_6)alkoxy, -(C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl. Non-limiting examples of 4- to 7-membered carbocyclyls include cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentendienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptenyl, and cycloheptadienyl.

As used herein, the term "bicycloalkyl" refers to a cycloalkyl as defined above which is bridged to a second carbocyclic ring (e.g., bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.). Bicycloalkyls include -(C_6-C_{10})bicycloalkyl.

As used herein, the term "bicycloalkenyl" refers to a bicycloalkyl as defined above and further containing 1 or 2 double bonds. Bicycloalkenyls include -(C_6-C_{10})bicycloalkenyl.

As used herein, the term "(C_6-C_{10})aryl" means aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like; optionally substituted by 1 to 3 suitable substituents as defined above.

As used herein, the term "(C_1-C_9)heteroaryl" refers to an aromatic heterocyclic group having from 1 to 9 carbon atoms and containing from 1 to 4 heteroatoms in the ring selected from the group consisting of O, S and N. In addition to said heteroatom, the aromatic group may optionally have up to four N atoms in the ring. For example, heteroaryl group includes pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), quinolyl, isoquinolyl, benzothienyl, benzofuryl, indolyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, -(C_1-C_6)alkoxy, -(C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl.

The term "5- to 6-membered heteroaryl ring" refers to an aromatic ring containing from 1 to 5 carbon atoms ring atoms and from 1 to 4 hetero ring atoms, and optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, -(C_1-C_6)alkoxy, -(C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl. Non-limiting examples of 5- to 6-membered heteroaryl rings include furanyl, pyrrolyl, thiopenyl, thiazolyl, isothiazolyl, pyrazolyl, oxazoyl, isoxazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, oxadiazoyl, thiadiazoyl, benzothiazolyl, and benzooxazolyl.

As used herein, the term heteroatom refers to an atom or group selected from N, O, $S(O)_q$ or NR, where q is an integer from 0 to 2 and R is a substituent group.

The term "(C_1-C_9)heterocycloalkyl" as used herein refers to a cyclic group containing 1 to 9 carbon atoms and 1 to 4 hetero atoms. Non-limiting examples of said monocyclic saturated or partially saturated ring systems are tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, thiomorpholin-yl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazin-yl, morpholin-yl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-oxazin-2-yl, 1,2,5-oxathiazin-4-yl and the like; optionally containing 1 or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, -(C_1-C_6)alkoxy, -(C_5-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl.

As used herein, the term "heterocycloalkenyl" refers to a heterocycloalkyl as defined above and further containing 1 or 2 double bonds. Heterocycloalkenyls include -(C_4-C_9)heterocycloalkenyl.

The term "4- to 7-membered heterocyclyl" refers to a non-aromatic ring containing from 1 to 6 carbon atoms ring atoms and from 1 to 4 hetero ring atoms, optionally containing 1 or 2 double bonds, and optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, -(C_1-C_6)alkoxy, -(C_5-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or -(C_1-C_6)alkyl. Non-limiting examples of 4- to 7-membered heterocyclyls include azetidinyl, oxetanyl, pyrrolidinyl, dihydropyrazolyl, tetrahydropyrazolyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothiophenyl, tetrahydrothiophenyl, dihydropyridinyl, tetrahydropyridinyl, piperidinyl, piperazinyl, pyranyl, dihydropyranyl, tetrahydropyranyl, thiopyrianyl, dihydrothiopyranyl, tetrahydrothiopyranyl, morpholinyl, dihydroazepinyl, tetrahydroazepinyl, dihydrooxepinyl, tetrahydrooxepinyl, oxepanyl, dihyrothiepinyl, tetrahydrothiepinyl and thiepanyl.

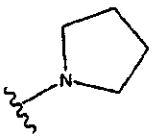
As used herein, the term "heterobicycloalkyl" refers to a bicycloalkyl as defined above, wherein at least one of the carbon ring atoms has been replaced by at least one heteroatom (e.g. tropane). Heterobicycloalkyls include -(C_6-C_9)heterobicycloalkyl.

As used herein, the term "heterobicycloalkenyl" refers to a heterobicycloalkyl as defined above and further containing 1 or 2 double bonds. Heterobicycloalkenyls include -(C_6-C_9)heterocycloalkenyl.

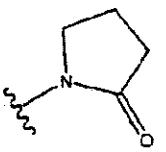
Nitrogen heteroatoms as used herein refers to N=, >N and -NH; wherein -N= refers to a nitrogen double bond; >N refers to a nitrogen containing two bond connections and –N refers to a nitrogen containing one bond.

The term "perfluorinated" or "perfluoro" refer to a compound having 4 or more fluorine groups.

The term "replaced by" refers to compounds in which an element selected from the group consisting of -C(O)- and –C(S)- replaces a methylene moiety in a non-aromatic cyclic ring system. For example, if a substituent is a heterocycloalkyl group, such as an azetidine group:



a methylene ring moiety may be replaced by, e.g., a –C(O)- to form a pyrrolidinone group:



Compounds of the invention can accommodate up to three such replacements.

The present invention also includes isotopically-labeled compounds, which are identical to those recited in formulae I, Ia, Ib, Ic, Id and II, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with

heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labeled reagent for a non-isotopically-labeled reagent.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include a basic moiety, such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

The invention also relates to base addition salts of the compounds of the invention. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of the compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

Suitable base salts are formed from bases which form non-toxic salts. Non-limiting examples of suitable base salts include the aluminum, arginine, benzathine,

calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002). Methods for making pharmaceutically acceptable salts of compounds of the invention are known to one of skill in the art.

This invention also encompasses compounds of the invention containing protective groups. One skilled in the art will also appreciate that compounds of the invention can also be prepared with certain protecting groups that are useful for purification or storage and can be removed before administration to a patient. The protection and deprotection of functional groups is described in "Protective Groups in Organic Chemistry", edited by J.W.F. McOmie, Plenum Press (1973) and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of this invention include all stereoisomers (e.g., cis and trans isomers) and all optical isomers of compounds of the invention (e.g., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

The compounds, salts and prodrugs of the present invention can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds.

The present invention also includes atropisomers of the present invention. Atropisomers refer to compounds of the invention that can be separated into rotationally restricted isomers.

The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

The compounds of the invention may also exist in unsolvated and solvated forms. Accordingly, the invention also relates to the hydrates and solvates of the compounds of

the invention. Thus, it will be understood that the compounds of formula I, and pharmaceutically acceptable salts thereof also include hydrates and solvates of said compounds of formula I, and pharmaceutically acceptable salts thereof, as discussed below.

The term "solvate" is used herein to describe a noncovelent or easily reversible combination between solvent and solute, or dispersion means and disperse phase. It will be understood that the solvate can be in the form of a solid, slurry (e.g., a suspension or dispersoid), or solution. Non-limiting examples of solvents include ethanol, methanol, propanol, acetonitrile, dimethyl ether, diethyl ether, tetrahydrofuan, methylene chloride, and water. The term 'hydrate' is employed when said solvent is water.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

The invention also relates to prodrugs of the compounds of the invention. Thus certain derivatives of compounds of the invention which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of the invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as "prodrugs". Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (Ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of the invention with

certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some non-limiting examples of prodrugs in accordance with the invention include

(i) where the compound of the invention contains a carboxylic acid functionality (-COOH), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula (I) is replaced by (C_1-C_6)alkyl;

(ii) where the compound of the invention contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of the invention is replaced by (C_1-C_6)alkanoyloxymethyl; and

(iii) where the compound of the invention contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogen atoms of the amino functionality of the compound of the invention is/are replaced by (C_1-C_6)alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Moreover, certain compounds of the invention may themselves act as prodrugs of other compounds of the invention.

Also included within the scope of the invention are metabolites of compounds of the invention, that is, compounds formed in vivo upon administration of the drug. Some examples of metabolites in accordance with the invention include:

(i) where the compound of the invention contains a methyl group, an hydroxymethyl derivative thereof (e.g., -CH_3 -> -CH_2OH):

(ii) where the compound of the invention contains an alkoxy group, an hydroxy derivative thereof (e.g., -OR^7 -> -OH);

(iii) where the compound of the invention contains a tertiary amino group, a secondary amino derivative thereof (e.g., -NR^3R^4 -> -NHR^3 or –NHR^4);

(iv) where the compound of the invention contains a secondary amino group, a primary derivative thereof (e.g., -NHR^3 -> -NH_2);

(v) where the compound of the invention contains a phenyl moiety, a phenol derivative thereof (e.g., -Ph -> -PhOH); and

(vi) where the compound of the invention contains an amide group, a carboxylic acid derivative thereof (e.g., $-CONH_2$ -> COOH).

Compounds of the invention containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of the invention contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of the invention containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of the invention, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartrate or dl-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of the invention contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of an alcoholic solvent such as

isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, 1994).

In one embodiment, the invention relates to compositions comprising a compound of the invention and at least one additional ingredient (hereinafter "the compositions of the invention"). It will be understood that the compositions of the invention will encompass any combination of the compound of the invention and the at least one additional ingredient. Non-limiting examples of the at least one additional ingredient include impurities (e.g., intermediates present in the unrefined compounds of the invention), active ingredients as discussed herein (e.g., an additional anti-tumor agent), pharmaceutically acceptable excipients, or one or more solvents (e.g., a pharmaceutically acceptable carrier as discussed herein).

The term "solvent" as it relates to the compositions of the invention includes organic solvents (e.g., methanol, ethanol, isopropanol, ethyl acetate, methylene chloride, and tetrahydrofuran) and water. The one or more solvents may be present in a non-stoichiometric amount, e.g., as a trace impurity, or in sufficient excess to dissolve the compound of the invention. Alternatively, the one or more solvents may be present in a stoichiometric amount, e.g., 0.5:1, 1:1, or 2:1 molar ratio, based on the amount of compound of the invention.

In one embodiment, the at least one additional ingredient that is present in the composition of the invention is an organic solvent.

In another embodiment, the at least one additional ingredient that is present in the composition of the invention is water.

In one embodiment, the at least one additional ingredient that is present in the composition of the invention is a pharmaceutically acceptable carrier.

In another embodiment, the at least one additional ingredient that is present in the composition of the invention is a pharmaceutically acceptable excipient.

In one embodiment, the composition of the invention is a solution.

In another embodiment, the composition of the invention is a suspension.

In another embodiment, the composition of the invention is a solid.

In another embodiment, the composition of the invention comprises an amount of the compound of the invention effective for treating abnormal cell growth.

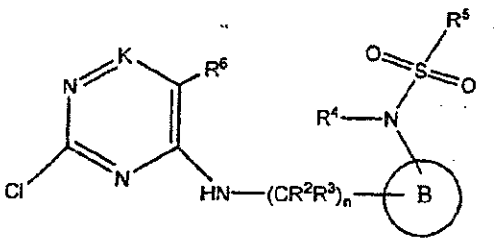
In yet another embodiment, the invention relates to a composition comprising an effective amount of the compound of the invention, and a pharmaceutically acceptable carrier.

In another embodiment, the invention relates to a composition comprising a therapeutically effective amount of the compound the invention as defined above, a pharmaceutically acceptable carrier and, optionally, at least one additional medicinal or pharmaceutical agents (hereinafter "the pharmaceutical compositions of the invention"). In a preferred embodiment, the at least one additional medicinal or pharmaceutical agent is an anti-cancer agent.

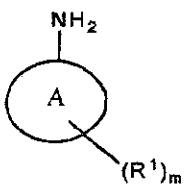
In another embodiment, the invention relates to a composition useful for treating abnormal cell growth in a mammal comprising an effective amount of the compound of the invention, and a pharmaceutically acceptable carrier.

The invention also relates to methods of making the compounds of the invention.

In one embodiment, the invention relates to a method for making a compound of formula I comprising allowing a compound of formula

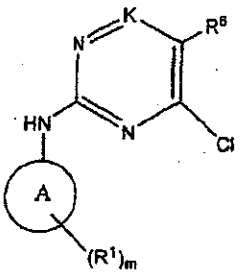


to react with a compound of formula

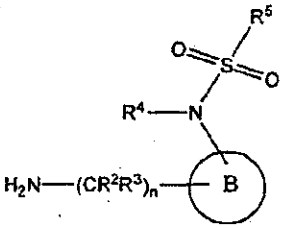


to provide the compound of formula I.

In another embodiment, the invention relates to a method for making the compounds of the invention comprising allowing a compound of formula



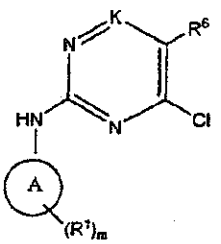
to react with a compound of formula



When preparing compounds of the invention in accordance with the invention, it is open to a person skilled in the art to routinely select the form of the intermediate compound which provides the best combination of features for this purpose. Such features include the melting point, solubility, processability and yield of the intermediate form and the resulting ease with which the product may be purified on isolation.

The invention also relates to intermediate compounds that are useful for making the compounds of the invention.

In one embodiment, the invention relates to intermediate compounds having the formula II:



II

wherein A, K, R^1, R^6 and m are as defined above for the compound of formula I.

The invention also relates to methods for the treatment of abnormal cell growth in a mammal. In one embodiment, the invention relates to a method for the treatment of abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound of the invention that is effective in treating abnormal cell growth.

In another embodiment, the abnormal cell growth is cancer.

In another embodiment, the cancer is selected from the group consisting of lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.

The invention also relates to methods for the treatment of cancer solid tumors in a mammal. In one embodiment, the invention relates to the treatment of cancer solid tumor in a mammal comprising administering to said mammal an amount of a compound of the invention that is effective in treating said cancer solid tumor.

In another embodiment, the cancer solid tumor is breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, or bladder.

In another embodiment, the invention relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of the invention that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

A particular aspect of this invention is directed to methods for treating or preventing a condition that presents with low bone mass in a mammal (including a

human being) which comprise administering to a mammal in need of such treatment a condition that presents with low bone mass treating amount of a compound of the invention or a pharmaceutically acceptable salt of said compound of the invention. This invention is particularly directed to such methods wherein the condition that presents with low bone mass is osteoporosis, frailty, an osteoporotic fracture, a bone defect, childhood idiopathic bone loss, alveolar bone loss, mandibular bone loss, bone fracture, osteotomy, periodontitis or prosthetic ingrowth.

A particular aspect of this invention is directed to methods for treating osteoporosis in a mammal (including a human being) which comprise administering to a mammal in need of such treatment an osteoporosis treating amount of a compound of the invention or a pharmaceutically acceptable salt of said compound.

Another aspect of this invention is directed to methods for treating a bone fracture or an osteoporotic fracture in a mammal which comprise administering to a mammal in need of such treatment a bone fracture treating or an osteoporotic fracture treating amount of a compound of the invention or a pharmaceutically acceptable salt of said compound.

The term "osteoporosis" includes primary osteoporosis, such as senile, postmenopausal and juvenile osteoporosis, as well as secondary osteoporosis, such as osteoporosis due to hyperthyroidism or Cushing syndrome (due to corticosteroid use), acromegaly, hypogonadism, dysosteogenesis and hypophospatasemia.

Detailed Description of the Invention

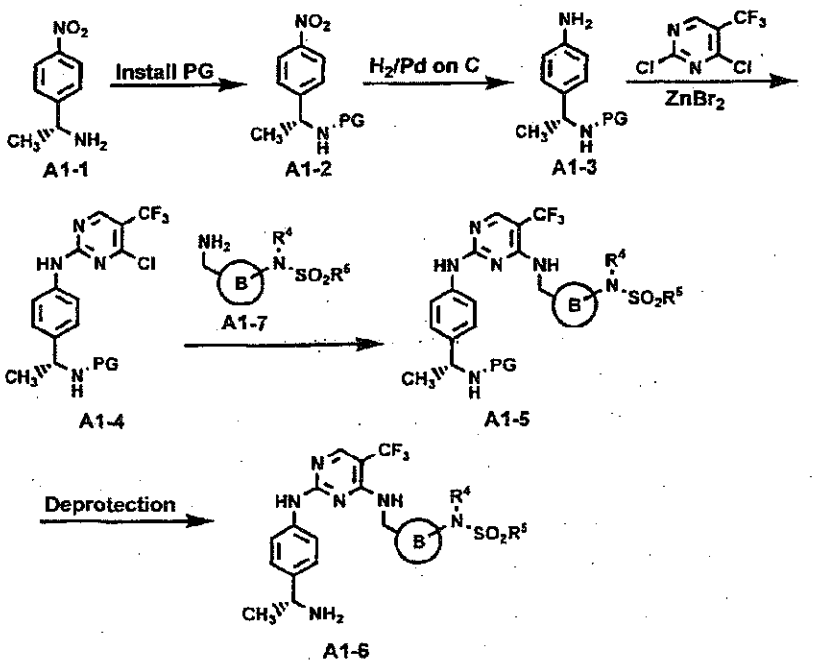
Synthesis of 2,4-Diamino Pyrimidines

The compounds of the invention can be prepared by the following general methods and by methods described in detail in the Experimental Section.

Non-limiting methods for making the sulfonyl amides of the invention are depicted in Schemes 1 -6 below. For sake of clarity, only the pyrimidine derivatives of the compounds of formula I are depicted in the Schemes (i.e., where K of the compound of formula I is CH). However, the same methods can be used for making the 1,2,4-triazine derivatives compounds of formula I (i.e., where K is N).

Scheme 1 shows one method for preparing 2,4-diamino pyrimidines.

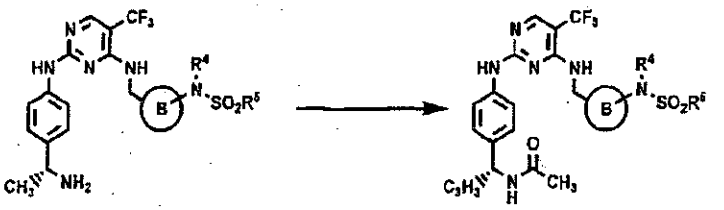
Scheme 1



In Scheme 1, the amino group of an amino-nitroaryl compound of structure **A1-1** is protected (PG = protecting group such as BOC) to form the protected compound **A1-2**. The nitro group of **A1-2** can then be selectively reduced to the corresponding aniline **A1-3**, using, e.g., hydrogen in the presence of a palladium-supported catalyst. Reaction of aniline **A1-3** with 2,4-dichloro-5-(trifluoromethyl)pyrimidine in the presence of an appropriate zinc salt (e.g., $ZnBr_2$) provides the corresponding C-2 addition product **A1-4**. Reaction of compounds of formula **A1-4** with amines of formula **A1-7** under basic conditions provides compound of formula I having the structure **A1-5**. Other compounds of formula I can be prepared by selectively deprotecting **A1-5** to provide the aminoalkyl compound of formula I having the structure **A1-6**.

Scheme 2 depicts a non-limiting method for making amide derivatives of the compound of formula I.

Scheme 2

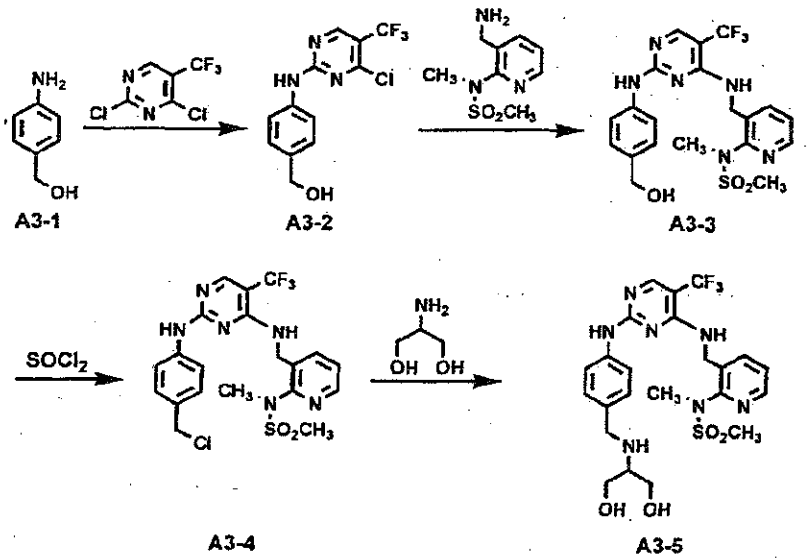


A1-6 A2-1

In Scheme 2, an aminoalkyl such as the compound of formula **I** having the structure **A1-6** can be reacted with an acid halide (e.g., acetyl chloride) under basic conditions to provide the amide derivative of the compound of formula I having the structure **A2-1**.

Scheme 3 represents another general non-limiting method of making compounds of formula **I**.

Scheme 3



A3-1 A3-2 A3-3

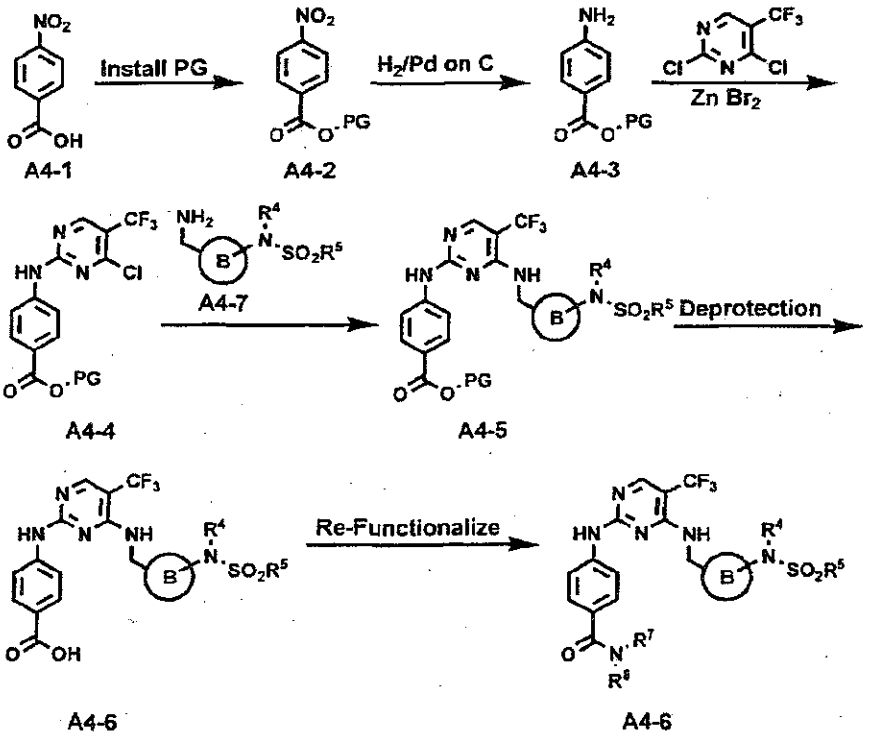
A3-4 A3-5

In Scheme 3, an hydroxyalkyl-aniline of formula **A3-1** is reacted with 2,4-dichloro-5-(trifluoromethyl) pyrimidine in the presence of a zinc salt (e.g., $ZnBr_2$) to provide the corresponding C-2 addition product **A3-2**. Treatment of the **A3-2** with an amine of formula **A3-6** provides hydroxyalkyl derivatives of the compound of formula **I** having the structure **A3-3**. Compound **A3-3** may further be selectively converted to a compound of formula **I** where the hydroxyl group is replaced for another reactive functional group (e.g., alkyl halide or alkyl sulfonate). For example, in Scheme 3, the hydroxylalkyl

compound of formula **A3-3** is reacted with thionyl chloride to provide the chloroalkyl compound of formula I having the structure **A3-4**. Compound **A3-4** may further be reacted with amines (e.g., HNR^7R^8) to provide aminoalkyl derivatives of the compounds of formula I having the structure **A3-5**. If desired, the compounds of structure **A3-5** can be used as a starting material to prepare other compounds of formula I.

Scheme 4 represents yet another general non-limiting method for making compounds of formula I.

Scheme 4

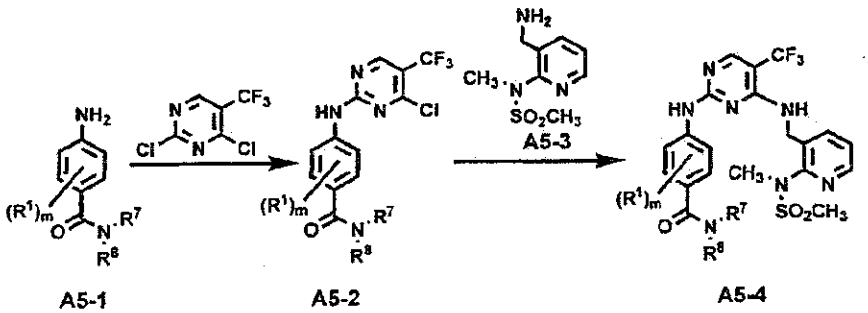


In Scheme 4, the acid group of a nitrobenzoate compound of structure **A4-1** is protected to form the protected compound **A4-2**. The nitro group of **A4-2** can then be selectively reduced to the corresponding aniline **A4-3**, using, e.g., hydrogen in the presence of a palladium-supported catalyst. Reaction of aniline **A4-3** with 2,4-dichloro-5-(trifluoromethyl)pyrimidine in the presence of an appropriate zinc salt (e.g., $ZnBr_2$) provides the corresponding C-2 addition product **A4-4**. Treatment of the chloro-pyrimidine compounds of formula **A4-4** with amines of formula **A4-7** provides benzoate-protected compounds of formula I having the structure **A4-5**. Selective deprotection of

compound **A4-5** can provide benzoic acid derivatives of the compound of formula I having the structure **A4-6**. The benzoic acid derivatives of formula **A4-6** may be further reacted with an amine to provide the amide derivatives of the compound of formula I having the structure **A4-6**.

Scheme 5 depicts yet another general non-limiting method for making compounds of formula I.

Scheme 5

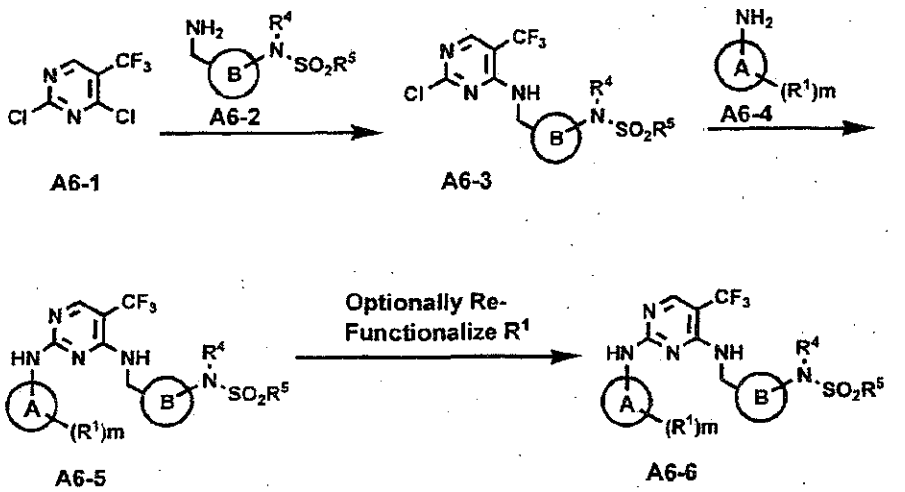


A5-1 A5-2 A5-4

In Scheme 5, an aniline amide compound of structure **A5-1** is be reacted with 2,4-dichloro-5-(trifluoromethyl)pyrimidine in the presence of a zinc salt (e.g., $ZnBr_2$) to provide the corresponding C-2 addition product **A5-2**. Treatment of the chloro pyrimidine compounds of formula **A5-2** with an amine of formula **A5-3** provides amide derivatives of the compounds of formula I having the structure **A5-4**. The amide derivatives of formula **A5-4** may be used as a starting material to provide other compounds of formula I.

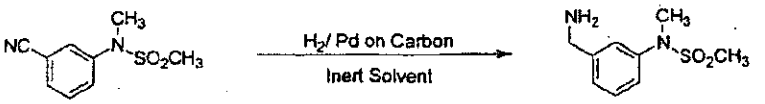
In Schemes 1 and 3-5, the 2,4-dichloro-5-(trifluoromethyl)pyrimidine first formed a C-2 addition product ("the C4-chloro intermediate"). The C-4 group was then added by allowing the C4-chloro intermediate to react with an aralkylamino reagent. Scheme 6 depicts another non-limiting method for making the compounds of the invention where the first formed intermediate is the C-4 addition intermediate ("the C2-chloro intermediate").

Scheme 6

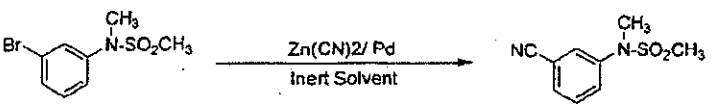


In Scheme 6, 2,4-dichloro-5-(trifluoromethyl)pyrimidine is reacted with an aralkylamino reagent of formula **A6-2** to provide the 2-chloro-pyrimidine addition product **A6-3**. Reaction of **A6-3** with an amino reagent of formula **A6-4** provides the compound of formula I having the structure **A6-5**. Depending on the substituent groups R^1, the compounds of formula **A6-5** can be further reacted as described above in Schemes 1-5 to provide additional compounds of formula **I**.

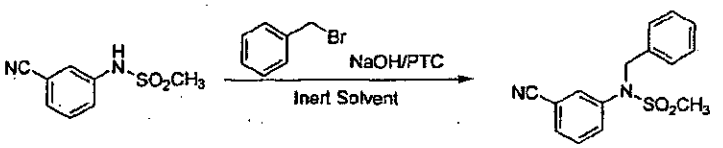
Arylalkylamines or heteroarylalkylamines (e.g., **A1-7** in Scheme 1) that are attached to the 4 position of the pyrimidine core (or the 5 position of the 1,2,4-triazine core) may be prepared from the corresponding nitrile by catalytic hydrogenation using catalysts such as Pd/C or Raney Nickel or by lithium aluminum hydride reduction, (see Rylander, Catalytic Hydrogenation in Organic Synthesis, Academic Press, 1979); or by methods described herein in the Examples section.



The nitrile starting materials can be either purchased or prepared from the corresponding aryl/heteroaryl bromide, iodide or triflate and $Zn(CN)_2$ using Pd coupling conditions found in Tschaen, D. M., et. al Synthetic Communications (1994), 24, 6, pp 887-890.



Appropriately protected amines may be converted to different amines of formula **A1-7** (see Scheme 1) according to methods familiar to those skilled in the art as, for example, N-alkylation of a sulfanilide under phase transfer using conditions as described by Brehme, R. "Synthesis", (1976), pp113-114.



As understood by those skilled in the art, the chemical transformation to convert an aryl halide or triflate or heteroaryl halide or triflate to an aromatic or heteroaromatic amine may be carried out using conditions currently outlined in the literature, see Hartwig, J. F.: "Angew. Chem. Int. Ed." (1998), 37, pp. 2046-2067, Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S.L.; "Acc. Chem. Res.", (1998), 31, pp 805-818, Wolfe, J. P.; Buchwald, S.L.; "J. Org. Chem.", (2000), 65, pp 1144-1157, Muci, A. R.; Buchwald, S. L.; "Topics in Current Chemistry" (2002), pp131-209 and references cited therein. Further, as understood by those skilled in the art, these same aryl or heteroaryl amination chemical transformations may alternatively be carried out on nitrile (or primary amide) precursors which provide amines after nitrile (or amide) reduction.

Other methods for making the intermediate compounds (e.g. **A1-7** in Scheme 1) can be found in U.S. Patent Appl. Publ. No. 20040220177, U.S. Patent No. 7,109,335, U.S. Patent No. 7,10,9,337, and PCT/IB2006/003349, the entire contents of each of the foregoing references being expressly incorporated herein by reference.

As noted above, amines comprising the ring moiety A (e.g., **A6-4** in Scheme 6) are attached to the 2 position of the pyrimidine core (or the 3 position of the 1,2,4-triazine core). Such amino-ring groups are commercially available or can be made by methods known to those skill in the art. For example, amines comprising alkyl-, hydroxyl-, carboxyl-, and halo-substituted ring moieties are commercially available. In addition, certain of these commercially available amines such as, e.g., the halo- and hydroxyl-substituted ring compounds, can be reacted to form other compounds of the invention using the methods described above, in the Examples section, or known to those skilled in the art. Such reactions can be carried out prior to the reaction with pyrimidine core. Alternatively, such reactions can be carried out after the cyclic amine is attached to the C2 position of the pyrimidine core.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a compound of the invention, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth. In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In one embodiment the method comprises comprising administering to a mammal an amount of a compound of the invention that is effective in treating said cancer solid tumor. In one preferred embodiment the solid tumor is breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder cancer.

In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

This invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the invention, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier. In one embodiment of said composition, said abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said pharmaceutical composition, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

The invention also contemplates a pharmaceutical composition for treating abnormal cell growth wherein the composition includes a compound of the invention, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth, and another anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

This invention also relates to a method for the treatment of a disorder associated with angiogenesis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the invention, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating said disorder in combination with one or more anti-tumor agents listed above. Such disorders include cancerous tumors such as melanoma; ocular disorders such as age-

related macular degeneration, presumed ocular histoplasmosis syndrome, and retinal neovascularization from proliferative diabetic retinopathy; rheumatoid arthritis; bone loss disorders such as osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, hypercalcemia from tumors metastatic to bone, and osteoporosis induced by glucocorticoid treatment; coronary restenosis; and certain microbial infections including those associated with microbial pathogens selected from adenovirus, hantaviruses, Borrelia burgdorferi, Yersinia spp., Bordetella pertussis, and group A Streptococcus.

This invention also relates to a method of (and to a composition for) treating abnormal cell growth in a mammal which comprise an amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of the invention in the methods and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (celecoxib), Bextra (valdecoxib), paracoxib, Vioxx (rofecoxib), and Arcoxia (etoricoxib). Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Publication No. EP0818442, European Patent Publication No. EP1004578, WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Publication No. WO99/007675, European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Patent No. 7,030,242, United States Patent No. 5,863,949 (issued January 26, 1999), United States Patent No. 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997). Preferred MMP-2 and

MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in combination with the compounds of the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid;

3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid;

4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid;

3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and

3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide;

and pharmaceutically acceptable salts, solvates and prodrugs of said compounds.

VEGF inhibitors, for example, SU-11248, SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, California, USA), can also be combined with a compound of the invention. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), U.S. Patent No. US 6,653,308 (issued November 25, 2003), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998). Other examples of some specific VEGF inhibitors are IM862 (Cytran Inc. of Kirkland, Washington, USA); Avastin, an anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California).

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), may be administered in combination with a compound of the invention. Such erbB2 inhibitors include Herceptin, 2C4, and pertuzumab. Such erbB2 inhibitors include those described in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999). ErbB2 receptor inhibitors useful in the present invention are also described in United States Patent No. 6,465,449, and in United States Patent No. 6,284,764. Other erbb2 receptor inhibitors include TAK-165 (Takeda) and GW-572016 (Glaxo-Wellcome).

Various other compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties, and some of tyrosine kinase inhibitors have been identified as erbB2 receptor inhibitors. More recently, five European patent publications, namely EP 0 566 226 A1 (published October 20, 1993), EP 0 602 851 A1 (published June 22, 1994), EP 0 635 507 A1 (published January 25, 1995), EP 0 635 498 A1 (published January 25, 1995), and EP 0 520 722 A1 (published December 30, 1992), refer to certain bicyclic derivatives, in particular quinazoline derivatives, as possessing anti-cancer properties that result from their tyrosine kinase inhibitory properties. Also, World Patent Application WO 92/20642 (published November 26, 1992), refers to certain bis-mono and bicyclic aryl and heteroaryl compounds as tyrosine kinase inhibitors that are useful in inhibiting abnormal cell proliferation. World Patent Applications WO96/16960 (published June 6, 1996), WO 96/09294 (published March 6, 1996), WO 97/30034 (published August 21, 1997), WO 98/02434 (published January 22, 1998), WO 98/02437 (published January 22, 1998), and WO 98/02438 (published January 22, 1998), also refer to substituted bicyclic heteroaromatic derivatives as tyrosine kinase inhibitors that are useful for the same purpose. Other patent applications that refer to anti-cancer compounds are World Patent Application WO00/44728 (published August 3, 2000), EP 1029853A1 (published August 23, 2000), and WO01/98277 (published December 12, 2001) all of which are incorporated herein by reference in their entirety.

Other antiproliferative agents that may be used with the compounds of the present invention include inhibitors of the enzyme farnesyl protein transferase and inhibitors of the receptor tyrosine kinase PDGFr, including the compounds disclosed and claimed in the following United States patent applications: 09/221946 (filed December 28, 1998); 09/454058 (filed December 2, 1999); 09/501163 (filed February 9, 2000); 09/539930 (filed March 31, 2000); 09/202796 (filed May 22, 1997); 09/384339 (filed August 26, 1999); and 09/383755 (filed August 26, 1999); and the compounds disclosed and claimed in the following United States provisional patent applications: 60/168207 (filed November 30, 1999); 60/170119 (filed December 10, 1999); 60/177718 (filed January 21, 2000); 60/168217 (filed November 30, 1999), and 60/200834 (filed May 1, 2000).

A compound of the invention may also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of

enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, *supra*. Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) .

A compound of formula I may be applied as a sole therapy or may involve one or more other anti-tumor substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, oxaliplatin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, capecitabine, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex (tamoxifen) or, for example anti-androgens such as Casodex (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide).

The compounds of the present invention may be used alone or in combination with one or more of a variety of anti-cancer agents or supportive care agents. For example, the compounds of the present invention may be used with cytotoxic agents, e.g., one or more selected from the group consisting of a camptothecin, irinotecan HCl (Camptosar), edotecarin, SU-11248, epirubicin (Ellence), docetaxel (Taxotere), paclitaxel, rituximab (Rituxan) bevacizumab (Avastin), imatinib mesylate (Gleevac), Erbitux, gefitinib (Iressa), and combinations thereof. The invention also contemplates the use of the compounds of the present invention together with hormonal therapy, e.g., exemestane (Aromasin), Lupron, anastrozole (Arimidex), tamoxifen citrate (Nolvadex), Trelstar, and combinations thereof. Further, the invention provides a compound of the present invention alone or in combination with one or more supportive care products, e.g., a product selected from the group consisting of Filgrastim (Neupogen), ondansetron (Zofran), Fragmin, Procrit, Aloxi, Emend, or combinations thereof. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

The compounds of the invention may be used with antitumor agents, alkylating agents, antimetabolites, antibiotics, plant-derived antitumor agents, camptothecin derivatives, tyrosine kinase inhibitors, antibodies, interferons, and/or biological response modifiers. In this regard, the following is a non-limiting list of examples of secondary agents that may be used with the compounds of the invention.

- Alkylating agents include, but are not limited to, nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, temozolomide, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, carmustine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, mafosfamide, and mitolactol; platinum-coordinated alkylating compounds include but are not limited to, cisplatin, carboplatin, eptaplatin, lobaplatin, nedaplatin, oxaliplatin or satrplatin;
- Antimetabolites include but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, tegafur, UFT, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, gemcitabine, fludarabin, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethynylcytidine, cytosine arabinoside, hydroxyurea, TS-1, melphalan, nelarabine, nolatrexed, ocfosfate, disodium premetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, vincristine, vinorelbine; or for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid;
- Antibiotics include but are not limited to: aclarubicin, actinomycin D, amrubicin, annamycin, bleomycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, galarubicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin or zinostatin;
- Hormonal therapy agents, e.g., exemestane (Aromasin), Lupron, anastrozole (Arimidex), doxercalciferol, fadrozole, formestane, anti-estrogens such as tamoxifen citrate (Nolvadex) and fulvestrant, Trelstar, toremifene, raloxifene, lasofoxifene, letrozole (Femara), or anti-androgens such as bicalutamide, flutamide, mifepristone, nilutamide, Casodex® (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide) and combinations thereof;
- Plant derived anti-tumor substances include for example those selected from mitotic inhibitors, for example vinblastine, docetaxel (Taxotere) and paclitaxel;

- Cytotoxic topoisomerase inhibiting agents include one or more agents selected from the group consisting of aclarubicin, amonafide, belotecan, camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, diflomotecan, irinotecan HCl (Camptosar), edotecarin, epirubicin (Ellence), etoposide, exatecan, gimatecan, lurtotecan, mitoxantrone, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, and topotecan, and combinations thereof;
- Immunologicals include interferons and numerous other immune enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a or interferon gamma-n1. Other agents include filgrastim, lentinan, sizofilan, TheraCys, ubenimex, WF-10, aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab ozogamicin, ibritumomab, imiquimod, lenograstim, lentinan, melanoma vaccine (Corixa), molgramostim, OncoVAX-CL, sargramostim, tasonermin, tecleukin, thymalasin, tositumomab, Virulizin, Z-100, epratuzumab, mitumomab, oregovomab, pemtumomab, and Provenge;
- 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. Such agents include krestin, lentinan, sizofiran, picibanil, or ubenimex;
- Other anticancer agents include alitretinoin, ampligen, atrasentan, bexarotene, bortezomib, Bosentan, calcitriol, exisulind, finasteride, fotemustine, ibandronic acid, miltefosine, mitoxantrone, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pegaspargase, pentostatin, tazarotne, TLK-286, Velcade, Tarceva, or tretinoin;
- Other anti-angiogenic compounds include acitretin, fenretinide, thalidomide, zoledronic acid, angiostatin, aplidine, cilengtide, combretastatin A-4, endostatin, halofuginone, rebimastat, removab, Revlimid, squalamine, ukrain and Vitaxin;
- Platinum-coordinated compounds include but are not limited to, cisplatin, carboplatin, nedaplatin, or oxaliplatin;
- Camptothecin derivatives include but are not limited to camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan, SN-38, edotecarin, and topotecan;
- Tyrosine kinase inhibitors are Iressa or SU5416;

- Antibodies include Herceptin, Erbitux, Avastin, or Rituximab; and
- Interferons include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a or interferon gamma-n1.

"Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or overexpression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (4) any tumors that proliferate by receptor tyrosine kinases; (5) any tumors that proliferate by aberrant serine/threonine kinase activation; and (6) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs.

The compounds of the present invention are potent inhibitors of the FAK protein tyrosine kinases, and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer), antitumor (e.g., effective against solid tumors), antiangiogenesis (e.g., stop or prevent proliferationation of blood vessels) in mammals, particularly in humans. In particular, the compounds of the present invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders such as malignant and benign tumors of the liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, head and neck, and other hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH). It is, in addition, expected that a compound of the present invention may possess activity against a range of leukemias and lymphoid malignancies.

In one preferred embodiment of the present invention cancer is selected from lung cancer, bone cancer, pancreatic cancer, gastric, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, gynecological, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, squamous cell, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the

kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain, pituitary adenoma, or a combination of one or more of the foregoing cancers.

In a more preferred embodiment cancer is selected a solid tumor, such as, but not limited to, breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder.

The compounds of the present invention may also be useful in the treatment of additional disorders in which aberrant expression ligand/receptor interactions or activation or signalling events related to various protein tyrosine kinases, are involved. Such disorders may include those of neuronal, glial, astrocytal, hypothalamic, and other glandular, macrophagal, epithelial, stromal, and blastocoelic nature in which aberrant function, expression, activation or signalling of the erbB tyrosine kinases are involved. In addition, the compounds of the present invention may have therapeutic utility in inflammatory, angiogenic and immunologic disorders involving both identified and as yet unidentified tyrosine kinases that are inhibited by the compounds of the present invention.

A particular aspect of this invention is directed to methods for treating or preventing a condition that presents with low bone mass in a mammal (including a human being) which comprise administering to a mammal in need of such treatment a condition that presents with low bone mass treating amount of a Formula I compound or a pharmaceutically acceptable salt of said compound.

This invention is particularly directed to such methods wherein the condition that presents with low bone mass is osteoporosis, frailty, an osteoporotic fracture, a bone defect, childhood idiopathic bone loss, alveolar bone loss, mandibular bone loss, bone fracture, osteotomy, periodontitis or prosthetic ingrowth.

A particular aspect of this invention is directed to methods for treating osteoporosis in a mammal (including a human being) which comprise administering to a mammal in need of such treatment an osteoporosis treating amount of a Formula I compound or a pharmaceutically acceptable salt of said compound.

Another aspect of this invention is directed to methods for treating a bone fracture or an osteoporotic fracture in a mammal which comprise administering to a mammal in need of such treatment a bone fracture treating or an osteoporotic fracture treating amount of a Formula I compound or a pharmaceutically acceptable salt of said compound.

The term "osteoporosis" includes primary osteoporosis, such as senile, postmenopausal and juvenile osteoporosis, as well as secondary osteoporosis, such as osteoporosis due to hyperthyroidism or Cushing syndrome (due to corticosteroid use), acromegaly, hypogonadism, dysosteogenesis and hypophospatasemia.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 1 mg to 1 gram, preferably 1 mg to 250 mg, more preferably 10 mg to 100 mg.

The present invention also encompasses sustained release compositions.

As noted above, the compounds of the invention are useful for treating abnormal cell growth such, e.g., cancer. Without being limited by theory, Applicants believe that the compounds of the invention are useful for treating or preventing abnormal cell growth by inhibiting the FAK kinases.

In Vitro and In Vivo Assays

As noted above, the compounds of the invention are useful as inhibitors of receptor tyrosine kinases such as, e.g., FAK, Aurora-1, Aurora-2, HgK and Pyk. Methods for determining the in vitro and in vivo activity of these compounds inhibitors of receptor tyrosine kinases are described below:

A. In-vitro Activity of FAK:

The in vitro activity of the compounds of the compounds of the invention may be determined by the following procedure. More particularly, the following assay provides a method to determine whether compounds of the compounds of the invention inhibit the tyrosine kinase activity of the catalytic construct FAK(410-689). The assay is an ELISA-based format, measuring the inhibition of poly-glu-tyr phosphorylation by FAK(410-689). The assay protocol has three parts:

I. Purification and cleavage of His-FAK(410-689)

II. FAK410-689 (a.k.a. FAKcd) Activation

III. FAKcd Kinase ELISA

Materials:

-Ni-NTA agarose (Qiagen)

-XK-16 column (Amersham-Pharmacia)

-300 mM Imidizole

-Superdex 200 HiLoad 16/60 prep grade column (Amersham Biotech.)

-Antibody: Anti-Phosphotyrosine HRP-Conjugated Py20 (Transduction labs)

-FAKcd: Purified and activated in house

-TMB Microwell Peroxidase Substrate (Oncogene Research Products #CL07)

-BSA: Sigma #A3294

-Tween-20: Sigma #P1379

-DMSO: Sigma #D-5879

-D-PBS: Gibco #14190-037

Reagents for Purification:

-Buffer A: 50mM HEPES pH 7.0

500mM NaCl

0.1mM TCEP

CompleteTM protease inhibitor cocktail tablets (Roche)

-Buffer B: 25mM HEPES pH 7.0

400mM NaCl

0.1mM TCEP

-Buffer C: 10mM HEPES pH 7.5

200mM Ammonium Sulfate

0.1mM TCEP

Reagents for Activation:

-FAK(410-689): 3 tubes of frozen aliquots at 150µl/tube for a total of 450µl at 1.48 mg/ml (660µg)

-His-Src(249-524): ~0.74 mg/ml stock in 10mM HEPES, 200mM (NH4)2SO4

-Src reaction buffer (Upstate Biotech):

100 mM Tris-HCl pH7.2

125mM MgCl2

25 mM MnCl2

2mM EDTA

250 µM Na3VO4

2 mM DTT

-Mn2+/ATP cocktail (Upstate Biotech)

75mM MnCl2

500 µM ATP

20mM MOPS pH 7.2

1mM Na3VO4

25mM -glycerol phosphate

5mM EGTA

1mM DTT

-ATP: 150mM stock

-MgCl2: 1 M Stock

-DTT: 1M stock

Reagents for FAKcd Kinase ELISA:

-Phosphorylation Buffer:

50mM HEPES, pH 7.5

125mM NaCl

48mM MgCl2

-Wash Buffer: TBS + 0.1% Tween-20.

-Blocking Buffer:

Tris Buffer Saline

3% BSA

0.05% Tween-20, filtered

-Plate Coating Buffer:

50mg/ml Poly-Glu-Tyr (Sigma #P0275) in Phosphate buffer Saline (DPBS).

-ATP: 0.1M ATP in H2O or HEPES, pH7

Note: ATP Assay Buffer:

Make up as 75 uM ATP in PBS, so that 80 µl in

120 µl reaction volume=50µM final ATP concentration.

I. **Purification of His-FAKcd(410-689):**

1. Resuspend 130 g baculovirus cell paste containing the over expressed His-FAKcd410-689 recombinant protein in 3 volumes (400ml) of Buffer A.
2. Lyse cells with one pass on a microfluidizer.
3. Remove cell debris by centrifugation at 4°C for 35 minutes at 14,000 rpm in a Sorval SLA-1500 rotor.
4. Transfer the supernatant to a clean tube and add 6.0 ml of Ni-NTA agarose (Qiagen).
5. Incubate the suspension with gentle rocking at 4°C for 1 hour.
6. Centrifuge suspension at 700 x g in a swinging bucket rotor.
7. Discard the supernatant and resuspend the agarose beads in 20.0 ml of Buffer A.
8. Transfer the beads to an XK-16 column (Amersham-Pharmacia) connected to a FPLCTM.
9. Wash the agarose-beads with 5 column volumes of Buffer A and elute off the column with a step gradient of Buffer A containing 300mM Imidizole.
10. Perform a buffer exchange of the eluted fractions into Buffer B.
11. Following buffer exchange, pool the fractions and add thrombin at a 1:300 (w/w) ratio and incubated overnight at 13°C to remove the N-terminal His-tag (His-FAK410-698 à FAK410-689 (a.k.a. FAKcd)).
12. Add the reaction mixture back onto the Ni-NTA column equilibrated with Buffer A and collect the flow-through.
13. Concentrate the flow-through down to 1.7 ml and load directly onto a Superdex 200 HiLoad 16/60 prep grade column equilibrated with Buffer C. The desired protein elutes between 85 - 95 ml.
14. Aliquot the FAKcd protein and store frozen at –80°C.

II. **FAK activation**

1. To 450ul of FAK(410-689) at 1.48 mg/ml (660µg) add the following:

30µl of 0.037 mg/ml (1µM) His-Src(249-524)

30µl of 7.5 mM ATP

12µl of 20 mM MgCl2

10µl Mn2+/ATP cocktail (UpState Biotech.)

4µl of 6.7mM DTT

60µl Src Reaction Buffer (UpState Biotech.)

2. Incubate Reaction for at least 3 hours at room temperature

At time t0, almost all of the FAK(410-689) is singly phosphorylated. The second phosphorylation is slow. At t120 (t = 120 minutes), add 10µl of 150 mM ATP.

T0 = (Start) 90% singly phosphorylated FAK(410-689) (1 PO4)

T43 = (43 min) 65% singly phosphorylated (1 PO4), 35% doubly phosphorylated (2 PO4)

T90 = (90 min) 45% 1 PO4, 55% 2 PO4

T150 = 15% 1 PO4, 85% 2 PO4

T210 = <10% 1 PO4, >90% 2 PO4 desalted sample

3. Add 180 µl aliquots of the desalted material to NiNTA spin column and incubate on spin column

4. Spin at 10k rpm (microfuge), for 5 minutes to isolate and collect flow through (Activated FAK(410-689)) and remove His-Src (captured on column)

III. FAKcd Kinase ELISA

1. Coat 96-well Nunc MaxiSorp plates with poly-glu-tyr (pGT) at 10 µg/well: Prepare 10 µg/ml of pGT in PBS and aliquot 100 µl/well. Incubate the plates at 37°C overnight, aspirate the supernatant, wash the plates 3 times with Wash Buffer, and flick to dry before storing at 4°C.

2. Prepare compound stock solutions of 2.5 mM in 100% DMSO. The stocks are subsequently diluted to 60X of the final concentration in 100% DMSO, and diluted 1:5 in Kinase Phosphorylation Buffer.

3. Prepare a 75 µM working ATP solution in Kinase phosphorylation buffer. Add 80 µl to each well for a final ATP concentration of 50 µM.

4. Transfer 10 µl of the diluted compounds (0.5log serial dilutions) to each well of the pGT assay plate, running each compound in triplicates on the same plate.

5. Dilute on ice, FAKcd protein to 1:1000 in Kinase Phosphorylation Buffer. Dispense 30 µl per well.

6. Note: Linearity and the appropriate dilution must be pre-determined for each batch of protein. The enzyme concentration selected should be such that quantitation of the assay signal will be approximately 0.8-1.0 at OD450, and in the linear range of the reaction rate.

7. Prepare both a No ATP control (noise) and a No Compound Control (Signal):

8. (Noise) One blank row of wells receives 10 µl of 1:5 diluted compounds in DMSO, 80µl of Phosphorylation buffer (minus ATP), and 30 µl FAKcd solution.

9. (Signal) Control wells receive 10 µl of 1:5 diluted DMSO (minus Compound) in Kinase phosphorylation buffer, 80 µl of 75 uM ATP, and 30 µl of 1:1000 FAKcd enzyme.

10. Incubate reaction at room temperature for 15 minutes with gentle shaking on a plate shaker.

11. Terminate the reaction by aspirating off the reaction mixture and washing 3 times with wash buffer.

12. Dilute phospho-tyrosine HRP-conjugated (pY20HRP) antibody to 0.250 µg/ml (1:1000 of Stock) in blocking buffer. Dispense 100 µl per well, and incubate with shaking for 30 minutes at 25°.

13. Aspirate the supernatant and wash the plate 3 times with wash buffer.

14. Add 100 µl per well of room temperature TMB solution to initiate color development. Color development is terminated after approximately 15-30 sec. by the addition of 100µl of 0.09M H_2SO_4 per well.

15. The signal is quantitated by measurement of absorbance at 450nm on the BioRad microplate reader or a microplate reader capable of reading at OD450.

16. Inhibition of tyrosine kinase activity would result in a reduced absorbance signal. The signal is typically 0.8-1.0 OD units. The values are reported as IC50s, µM concentration.

FAK Inducible cell-based ELISA: Final Protocol

Materials:

Reacti-Bind Goat Anti-Rabbit Plates 96-well (Pierce Product#15135ZZ @115.00 USD)

FAKpY397 rabbit polyclonal antibody (Biosource #44624 @315.00 USD)

ChromePure Rabbit IgG, whole molecule (Jackson Laboratories #001-000-003 @60/25mg USD)

UBI aFAK clone 2A7 mouse monoclonal antibody (Upstate#05-182 @ 289.00 USD)

Peroxidase-conjugated AffiniPure Goat Anti-Mouse IgG (Jackson Labs #115-035-146 @95/1.5ml USD)

SuperBlock TBS (Pierce Product#37535ZZ @99 USD)

Bovine Serum Albumin (Sigma #A-9647 @117.95/100 g USD)

TMB Peroxidase substrate (Oncogene Research Products #CL07-100ml @40.00 USD)

Na3VO4 Sodium Orthovanadate (Sigma #S6508 @43.95/50g USD)

MTT substrate (Sigma # M-2128 @25.95/500mg USD)

Growth Media: DMEM+10%FBS, P/S, Glu, 750 µg/ml Zeocin and 50 µg/ml Hygromycin (Zeocin InVitrogen #R250-05 @ 725 USD and Hygromycon InVitrogen #R220-05 @ 150 USD)

Mifepristone InVitrogen # H110-01 @ 125 USD

CompleteTM EDTA-free Protease Inhibitor pellet Boehringer Mannheim #1873580

FAK cell-based Protocol for selectivity of kinase-dependent phosphoFAKY397

Procedure:

An inducible FAK cell-based assay in ELISA format for the screening of chemical matter to identify tyrosine kinase specific inhibitors was developed. The cell-based assay exploits the mechanism of the GeneSwitchTM system (InVitrogen) to exogenously control the expression and phosphorylation of FAK and the kinase-dependent autophosphorylation site at residue Y397.

Inhibition of the kinase-dependent autophosphorylation at Y397 results in a reduced absorbance signal at OD450. The signal is typically 0.9 to 1.5 OD450 units with the noise falling in the range of 0.08 to 0.1 OD450 units. The values are reported as IC50s, µM concentration.

On day 1, grow A431•FAKwt in T175 flasks. On the day prior to running the FAK cell-assay, seed A431•FAKwt cells in growth media on 96-well U-bottom plates. Allow cells to sit at 37°C, 5% CO2 for 6 to 8 hours prior to FAK induction. Prepare Mifepristone stock solution of 10 µM in 100 % Ethanol. The stock solution is subsequently diluted to 10 X of the final concentration in Growth Media. Transfer 10 µl of this dilution (final concentration of 0.1 nM Mifepristone) into each well. Allow cells to sit at 37°C, 5% CO2 overnight (12 to 16 hours). Also, prepare control wells without Mifepristone induction of FAK expression and phosphorylation.

On day 2, coat Goat Anti-Rabbit plate(s) with 3.5 µg/ml of phosphospecific FAKpY397 polyclonal antibody prepared in SuperBlock TBS buffer, and allow plate(s) to shake on a plate shaker at room temperature for 2 hours. Optionally, control wells may be coated with 3.5 µg/ml of control Capture antibody (Whole Rabbit IgG molecules) prepared in SuperBlock TBS. Wash off excess FAKpY397 antibody 3 times using

buffer. Block Anti-FAKpY397 coated plate(s) with 200 µl per well of 3%BSA/0.5%Tween Blocking buffer for 1 hour at room temperature on the plate shaker. While the plate(s) are blocking, prepare compound stock solutions of 5 mM in 100 % DMSO. The stock solutions are subsequently serially diluted to 100X of the final concentration in 100% DMSO. Make a 1:10 dilution using the 100X solution into growth media and transfer 10 µl of the appropriate compound dilutions to each well containing either the FAK induced or uninduced control A431 cells for 30 minutes at 37°C, 5% CO2. Prepare RIPA lysis buffer (50 mM Tris-HCl, pH7.4, 1% NP-40, 0.25% Na-deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM Na3VO4, 1 mM NaF, and one CompleteTM EDTA-free protease inhibitor pellet per 50 ml solution). At the end of 30 minutes compound treatment, wash off compound 3 times using TBS-T wash buffer. Lyse cells with 100 µl/well of RIPA buffer.

To the coated plate, remove blocking buffer and wash 3 times using TBS-T wash buffer. Using a 96-well automated microdispenser, transfer 100 µl of whole cell-lysate (from step 6) to the Goat Anti-Rabbit FAKpY397 coated plate(s) to capture phosphoFAKY397 proteins. Shake at room temperature for 2 hours. Wash off unbound proteins 3 times using TBS-T wash buffer. Prepare 0.5 µg/ml (1:2000 dilution) of UBI aFAK detection antibody in 3%BSA/0.5% Tween blocking buffer. Dispense 100 µl of UBI aFAK solution per well and shake for 30 minutes at room temperature. Wash off excess UBI aFAK antibody 3 times using TBS-T wash buffer. Prepare 0.08 µg/ml (1:5000 dilution) of secondary Anti-Mouse Peroxidase (Anti-2MHRP) conjugated antibody. Dispense 100 µl per well of the Anti-2MHRP solution and shake for 30 minutes at room temperature. Wash off excess Anti-2MHRP antibody 3 times using TBS-T wash buffer. Add 100 µl per well of room temperature TMB substrate solution to allow for color development. Terminate the TMB reaction with 100 µl per well of TMB stop solution (0.09M H2SO4) and quantitate the signal by measurement of absorbance at 450 nm on the BioRad microplate reader.

In a preferred embodiment, the compounds of the present invention have an in vitro activity as determined by a kinase assay, e.g., such as that described herein, of less than 500 nM. Preferably, the compounds have an IC50 of less than 25 nM in the kinase assay, and more preferably less than 10 nM. In a further preferred embodiment, the compounds exhibit an IC50 in a FAK cell based assay, e.g., such as that described

herein, of less than 1 μM, more preferably less than 100 nM, and most preferably less than 25 nM.

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, preferably about 0.2 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compound may be applied as a sole therapy or may involve one or more other anti-tumour substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex® (tamoxifen) or, for example anti-androgens such as Casodex® (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for

topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefor, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist

as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated herein by reference in their entireties.

Examples

General Methods:

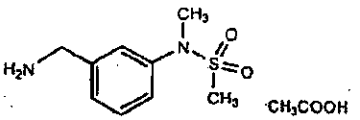
HPLC:

Where HPLC chromatography is referred to in the preparations and examples below, the general conditions used, unless otherwise indicated, are as follows. The column used is a ZORBAX™ RXC18 column (manufactured by Hewlett Packard) of 150 mm distance and 4.6 mm interior diameter. The samples are run on a Hewlett Packard-1100 system. A gradient solvent method is used running 100 percent ammonium acetate / acetic acid buffer (0.2 M) to 100 percent acetonitrile over 10 minutes. The system then proceeds on a wash cycle with 100 percent acetonitrile for 1.5 minutes and then 100 percent buffer solution for 3 minutes. The flow rate over this period is a constant 3 mL / minute.

Preparation of intermediates:

The groups attached to the 4 position of the pyridine core were prepared by the methods described below for compounds **B1-B19**.

Preparation of N-(3-aminomethyl-phenyl)-N-methyl-methanesulfonamide acetate (**B1**):



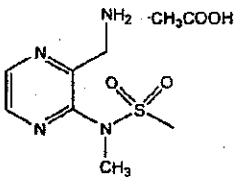
Step 1. Preparation of N-(3-cyano-phenyl)-methanesulfonamide (**B1-1**): A solution of 3-amino benzonitrile (10 g, 84.64 mmol) in pyridine (160 mL) was cooled to 0°C and methane sulphonyl chloride (8.6 mL, 74.8 mmol) was added. The reaction mixture was allowed to warm to 25°C and stirred for about 20 hours. The reaction mixture was then concentrated, and the resultant residue was dissolved in ethyl acetate (EtOAc) (250 mL), washed with 2N HCl (50 mL), brine (25 mL), and dried over anhydrous Na_2SO_4. The solution was then concentrated to provide (**B1-1**) as a brown

solid. Yield: 17.1 g. ^{1}HNMR (d_6-DMSO) δ: 10.25(s, 1H), 7.45-7.65(m, 4H) and 3.1(s, 3H). Mass: (M-1) 195 calculated for $C_8H_8N_2O_2S$.

Step. 2. Preparation of N-(3-cyano-phenyl)-N-methyl-methanesulfonamide (**B1-2**): A mixture of benzyltriethylammonium chloride (BTEAC) (2.44 g, 10.7 mmol) and **B1-1** (21 g, 107.1 mmol) in tetrahydrofuran (THF) (250 mL) and 40% NaOH solution (250 mL) was cooled to 10°C, treated with methyl iodide (8.6 mL, 139.0 mmol), and allowed to warm to 25°C. After about 20 hours the THF was removed by distillation, and the concentrated mixture was extracted with dichloromethane (DCM) (3x200 mL). The combined organic layers were washed with water (100 mL), brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The resultant residue was then purified by column chromatography (60-120 mesh silica gel; 20% EtOAc in hexane as eluting solvent) to provide **B1-2** as a white solid. Yield: 20 g, 89.3%. ^{1}HNMR (d_6-DMSO) δ: 7.9(s, 1H), 7.7-7.84(m, 2H), 7.52-7.65(m, 2H), 3.3(s, 3H) and 3.02(s, 3H). Mass: (M+1) 211 calculated for $C_9H_{10}N_2O_2S$.

Step 3. A solution of **B1-2** (20 g, 95.12 mmol) in THF(100 mL) and acetic acid (400 mL) was charged to a Parr reactor. The contents of the reactor were then treated with 10% Pd/C (10.12 g) and hydrogenated at 50 Psi hydrogen pressure and 25°C for 4 hours. The contents of the reactor were filtered through a bed of Celite® and washed with ethanol (50 mL). The combined filtrates were then concentrated under reduced pressure, and the resultant residue was azeotroped with EtOAc (3 x 50 mL). The resultant oily mass was dissolved in EtOAc and allowed stand at 25°C for about 20 hours. The resultant white solids were collected by filtration and dried to provide **B1** as the acetate salt. Yield: 15.2 g, 60%. ^{1}HNMR (d_6-DMSO) δ: 7.2-7.45(m, 4H), 4.6-5.65(broad, 4H), 3.75(s, 2H), 3.2(s, 3H), 2.95(s, 3H) and 1.9(s, 3H). Mass: (M+1) 215 calculated for $C_9H_{14}N_2O_2S$. HPLC Purity: 99.1%.

Preparation of N-(3-aminomethyl-pyrazin-2-yl)-N-methyl-methane sulfonamide acetate (**B2**):

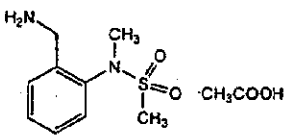


Step 1. Preparation of N-(3-cyano-pyrazin-2-yl)-N-methyl-methane sulfonamide (**B2-1**): A solution of chloropyrazine-2-carbonitrile (4.2 g, 30.21 mmol) in acetonitrile

(200 mL) at 25°C was treated sequentially with Cs_2CO_3 (13.7831 g, 42.293 mmol) and N-methyl-methane sulfonamide (3.957 g, 36.25 mmol). The mixture was then heated to 80°C. After about 20 hours the mixture was cooled to 25° and filtered. The solids were washed with EtOAc (3 x 25 mL) and the combined filtrates were concentrated. The resultant residue was treated with water (50 mL) and extracted with EtOAc (3x75mL). The combined organic layers were washed with water (50 mL), brine, dried over anhydrous sodium sulfate and concentrated. The resultant residue was purified by column chromatography (100-200 mesh silica gel; 40% EtOAc in petroleum ether as eluting solvent) to provide **B2-1** as a pale brown liquid. Yield: 4.7 g, 73.43%). ^{1}HNMR ($CDCl_3$) δ: 8.92(d, 2H), 3.4(s, 3H) and 3.25(s, 3H). Mass: (M+1) 213 calculated for $C_7H_8N_4O_2S$. (Note: The product contained unreacted N-methanesulfonamide as an impurity. The product was used without further purification to prepare **B2** in the step described below.

Step 2. A suspension of **B2-1** (5.345 g, 23.21 mmol) in 2N methanolic NH_3 (566.7 mL) in a Parr reactor was treated with 10% Pd/C (395 mg, 3.78 mmol), and the contents of the reactor were hydrogenated at 45 Psi hydrogen pressure and 25°C for 3 hours. The contents of the reactor were then filtered through a bed of Celite®, washed with methanol (MeOH), and concentrated. The resultant residue was treated with EtOAc (25 mL) and acetic acid (1.5 g), stirred at 25°C, and concentrated. The resultant residue was treated with EtOAc (100 mL) and allowed to stand at 25°C for about 20 hours. The resultant solids were collected, washed with EtOAc, and dried to provide **B2**. Yield: 3.5 g, 64.3%. IR (cm^{-1}): 3453, 3222, 2937, 3859, 1641, 1560, 1405, 1340 and 1155. ^{1}HNMR (d_6-DMSO) δ: 8.7(s, 1H), 8.5(s, 1H), 5.3-5.8(broad, 2H), 4.0(s, 2H), 3.2(s, 3H), 3.12(s, 3H) and 1.84(s, 3H). Mass: (M+1) 217 calculated for $C_7H_{12}N_4O_2S$.

Preparation of N-(2-aminomethyl-phenyl)-N-methyl-methanesulfonamide acetate (**B3**):



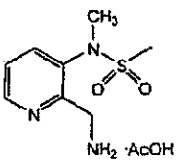
Step 1. Preparation of N-(2-cyano-phenyl)-N-dimethanesulfonamide (**B3-1**): A solution of 2-amino benzonitrile (10 g, 8.46 mmol) in pyridine (250 mL) at 25°C was treated drop-wise over 30 minutes with methane sulphonyl chloride (21.33 g, 18.62 mmol). The reaction mixture was then stirred at 25°C for about 20 hours and

concentrated The resultant residue was dissolved in EtOAc (200 mL), washed with 2 N HCl (200 mL) and brine (30 mL), and dried over anhydrous sodium sulfate. The solution was then concentrated to provide **B3-1** as a yellow solid. Yield: 20.7 g, 89%. ^{1}HNMR (d_6-DMSO) δ: 8.06(d, 1H), 7.82-7.85(m, 2H), 7.7-7.75(m, 1H), 3.62(s, 6H).

Step 2. Preparation of N-(2-cyano-phenyl)-N-methyl-methanesulfonamide (**B3-2**): A solution of **B3-1** (4 g, 1.45 mmol) in THF (30 mL) at 25°C was treated with 40% NaOH solution (30 mL) and BTEAC (0.331 g, 0.145 mmol) and stirred vigorously for 30 minutes. The mixture was then treated with methyl iodide (2.48 g, 1.7 mmol) and stirred at 25°C for about 20 hours. The THF was removed under reduced pressure and the mixture extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated to provide **B3-2** as a pale yellow solid. Yield: 3 g, 96%. ^{1}HNMR ($CDCl_3$) δ: 7.62-7.8(m, 2H), 7.55-7.56(m, 1H), 7.4-7.52(m, 1H), 3.4(s, 3H) and 3.15(s, 3H). Mass: (M-1) 209 calculated for $C_9H_{10}N_2O_2S$. The product was used without further purification to prepare **B3** in the step described below.

Step 3. A solution of **B3-2** (2 g, 9.5 mmol) in a mixture of acetic acid (100 mL) and THF (25 mL) was charged to a Parr shaker. The contents of the reactor were treated with 10% Pd/C (1.01 g) and hydrogenated at 60 Psi hydrogen pressure and 25°C for 3.5 hours. The contents of the reactor were then filtered through a bed of Celite® and washed with MeOH (20 mL). The combined filtrates were then concentrated. The resultant residue was azeotroped with toluene (2x20 mL) and EtOAc (20 mL) and dried under vacuum to provide **B3** as a white solid. Yield: 1.9 g, 95%. ^{1}HNMR (d_6-DMSO) δ: 7.5-7.62(m, 1H), 7.25-7.5(m, 3H), 3.92-5.6(broad, 3H), 3.8(s, 2H), 3.16(s, 3H), 3.04(s, 3H) and 1.9(s, 2H). Mass: (M+1) 215 calculated for $C_9H_{14}N_2O_2S$. HPLC Purity: 98.8%.

Preparation of N-(2-aminomethyl-pyridin-3-yl)-N-methyl-methanesulfonamide acetate salt (**B4**):



Step 1. Preparation of 6-chloro-pyridin-3-ylamine (**B4-1**): A solution of 2-chloro-5-nitro pyridine (30 g, 189 mmol) in MeOH (600 mL) was charged to a Parr reactor. The contents of the reactor were treated with Raney nickel (2 g) and hydrogenated at 60 Psi

hydrogen pressure and 25°C for 16 hours. The contents of the reactor were then filtered through a Celite® bed and washed with MeOH (100 mL). The combined filtrates were concentrated, and the resultant residue was purified by column chromatography (60-120 mesh silica gel column; 10% MeOH in $CHCl_3$ as eluting solvent) to provide **B4-1** as a pale yellow solid. Yield: 19 g, 78%. ^{1}HNMR ($CDCl_3$) δ: 7.85(d, 1H), 7.1(d, 1H), 6.95(dd, 1H) and 3.52-3.98(broad s, 2H).

Step 2. Preparation of N-(6-chloro-pyridin-3-yl)-methanesulfonamide (**B4-2**): A solution of **B4-1** (38 g, 295.7 mmol) and pyridine (28 g, 354 mm) in DCM (874 mL) at 10°C was treated drop-wise over 30 minutes with methane sulphonyl chloride (37.2 g, 325 mmol). The reaction mixture was allowed to warm to 25°C, and stirred at 25°C for 20 hours. The mixture was then treated with DCM (300 mL) and washed with water (1500 mL) and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The resultant residue was washed with petroleum ether (80 mL), filtered, and dried to provide **B4-2** as an off-white solid. Yield: 36 g, 60%. ^{1}HNMR (d_6-DMSO) δ: 10.12(s, 1H), 8.22(d, 1H), 7.65(dd, 1H), 7.46(d, 1H) and 3.08(s, 3H).

Step 3. Preparation of N-(6-chloro-pyridin-3-yl)-N-methyl-methanesulfonamide (**B4-3**): A solution of **B4-2** (13 g, 62.8 mmol), BTEAC (1.42 g, 6.2 mmol) and 40% aq. NaOH (117 mL) in THF (117 mL) at 0°C was treated drop-wise over 30 minutes with methyl iodide (10.6 g, 75.3 mmol). The reaction mixture was allowed to warm to 25°C and stirred for an additional 3 hours. The mixture was then treated with THF (100 mL), and the resultant organic layer was collected. The aqueous layer was extracted with EtOAc (2 x 100 mL), and the combined organic layers were washed with 1N NaOH and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The resultant residue was then triturated with petroleum ether to provide **B4-3** as a pale yellow solid. Yield: 12 g, 86%. ^{1}HNMR ($CDCl_3$) δ: 8.4(d, 1H), 7.72(dd, 1H), 7.35(d, 1H), 3.38(s, 3H) and 2.88 (s, 3H). Mass: (M+1) 221 calculated for $C_7H_9ClN_2O_2S$.

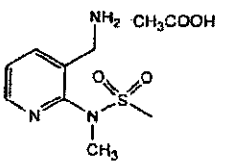
Step 4. Preparation of N-(6-chloro-1-hydroxy-pyridin-3-yl)-N-methyl-methanesulfonamide (**B4-4**): A solution of **B4-3** (15 g, 68.1 mmol) in DCM (172 mL) was cooled to 0°C and treated slowly over 10 minutes with a solution of 77% m-chloroperoxybenzoic acid (MCPBA) (27.9 g, 124 mm) in DCM (200 mL). The rate of addition was controlled so that the temperature of the reaction mixture did not exceed 3 to 5°C. The reaction mixture was allowed to warm to 25°C and stirred at 25°C for 20 hours. The mixture was then cooled to 0°C and treated with 1N NaOH (300mL). The resultant organic layer was collected and washed with 1N NaOH (100mL) and 10%

sodium sulfite (100mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated to provide **B4-4** as a white crystalline solid. Yield: 8 g, 49%. ^{1}HNMR (d_6-DMSO) δ: 8.55(s, 1H), 7.85(d, 1H), 7.46(dd, 1H), 3.26(s, 3H) and 3.1(s, 3H). Mass: (M+1) 237 calculated for $C_7H_{11}ClN_2O_3S$.

Step 5. Preparation of N-(6-chloro-2-cyano-pyridin-3-yl)-N-methyl-methanesulfonamide (**B4-5**): Dimethylsulfate (3.2 mL) was cooled to 0°C and treated portion-wise with **B4-4** (8 g, 33.6 mmol) over 3 hours. The resultant suspension was allowed to warm to 25° and maintained at 25°C for 16 hours. The resulted gummy mass was then washed with diethyl ether. The resultant white residue was dissolved in water (37.6 mL) and added drop-wise over 30 minutes to an aqueous solution of sodium cyanide (6.5 g, 134.4 mm) at 10°C. The reaction mixture was allowed to warm to 25°C, and it was maintained at 25°C for 16 hours. The resultant brown solids were collected and dissolved in EtOAc (200 mL). The organic solution was then washed with water (500 mL) and brine, and dried over anhydrous sodium sulfate. The organic solution was concentrated, and the resultant residue was purified by column chromatography (silica gel; 10% MeOH in $CHCl_3$ as eluting solvent) to provide **B4-5** as a white solid. Yield: 2.5 g, 30%. ^{1}HNMR (d_6-DMSO) δ: 8.38(d, 1H), 8.02(d, 1H), 3.3(s, 3H) and 3.28(s, 3H).

Step 6. A solution of **B4-5** (2.5 g, 10.2 mmol) in a mixture of THF (80 mL) and acetic acid (200 mL) was charged to a Parr reactor. The contents of the Parr reactor were then treated with 10% Pd/C (2.4 g, 22.4 mmol) and hydrogenated at 60 Psi hydrogen pressure and 25°C for 16 hours. The contents of the reactor were filtered through a Celite® bed and washed with MeOH (100 mL). The combined organic filtrates were concentrated, and the resultant residue was azeotroped with EtOAc (2x50 mL). The resultant solids were collected and dried to provide **B4** as an off-white solid. Yield: 2.0 g, 95%. IR (cm^{-1}): 3438, 3245, 2994, 2601, 1590, 1467, 1328, 1151 and 1047. ^{1}HNMR (d_6-DMSO) δ: 8.65(d, 1H), 8.25-8.55(broad s, 2H), 8.15(d, 1H), 7.5-7.7(m, 1H), 4.0-4.42(s, 2H), 3.25(s, 3H) and 3.14(s, 3H). Mass: (M+1) 216 calculated for $C_8H_{13}N_3O_2S$.

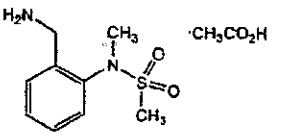
Preparation of N-(3-Aminomethyl-pyridin-2-yl)-N-methyl-methanesulfonamide acetate (**B5**):



Step 1. Preparation of N-(3-cyano-pyridin-2-yl)-N-methyl-methanesulfonamide (**B5-1**): A solution of 2-chloro-3-cyano-pyridine (10 g, 72.4 mmol) in acetonitrile (200 mL) at 25°C was treated with N-methyl-methanesulfonamide (14 g, 128.2 mmol) and Cs_2CO_3 (33 g, 101.2 mmol). The reaction mixture was slowly heated to 80°C and maintained at 80°C for 8 hours. The reaction mixture was then cooled to 25C, filtered through a Celite® bed, and concentrated. The resultant residue was treated with water (300 mL) and extracted with EtOAc (3x200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, treated with carbon, and filtered. The filtrate was then concentrated, and the resultant residue was triturated with ether (100 mL). The resultant solids were collected and dried to provide **B5-1** as an off-white solid. Yield: 7 g, 46%. ^{1}HNMR ($CDCl_3$) δ: 8.6-8.72(m, 1H), 8.02-8.12(d, 1H), 7.3-7.45(m, 1H), 3.4(s, 3H) and 3.2(s, 3H). Mass: (M+1) 212 calculated for $C_8H_9N_3O_2S$. HPLC purity: 99.9%.

Step 2. A solution of **B5-1** (10 g, 47.3 mmol) in ethanol was charged to a Parr reactor, and the contents of the reactor were treated with 300 mL of a 2M ammonia solution in ethanol and 5% Pd/C (1.2 g). The contents of the reactor were then hydrogenated at 60 Psi hydrogen pressure and 37°C for 3 hours and then at 30°C for 20 hours. The contents of the reactor were filtered through a Celite® bed and concentrated. The resultant residue was treated with EtOAc, cooled to 20°C, and treated with acetic acid (10 mL). The mixture was then stirred for 10 minutes and concentrated. The resultant residue was dissolved in EtOAc (150 mL) in a glass flask. The walls of the flask were then scratched, and white solids began to form. The solids were collected and washed with EtOAc followed by petroleum ether. The solids were then dried to provide **B5**. Yield: 11 g, 85%. ^{1}HNMR ($CDCl_3$) δ: 8.3-8.5(m, 1H), 8.04(d, 1H), 7.4-7.55(m, 1H), 6.02-7.15(broad, 3H), 3.85(s, 2H), 3.14(d, 6H), 1.9(s, 3H). Mass: (M+1) 216 calculated for $C_8H_{13}N_3O_2S$.

Preparation of N-(2-Aminomethyl-phenyl)-N-methyl-methanesulfonamide acetate (**B6**):



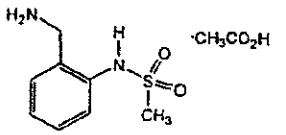
Step 1. Preparation of N-(2-Cyano-phenyl)-N-dimethanesulfonamide (**B6-1**): A solution of 2-amino benzonitrile (10 g, 8.46 mmol) in pyridine (250 mL) was treated

drop-wise at 25°C over 30 minutes with methane sulphonyl chloride (21.33 g, 18.62 mmol). The reaction mixture was then stirred at 25°C for 20 hours and concentrated. The resultant residue was dissolved in EtOAc (200 mL) and washed with 2 N HCl (200 mL) and brine (30 mL). The solution was dried over anhydrous sodium sulfate and concentrated to provide **B6-1** as a yellow solid. Yield: 20.7 g, 89%. ^{1}HNMR (d_6-DMSO): δ 8.06(d, 1H), 7.82-7.85(m, 2H), 7.7-7.75(m, 1H), 3.62(s, 6H). The product was used without further purification to prepare **B6-2** in the step described below.

Step 2. Preparation of N-(2-Cyano-phenyl)-N-methyl-methanesulfonamide (**B6-2**): A solution of **B6-1** (4 g, 1.45 mmol) in THF (30 mL) was treated with 40% NaOH (30 mL) and BTEAC (0.331 g, 0.145 mmol) at 25°C and stirred vigorously for 30 minutes. The mixture was then treated with methyl iodide (2.48 g, 1.7 mmol) and stirred at 25°C for 20 hours. The THF was removed under reduced pressure, and the concentrated mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated to provide **B6-2** as pale yellow solid. Yield: 3 g, 96%. ^{1}H NMR($CDCl_3$): δ 7.62-7.8(m, 2H), 7.55-7.56(m, 1H), 7.4-7.52(m, 1H), 3.4(s, 3H) and 3.15(s, 3H). Mass: (M-1) 209 calculated for $C_9H_{10}N_2O_2S$. The product was used without further purification to prepare **B6** in the step described below.

Step 3. A solution of **B6-2** (2 g, 9.5 mmol) in a mixture of acetic acid (100 mL) and THF (25 mL) was charged to a Parr reactor. The contents of the reactor were treated with Pd/C (1.01 g) and hydrogenated at 60 Psi hydrogen pressure and 25°C for 3.5 hours. The mixture was then filtered through a bed of Celite® and washed with methanol (20 mL). The combined filtrates were concentrated, and the resultant residue was azeotroped with toluene (2x20 mL) followed by EtOAc (20 mL). The residue was then dried under reduced pressure to provide **B6** as a white solid. Yield: 1.9 g, 95%. ^{1}HNMR (d_6-DMSO): δ 7.5-7.62(m, 1H), 7.25-7.5(m, 3H), 3.92-5.6(broad, 3H), 3.8(s, 2H), 3.16(s, 3H), 3.04(s, 3H) and 1.9(s, 2H). Mass: (M+1) 215 calculated for $C_9H_{14}N_2O_2S$. HPLC Purity: 98.8%.

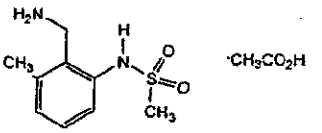
Preparation of N-(2-Aminomethyl-phenyl)-methanesulfonamide acetate (**B7**):



Step 1. Preparation of N-(2-cyano-phenyl)-methanesulfonamide (**B7-1**): A solution of **B6-1** (4 g, 14.8 mmol) in THF (29.26 mL) was treated with 40% aqueous NaOH (29.26 mL) and BTEAC (0.331 g, 1.45 mmol) and stirred at 25°C for 20 hours. The reaction mixture was then concentrated, and the resultant residue was diluted with water (100 mL) and neutralized with 6N HCl (30 mL). The mixture was extracted with DCM (200 mL), and the organic layer was washed with water (150 mL) and brine. The organic solution was then dried over anhydrous sodium sulfate and concentrated to provide **B7-1** as a white solid. Yield: 2.8 g, 92%. ^{1}HNMR(CDCl3): δ 7.7-7.76(m, 1H), 7.6-7.65(m, 1H), 6.8-6.98(broad, 1H) and 3.14(s, 3H). Mass: (M-1) 195 calculated for $C_8H_8N_2O_2S$.

Step 2. A solution of **B7-1** (2 g, 10.19 mmol) in a mixture of THF (133 mL) and acetic acid (250mL) was charged to a Parr reactor. The contents of the reactor were then treated with 10% Pd/C (2 g) and hydrogenated at 60 Psi hydrogen pressure and 25°C for 4 hours. The reaction mixture was filtered through Celite® bed and concentrated. The resultant residue was diluted with toluene (20 mL) and concentrated. The resultant residue was then diluted with EtOAc (20 mL) and concentrated to provide **B7** as white solid. Yield: 2 g, 98%. ^{1}HNMR (d_6-DMSO): δ 7.32-8.6(broad, 4H), 7.25-7.32(m, 1H), 7.1-7.32(m, 2H), 6.82(t, 1H), 3.9(s, 2H), 2.85(s, 3H) and 1.9(s, 3H). Mass: (M+1) 201 calculated for $C_8H_{12}N_2O_2S$. HPLC Purity: 98.9%.

Preparation of N-(2-Aminomethyl-3-methyl-phenyl)-methanesulfonamide acetate (**B8**):



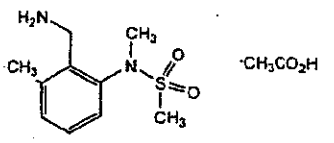
Step 1. Preparation of N-(2-cyano-3-methyl-phenyl)-N-dimethanesulfonamide (**B8-1**): A suspension of 2-amino-6-methyl benzonitrile (35 g, 265.5 mmol) in pyridine (600 mL) was cooled to about 0°C to -5°C and slowly treated with mesyl chloride (30 mL, 397.71 mmol) over 10 minutes. The reaction mixture was allowed to warm to 26°C and stirred at 25°C for 20 hours. The reaction mixture was concentrated and the resultant residue was diluted with EtOAc (600 mL). The organic solution was then washed with water (100 mL), 2N HCl (100 mL), and saturated brine (100 mL). The organic solution was then dried over anhydrous sodium sulfate and concentrated to provide **B8-1** as a mixture of di- and mono-mesylated products. Yield: 49 g. The

product was used without further purification to prepare **B8-2** in the step described below.

Step 2. Preparation of N-(2-cyano-3-methyl-phenyl)-methanesulfonamide (**B8-2**): A solution of **B8-1** (35 g, 166.6 mmol) in THF (300 mL) was treated with 40% aq. NaOH solution (300 mL) and BTEAC (1.84 g, 8.09 mmol) at 25°C and stirred for 1 hour. The THF was removed under reduced pressure, and the concentrated mixture was extracted with DCM (500 mL). The aqueous layer was acidified with 2N HCl and extracted with DCM (250 mL). The combined organic layers were washed with water (100 mL) and brine (50 mL). The organic solution was then dried over anhydrous sodium sulfate and concentrated. The resultant residue was purified by column chromatography (60-120 mesh silica gel; 3% MeOH in $CHCl_3$ as eluting solvent) to provide **B8-2** as a brown solid. Yield: 24 g. ^{1}HNMR (d_6-DMSO): δ 9.98(s, 1H), 7.6(t, 1H), 7.26-7.4(m, 2H), 3.1(s, 3H), 2.5(s, 3H). Mass: (M-1) 209 calculated for $C_9H_{10}N_2O_2S$.

Step 3. A solution of **B8-2** (10 g, 47.6 mmol) in acetic acid (75 mL) and THF (250 mL) was charged to a Parr reactor and treated with 10% Pd/C (6 g). The reaction mixture was then hydrogenated at 50 Psi hydrogen pressure and 25°C for 16 hours. The reaction mixture was filtered through a Celite® bed and washed with ethanol (3 x 20 mL). The combined filtrates were concentrated, and the resultant residue was co-distilled with EtOAc (100 mL). The resultant brown oil was dissolved in EtOAc (100 mL) and allowed to stand at 25°C for 20 hours. The resultant white solids were collected and dried to provide **B8**. Yield: 11 g. ^{1}HNMR (d_6-DMSO): δ 7.65-8.65(broad, 3H), 7.15(d, 1H), 7.05(t, 1H), 6.68(d, 1H), 3.9(s, 2H), 2.8(s, 3H), 2.26(s, 3H) and 1.9(s, 3H). Mass: (M+1) 215 calculated for $C_9H_{14}N_2O_2S$. HPLC Purity: 98.6%.

Preparation of N-(2-Aminomethyl-3-methyl-phenyl)-N-methyl-methanesulfonamide acetate (**B9**):

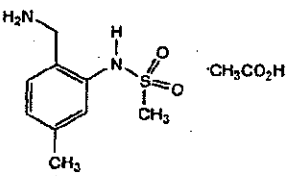


Step 1. Preparation of N-(2-cyano-3-methyl-phenyl)-N-methyl-methanesulfonamide (**B9-1**): A solution of **B8-1** (15 g, 71.42 mmol) in THF (150 mL) was treated with 40% aq. NaOH (150 mL) and BTEAC (1.6 g, 7.14 mmol) at 25°C and stirred for 10 minutes. The reaction mixture was then cooled to 10°C and treated with methyl iodide (5.78 mL, 85.7 mmol). The reaction mixture was allowed to warm to 25°C

and stirred at 25°C for 20 hours. The reaction mass was concentrated, and the resultant residue was diluted with DCM (600 mL). The organic solution was then washed with water (100 mL) and brine (50 mL). The organic solution was dried over anhydrous sodium sulfate and concentrated. The resultant residue was then purified by column chromatography (60-120 mesh silica gel; 2% MeOH in $CHCl_3$ as eluting solvent) to provide **B9-1** as pale brown solid. Yield: 20 g, 98%. ^{1}HNMR (d_6-DMSO): δ 7.65(d, 1H), 7.56(d, 1H), 7.45(d, 1H), 3.25(s, 3H), 3.14(s, 3H) and 2.5(s, 3H). Mass: (M+1) 225 calculated for $C_{10}H_{12}N_2O_2S$.

Step 2. A solution of **B9-1** (10 g, 47.6 mmol) in a mixture of THF (100 mL) and acetic acid (300 mL) was charged to a Parr reactor and treated with Pd/C (6 g). The contents of the reactor were then hydrogenated at 50 Psi hydrogen pressure and 25°C for 6 hours. The reaction mixture was filtered through a bed of Celite® and washed with ethanol (3 x 30 mL). The combined filtrates were concentrated, and the resultant residue was co-distilled with EtOAc (100 mL). The resultant brown oil was taken into EtOAc (100 mL) and stirred at 25°C for 16 hours. The resultant white solids were collected, washed with EtOAc (2 x 25 mL), and dried to provide **B9**. Yield: 11.6 g, 89%. ^{1}HNMR (d_6-DMSO): δ 7.15-7.36(m, 3H), 4.64-5.45(broad, 3H), 3.76(d, 2H), 3.15(s, 3H), 3.05(s, 3H), 2.42(s, 3H) and 1.9(s, 3H). Mass: (M+1) 229 calculated for $C_{10}H_{16}N_2O_2S$. HPLC Purity: 97.4%.

Preparation of N-(2-Aminomethyl-5-methyl-phenyl)-methanesulfonamide acetate (**B10**):



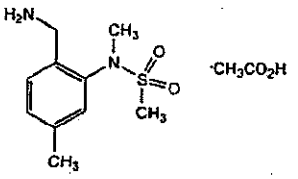
Step 1. Preparation of 2-amino-4-methyl-benzonitrile (**B10-1**): A solution of 4-methyl-2-nitrobenzonitrile (10 g, 61.72 mmol) in ethanol (200 mL) was charged to a Parr reactor and treated with 10% Pd/C (1 g). The contents of the reactor were then hydrogenated at 50 Psi hydrogen pressure 25°C for 90 minutes. The reaction mixture was filtered through a Celite® bed and washed with ethanol. The combined filtrates were the concentrated to provide **B10-1**. Yield: 8.5 g. ^{1}HNMR ($CDCl_3$): δ 7.28(s, 1H), 6.5-6.62(m, 2H), 4.2-4.42(broad, 2H) and 2.3(s, 3H). Mass: (M-1) 132 calculated for $C_8H_8N_2$. The product was used without further purification to prepare **B10-2** in the step described below.

Step 2. Preparation of N-(2-cyano-5-methyl-phenyl)-methanesulfonamide and N-(2-cyano-5-methyl-phenyl)-N-(methylsulfonyl)methanesulfonamide (**B10-2**): A solution of **B10-1** (8.5 g, 64.39 mmol) in pyridine (50 mL) was cooled to 0°C and treated drop-wise with mesyl chloride (8.85 g, 77.22 mmol) over 15 minutes. The reaction mixture was allowed to warm to 25°C, and it was stirred at 25°C for 20 hours. The reaction mixture was then concentrated, and the resultant residue acidified with 2N HCl (50 mL) and extracted with EtOAc (200 mL). The resultant organic layer was washed with water (50 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The organic solution was then concentrated to provide **B10-2** as a mixture of both mono and di mesylated product. Yield: 9.2 g. The product was used without further purification to prepare **B10-3** in the step described below.

Step 3. Preparation of N-(2-cyano-5-methyl-phenyl)-methanesulfonamide (**B10-3**): A solution of **B10-2** (17 g, 80.95 mmol) in a mixture of THF (70 mL) and 40% NaOH solution (70 mL) was treated with BTEAC (1.84 g, 8.09 mm) at 25°C and stirred at 25°C for 20 hours. The THF was removed under reduced pressure, and the concentrated mixture was extracted with DCM (300 mL). The aqueous layer was acidfied with 2N HCl and extracted with DCM (200 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), and dried over anhydrous sodium sulfate. The organic solution was then concentrated, and the resultant residue was purified by column chromatography (60-120 mesh silica gel; 30% EtOAc in DCM as eluting solvent) to provide **B10-3** as a pale brown solid. Yield: 16 g, 97%. ^{1}HNMR (d_6-DMSO): δ 7.9(d, 1H), 7.7(s, 1H), 7.55(d, 1H), 3.62(s, 6H) and 2.45(s, 3H). Mass: (M-1) 209 calculated for $C_9H_{10}N_2O_2S$.

Step 4. A solution of **B10-3** (17 g, 80.95 mmol) in a mixture of THF (250 mL) and acetic acid (250 mL) was charged to a Parr reactor and treated with 10% Pd/C (8 g). at 25°C. The reaction mixture was then hydrogenated at 50Psi hydrogen pressure and 25°C for 4 hours. The mixture was filtered through a Celite® bed and washed with ethanol (3 x 20 mL). The combined filtrates were concentrated and the resultant residue was azeotroped with EtOAc (2 x 20 mL). The resultant brown-colored oil was taken into EtOAc (50mL) and allowed to stand at 25°C for 20 hours. The resultant white solids were collected and dried to provide **B10**. Yield: 15.1 g, 71.2%. ^{1}HNMR (d_6-DMSO): δ 7.62-8.2(broad, 3H), 7.02-7.18(m, 2H), 6.7(d, 1H), 3.85(s, 2H), 2.88(s, 3H), 2.25(s, 3H) and 1.9(s, 3H). Mass: (M+1) 215 calculated for $C_9H_{14}N_2O_2S$. HPLC Purity: 99.7%.

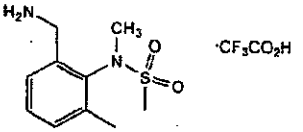
Preparation of N-(2-Aminomethyl-5-methyl-phenyl)-N-methyl-methanesulfonamide acetate (**B11**):



Step 1. Preparation of N-(2-cyano-5-methyl-phenyl)-N-methyl-methanesulfonamide (**B11-1**): A solution of **B10-2** (10 g, 47.61 mmol) in a mixture of THF (100 mL) and 40% aq. NaOH solution (100 mL) at 25°C was treated with BTEAC (1.1 g, 4.7 mmol) and methyl iodide (8.78 g, 61.89 mmol). The reaction mixture was then stirred at 25°C for 20 hours. The THF was removed under reduced pressure, and the concentrated mixture was extracted with DCM (300 mL). The organic layer was washed with water (100 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The organic solution was then concentrated, and the resultant residue was purified by column chromatography (60-120 mesh silica gel; 10% EtOAc in $CHCl_3$ as eluting solvent) to provide **B11-1** as a brown solid. Yield: 10.3 g, 96%. ^{1}HNMR ($CDCl_3$): δ 7.62(d, 1H), 7.38(s, 1H), 3.38(s, 3H), 3.1(s, 3H) and 2.45(s, 3H). Mass: (M-1) 223 calculated for $C_{10}H_{12}N_2O_2S$.

Step 2. A solution of **B11-1** (4 g, 17.85 mmol) in acetic acid (150 mL) was charged to a Parr reactor and treated with Pd/C (2 g). The contents of the reactor were then hydrogenated at 50 Psi hydrogen pressure and 25°C for 6 hours. The reaction mixture was filtered through a Celite® bed and washed with ethanol (2 x 20 mL). The combined filtrates were concentrated, and the resultant brown solid was azeotroped with EtOAc (3 x 25 mL). The resultant solid was taken into EtOAc (25 mL) at stirred at 25°C for 20 hours. The resultant solids were collected and dried under reduced pressure to provide **B11**. Yield: 2.7 g, 53%. ^{1}HNMR (d_6-DMSO): δ 7.45(d, 1H), 7.3(s, 1H), 7.2(d, 1H), 5.04-5.7(broad, 2H), 3.75-3.92(broad, 2H), 3.15(s, 3H), 3.05(s, 3H), 2.3(s, 3H) and 1.9(s, 2H). Mass: (M+1) 229 calculated for $C_{10}H_{16}N_2O_2S$. HPLC Purity: 97.7 %.

Preparation of N-(2-Aminomethyl-6-methyl-phenyl)-N-methyl-methanesulfonamide trifluoroacetate (**B12**):



Step 1. Preparation of potassium di-tert-butyl iminodicarboxylate (**B12-1**): A solution of di-tert-butyl iminodicarboxylate (56 g, 258 mmol) in ethanol (200 mL) was cooled to 15°C and treated over 30 minutes with a solution of KOH (17g) in ethanol (150 mL). The reaction mixture was allowed to warm to 25°C, and it was stirred at 25°C for 4 hours. The reaction mixture was then concentrated, and the resultant residue was diluted with diethyl ether (300 mL) and stirred for 3 hours. The resultant solids were collected and immediately dried under reduced pressure to provide **B12-1** as a white crystalline solid. Yield: 57 g, 82%. ^{1}HNMR (d_6-DMSO): δ 1.35(s, 18H). Mass: (M-1) 216 calculated for $C_{10}H_{19}NO_4$.

Step 2. Preparation of 1-chloromethyl-3-methyl-2-nitro-benzene (**B12-2**): A solution of 3-(methyl-2-nitro-phenyl)-methanol (12 g, 71.78 mmol) in DCM (500 mL) was cooled to -5°C and treated with dimethylaminopyridine (DMAP) (11.4 g, 93.3 mm) followed by treatment with a solution of tosyl chloride (17.79 g, 93.3 mmol) in DCM. The reaction mixture was stirred at -5°C for 30 minutes. The reaction mixture was then allowed to warm to 25°C, and it was stirred at 25°C for 20 hours. The reaction mixture was diluted with DCM (100 mL) and washed with 1N HCl (2 x 50 mL), saturated $NaHCO_3$ (2 x 25 mL), and brine. The organic solution was then dried over anhydrous $MgSO_4$ and concentrated. The resultant residue was purified by column chromatography (silica gel column; 15% EtOAc in hexane as eluting solvent) to provide **B12-2** as a pale greenish-yellow oil. Yield: 14 g, 89%. ^{1}HNMR ($CDCl_3$): δ 7.35-7.46(m, 2H), 7.26-7.35(m, 1H), 4.6(s, 2H) and 2.36(s, 3H).

Step 3. Preparation of 3-methyl-2-nitro-benzyl di-tert-butyl iminodicarboxylate (**B12-3**): A solution of **B12-2** (14 g, 75.6 mmol) in N-methylpyrrolidinone (NMP) (135 mL) was cooled to -5°C and treated with **B12-1** (29.7 g, 116.4 mmol) over 20 minutes. The mixture was then heated at 50°C for 4 hour. The reaction mixture was diluted with water (150 mL) and extracted with EtOAc (4 x 250 mL). The combined organic layers were washed with water (300 mL) and brine. The organic solution was then dried over anhydrous $MgSO_4$ and concentrated. The resultant residue was purified by column chromatography (silica gel; 20% EtOAc in hexane as eluting solvent) to provide **B12-3** as an-off white solid. Yield: 21 g, 76%. ^{1}HNMR ($CDCl_3$): δ 7.35(t, 1H), 7.1-7.25(m, 2H), 4.76(s, 2H), 2.3(s, 3H) and 1.42(s, 18H).

Step 4. Preparation of 2-amino-3-methyl benzyl di-tert-butyl iminodicarboxylate (**B12-4**): A solution of **B12-3** (20 g, 54.64 mmol) in ethanol (500 mL) was charged to a Parr reactor and treated with 10% Pd/C (7 g). The contents of the reactor were then

hydrogenated at 55 Psi hydrogen pressure and 25°C for 5 hours. The reaction mixture was filtered through a Celite® bed and concentrated to provide **B12-4** as a pale greenish-yellow oil (19 g). ^{1}HNMR ($CDCl_3$): δ 7.1(d, 1H), 6.96(d, 1H), 6.6(t, 1H), 4.7(s, 2H), 4.3-4.5(broad, 2H), 2.15(s, 3H) and 1.45(s, 18H).

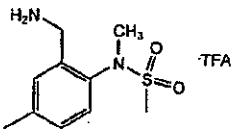
Step 5. Preparation of di-BOC 3-methyl-2-(methylsulfonamido)benzylamine (**B12-5**): A solution of **B12-4** (20 g, 59.6 mmol) in pyridine (150 mL) was cooled to 0°C and treated over 25 minutes with mesyl chloride (6.15 mL, 79.4 mmol). The mixture was allowed to warm to 25°C, and it was stirred at 25°C for 20 hours. The reaction mixture was diluted with EtOAc (300 mL) and washed with 1N HCl solution. The aqueous layer was collected and extracted with EtOAc (100 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The organic solution was then concentrated, and the resultant residue was taken into petroleum ether and stirred for 1 hour. The resultant solids were collected and dried under reduced pressure to provide **B12-5** as an off white solid. Yield: 22 g, 89%. ^{1}HNMR ($CDCl_3$): δ 7.9(s, 1H), 7.35(d, 1H), 7.05-7.25(m, 2H), 4.9(s, 2H), 3.1(s, 3H), 2.45(s, 3H) and 1.45(s, 18H). Mass: (M-1) 413 calculated for $C_{19}H_{30}N_2O_6S$.

Step 6. Preparation of di-BOC 3-methyl-2-(N-methylmethan-2-ylsulfonamido)benzylamine (**B12-6**): A solution of **B12-5** (22 g, 53.14 mmol) in THF (58.6 mL) was cooled to 15°C and treated with 40% aq NaOH solution (58.6 mL) followed by BTEAC (1.25 g, 5.5 mm). The mixture was stirred for 15 minutes and the treated over 20 minutes with methyl iodide (4.2 mL, 67.4 mmol). The reaction mixture was allowed to warm to 25°C, and it was stirred at 25°C for 20 hours. The reaction mixture was then diluted with water (300 mL) and extracted with DCM (3 x 200 mL). The combined organic layers were washed with water (3 x 400 mL) and brine, dried over anhydrous $MgSO_4$, and concentrated. The resultant residue was dissolved in petroleum ether in a glass flask, and the wall of the flask was scratched to induce solids formation. The resultant solids were collected and dried to provide **B12-6** as a pale yellow solid. Yield: 20 g, 88%. ^{1}HNMR ($CDCl_3$): δ 7.1-7.25(m, 2H), 7.04(d, 1H), 5.05(d, 1H), 4.8(d, 1H), 3.25(s, 3H), 3.1(s, 3H), 2.36(s, 3H) and 1.45(s, 18H).

Step 7. A solution of **B12-6** (13 g, 30.3 mmol) in DCM (35 mL) was cooled to 0°C and treated with trifluoroacetic acid (TFA) (70 mL). The reaction mixture was allowed to warm to 25°C, and it was stirred at 25°C for 2 hours. The reaction mixture was concentrated, and the resultant residue was azeotroped with EtOAc (2 x 100 mL). The resultant residue was diluted with a mixture of DCM and pentane (1:1) in a glass flask,

and the wall of the flask was scratched. The contents of the flask were stirred for 1 hour, and the resultant precipitate was collected and dried to provide **B12** as an off white solid. Yield: 9 g, 87%. ^{1}HNMR (d_6-DMSO): δ 8.3-8.45(broad, 2H), 7.38-7.5(m, 3H), 4.2(s, 2H), 3.14(s, 6H), and 2.44(s, 3H). Mass: (M+1) 229 calculated for $C_{10}H_{16}N_2O_2S$. HPLC Purity: 97.5%.

Preparation of N-(2-Aminomethyl-4-methyl-phenyl-N-methyl-methanesulfonamide trifluoroacetate (**B13**):



Step 1. Preparation of di-BOC-5-methyl-2-nitrobenzylamine (**B13-1**): A solution of 2-chloromethyl-4-methyl-1-nitro-benzene (20 g, 107.5 mmol) in NMP (140 mL) was cooled to 0°C and treated over 30 minutes with potassium di-tert-butyl iminodicarboxylate (40 g, 156 mmol). The reaction mixture was allowed to warm to 25°C, and it was stirred at 25°C for 20 hours. The reaction mixture was then diluted with water (150 mL) and extracted with EtOAc (2 x 500 mL). The resultant organic layer was washed with water (250 mL) and brine, and dried over anhydrous $MgSO_4$. The organic solution was then concentrated, and the resultant residue was purified by column chromatography (silica gel; 20% EtOAc in hexane as eluting solvent) to provide **B13-1** as a pale yellow solid. Yield: 29 g, 73%. ^{1}HNMR ($CDCl_3$): δ 7.98(d, 1H), 7.2(d, 1H), 7.1(s, 1H), 5.15(s, 2H), 2.4(s, 3H) and 1.44(s, 18H).

Step 2. Preparation of di-BOC 2-amino-5-methylbenzylamine (**B13-2**): A solution of **B13-1** (29 g, 79.23 mmol) in ethanol (500 mL) was charged to a Parr reactor and treated with Pd/C (9 g). The contents of the reactor were then hydrogenated 55 Psi hydrogen pressure and 25°C for 2 hours. The reaction mixture was filtered through a Celite® bed and concentrated to provide **B13-2** as an oil. Yield: 26 g. ^{1}HNMR ($CDCl_3$): δ 7.02(s, 1H), 6.85(d, 1H), 6.55(d, 1H) 4.7(s, 2H), 4.02-4.38(broad, 2H), 2.22(s, 3H) and 1.46(s, 18H).

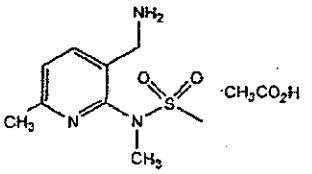
Step 3. Preparation of di-BOC 5-methyl-2-(methylsulfonamido)benzylamine (**B13-3**): A solution of **B13-2** (26 g, 77.38 mmol) in pyridine (165 mL) was cooled to 0°C and treated over 20 minutes with mesyl chloride (12.18 g, 106.4 mmol) was added over a period of 20 min. The mixture was allowed to warm to 25°C, and it was stirred at 25°C for 20 hours. The reaction mixture was then diluted with EtOAc (350 mL) and

washed with 1N HCl solution (2 x 250 mL). The resultant organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The resultant residue was treated with petroleum ether and stirred at 25°C for 1 hour. The resultant solids were then collected and dried under reduced pressure to provide **B13-3** as a pale yellow solid. Yield: 23 g, 71%. ^{1}HNMR ($CDCl_3$): δ 8.7(s, 1H), 7.45(d, 1H), 7.1(d, 1H), 4.72(s, 2H), 2.96(s, 3H), 2.3(s, 3H) and 1.46(s, 18H). Mass: (M-1) 413 calculated for $C_{19}H_{30}N_2O_6S$.

Step 4. Preparation of di-BOC 5-methyl-2-(N-methylmethan-2-ylsulfonamido)benzylamine (**B13-4**): A solution of **B13-3** (22 g, 53.14 mmol) in THF (70 mL) was cooled to 0°C and treated with 40% aq. NaOH solution (70 mL) followed by BTEAC (1.5 g, 6.6 mmol). After 15 minutes the mixture was treated with methyl iodide (9.51 g, 67.4 mmol) over a period of 20 minutes. The reaction mixture was allowed to warm to 25°C, and it was stirred at 25°C for 20 hours. The reaction mixture was then diluted with DCM (800 mL). The organic layer was collected and washed with water (2 x 200 mL) and brine, and dried over anhydrous $MgSO_4$. The organic solution was concentrated, and the resultant residue was triturated with petroleum ether to provide **B13-4** as a pale yellow solid. Yield: 20 g, 88%. ^{1}HNMR ($CDCl_3$): δ 7.0-7.4(m, 3H), 4.85-5.1(d, 2H), 3.25(s, 3H), 2.92(s, 3H), 2.35(s, 3H) and 1.45(s, 18H).

Step 5. A solution of **B13-4** (15 g, 35.04 mmol) in DCM (45 mL) was cooled to 0°C and treated over 30 minutes with TFA (90 mL). The mixture was then allowed to warm to 25°C. After 3 hours the mixture was concentrated, and the resultant residue was azeotroped with EtOAc (2 x 200 mL). The resultant residue was diluted with a mixture of DCM and ether (8:2) and stirred for 1 hour. The resultant precipitate was collected and dried under reduced pressure to provide **B13** as an off-white solid. Yield: 12 g, 98%. ^{1}HNMR (d_6-DMSO): δ 7.98-8.2(broad, 2H), 7.5(d, 1H), 7.4(s, 1H), 7.3(d, 1H), 3.96-4.28(broad, 2H), 3.2(s, 3H), 3.05(s, 3H) and 2.35(s, 3H). Mass: (M+1) 229 calculated for $C_{10}H_{16}N_2O_2S$.

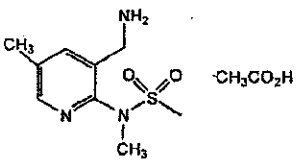
Preparation of N-(3-Aminomethyl-6-methyl-pyridin-2-yl-N-methyl-methanesulfonamide acetate (**B14**):



Step 1. Preparation of N-(3-cyano-6-methyl-pyridin-2-yl)-N-methyl-methanesulfonamide (**B14-1**): A solution of 2-chloro-6-methyl-nicotinonitrile (20 g, 131.5 mmol) in acetonitrile (300 mL) at 25°C was treated with $HN(CH_3)SO_2Me$ (13.1 mL, 124.1 mmol) and Cs_2CO_3 (60 g, 184.0 mm). The reaction mixture was then stirred at 80°C for 15 hours. The reaction mixture was allowed to cool to 25°C and filtered. The resultant filtrate was concentrated and diluted with EtOAc (600 mL). The organic solution was then washed with water (2 x 250 mL) and brine, and dried over anhydrous sodium sulfate. The organic solution was then concentrated, and the resultant residue was recrystallized with ether to provide **B14-1** as an off white solid. Yield: 18.5 g, 62.5%. ^{1}HNMR($CDCl_3$): δ 7.9(d, 1H), 7.16-7.26(m, 1H), 3.28(s, 3H), 3.24(s, 3H) and 2.22(s, 3H). Mass: (M+1) 226 calculated for $C_9H_{11}N_3O_2S$.

Step 2. A solution **B14-1** (10 g, 44.4 mmol) in a mixture of THF (100 mL) and acetic acid (900 mL) was charged to a Parr reactor and treated with 10% Pd/C (9 g, 84.9 mmol). The contents of the reactor were then hydrogenated at 55 Psi hydrogen pressure and 40°C for 4 hours. The reaction mixture was then filtered through a Celite® bed and concentrated. The resultant residue was diluted with EtOAc (100 mL) and stirred for 3 hours. The resultant solids were collected and dried under reduced pressure to provide **B14** as an off-white solid. Yield: 10 g, 98%. ^{1}HNMR (d_6-DMSO): δ 7.9(d, 1H), 7.3(d, 1H), 7.0-7.25(broad, 2H), 3.82(s, 2H), 3.06-3.18(d, 5H), 2.45(s, 3H) and 1.82-1.96(m, 5H). Mass: (M+1) 230 calculated for $C_9H_{15}N_3O_2S$. HPLC Purity: 98.1%.

Preparation of N-(3-Aminomethyl-5-methyl-pyridin-2-yl)-N-methyl-methanesulfonamide acetate (**B15**):



Step 1. Preparation of 5-methyl-nicotinic acid (**B15-1**): A solution of 3,5 lutidine (100 g, 934.57 mmol) in water at 25°C was treated portion-wise over 5 hours with $KMnO_4$ (221.1 g, 1401.86 mmol). The reaction mixture was then heated at 45°C for about 20 hours. The reaction mixture was filtered and washed with water. The resultant filtrates were concentrated, and the resultant residue was diluted with ethanol (3 x 500 mL), boiled, and filtered. The filtrate was then concentrated under reduced pressure to

provide **B15-1** as a white solid. Yield: 76 g, 59.4%. ^{1}HNMR (D_2O): δ 8.6-8.7(s, 1H), 8.3-8.4(m, 1H), 7.92(s, 1H) and 2.3(s, 3H). Mass: (M+1) 138 calculated for $C_7H_7NO_2$.

Step 2. Preparation of 5-methyl-nicotinamide (**B15-2**): A suspension of **B15-1** (70 g, 510 mmol) in thionyl chloride (350 mL) was heated at 80°C for 20 hours. The resultant clear solution obtained was allowed to cool to 25°C and concentrated. The resultant residue was diluted with 1,2 dichloroethane (1.5 L), cooled to –5°C, and treated with NH_3 gas via bubbler until the mixture was saturated. The mixture was allowed to warm to 25°C, stirred for 3 hours, and concentrated. The resultant brown solid was taken in EtOAc (3 x 800 mL), refluxed for 20 min, and filtered. The resultant filtrate was then concentrated to provide **B15-2** as a brown solid. Yield: 52 g, 75%. ^{1}HNMR (d_6-DMSO): δ 8.85-8.9(s, 1H), 8.55(s, 1H), 8.05-8.18(m, 1H), 8.02(s, 1H), 7.48-7.65(s, 1H) and 2.35(s, 3H). Mass: (M+1) 137 calculated for $C_7H_8N_2O$.

Step 3. Preparation of 1-Hydroxy-5-methyl-nicotinamide (**B15-3**): A solution of **B15-2** (35 g) in acetic acid (200 mL) was cooled to 10°C and treated over 10 minutes with H_2O_2 (40% solution in water, 200 mL). The reaction mixture was allowed to warm to 25°C and then heated at 80°C for 20 hours. The reaction mixture was cooled to 0°C, treated with 20% sodium sulfite solution (200 mL) and basified with 35% NH_4OH (200 mL). The mixture was then allowed to warm to 25°C and stirred for an additional 2 hours. The resultant solids were collected and dried under reduced pressure to provide **B15-3** as a white solid. Yield: 30.1 g. ^{1}HNMR (d_6-DMSO): δ 8.45(s, 1H), 8.3(s, 1H), 7.6(s, 1H), 4.42-4.7(broad m, 2H), 2.3(s, 3H). Mass: (M-1) 153 calculated for $C_7H_{10}N_2O_2$.

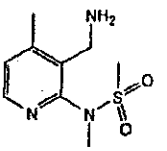
Step 4. Preparation of 2-chloro-5-methyl-nicotinonitrile (**B15-4**): Neat $POCl_3$ (120 mL) was cooled to about 10°C and treated portion-wise over 10 minutes with **B15-3**. The reaction mixture was then heated at 60°C for 2 hours. The reaction mixture was concentrated, cooled to about 10°C, basified with saturated Na_2CO_3, and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (50 mL), and brine (50 mL), and dried over anhydrous sodium sulfate. The organic solution was then concentrated, and the resultant residue was purified by column chromatography (silica gel; 35% EtOAc in hexane as eluting solvent) to provide to **B15-4** as a white solid. Yield: 3.5 g, 68%. ^{1}HNMR (d_6-DMSO): δ 8.42(s, 1H), 7.82(s, 1H) and 2.4(s, 3H). Mass: (M+1) 153 calculated for $C_7H_5ClN_2$.

Step 5. Preparation of N-(3-cyano-5-methyl-pyridin-2-yl)-N-methyl-methanesulfonamide (**B15-5**): A suspension of **B15-4** (16 g, 0.1049 mmol) in

acetonitrile (150 mL) at 25°C was treated with Cs_2CO_3 (51.3 g, 0.157 mmol) and N-methyl methane sulphonamide (12.5 g, 0.115 mmol). The reaction mixture was then heated at 80°C for 20 hours. The reaction mixture was filtered through a Celite® bed and washed with acetonitrile (3 x 50 mL). The combined filtrates were concentrated, and the resultant residue was diluted with EtOAc (500 mL) and washed with water (3 x 100 mL). The resultant organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The resultant residue was purified by column chromatography (silica gel; 40% EtOAc in hexane as eluting solvent) to provide **B15-5** as pale yellow solid. Yield: 15.1 g, 62.8%. ^{1}HNMR (d_6-DMSO): δ 8.65(s, 1H), 8.3(s, 1H), 3 3.22-3.26(s, 3H), .15-3.22(s, 3H) and 2.36(s, 3H). Mass: (M+1) 226 calculated for $C_9H_{11}N_3O_2S$.

Step 6. A solution of **B15-5** (15 g) in a mixture of acetic acid (200 mL) and THF (200 mL) was charged to a Parr reactor and treated with Pd/C (4 g). The contents of the reactor were then hydrogenated at 50 Psi hydrogen pressure and 25°C for 5 hours. The mixture was filtered through a Celite® bed and washed with ethanol (50 mL). The filtrate was concentrated under reduced pressure, and the resultant residue was purified by column chromatography (silica gel; 5% MeOH in $CHCl_3$ as eluting solvent) to provide **B15** as a reddish brown solid. Yield: 12.3 g, 98%. IR (cm^{-1}): 3450, 3264, 2937, 2161, 1706, 1633, 1548, 1413, 1321 and 1151. ^{1}HNMR (d_6-DMSO): δ 8.3(s, 1H), 7.9(s, 1H), 7.02-7.25(broad s, 2H), 3.92(s, 2H), 3.15(d, 6H), 2.4(s, 3H), 1.92(s, 3H). Mass: (M+1) $C_9H_{15}N_3O_2S$. (Note: Few drops of triethylamine was added to the mobile phase during the process of silica gel column purification.)

Preparation of N-(3-Aminomethyl-4-methyl-pyridin-2-yl)-N-methyl-methanesulfonamide (**B16**):

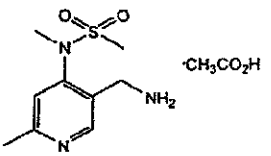


Step 1. Preparation of N-(3-cyano-4-methyl-pyridin-2-yl)-N-methyl-methanesulfonamide (**B16-1**): A suspension of 2-chloro-4-methyl-nicotinonitrile (4 g, 26.2 mmol) (see WO 02/30901), N-methyl methane sulphonamide (3.43 g, 31.4 mmol) and $CsCO_3$ (12 g, 36.7 mmol) in acetonitrile (40 mL) was heated at 60°C for 20 hours. The reaction mixture was filtered through a Celite® bed and washed with acetonitrile (40 mL). The combined filtrates were concentrated, and the resultant residue was diluted

with EtOAc (100 mL). The organic solution was washed with water (100 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The organic solution was then concentrated, and the resultant residue was stirred in methanol. The resultant solids were collected and dried under reduced pressure to provide **B16-1** as a white solid. Yield: 1.6 g, 26%. ^{1}HNMR ($CDCl_3$): δ 8.46(d, 1H), 7.25(m, 1H), 3.26(s, 3H), 3.18(s, 3H) and 2.6(s, 3H). Mass: (M+1) 226 calculated for $C_9H_{11}N_3O_2S$.

Step 2. A solution of **B16-1** (5 g, 22.1 mmol) in 2N ethanolic ammonia (250 mL) was charged to a Parr reactor and treated with 10% Pd/C (5 g, 47 mm). The contents of the reactor were then hydrogenated at 60 Psi hydrogen pressure and 25°C for 6 hours. The reaction mixture was filtered through a Celite® bed and washed with ethanol (50 mL). The combined filtrates were concentrated, and the resultant oily residue was triturated with diethyl ether (20 mL). The resultant white solids were collected and dried to provide **B16** as a white solid. Yield: 5 g, 90%. ^{1}HNMR (d_6-DMSO): δ 8.46(d, 1H), 8.2-8.38(broad s, 2H), 7.42(d, 1H), 4.55-4.9(broad s, 4H), 4.15-4.3(broad s, 2H), 325(s, 3H), 3.1(s, 3H) and 2.5(s, 3H). Mass: (M+1) 230 calculated for $C_9H_{15}N_3O_2S$. HPLC Purity: 95.03%.

Preparation of N-(5-aminomethyl-2-methyl-pyfridin-4-yl)-N-methyl-methansulfonamide acetate (**B17**):



Step 1. Preparation of 2,4-dihydroxy-6-methyl-nicotinic acid ethyl ester (**B17-1**): Sodium metal pieces (33 g, 1434 mmol) were slowly added to dry ethanol (800 mL) at 25°C and stirred until all the sodium pieces had reacted. The resultant suspension was then treated over 15 minutes with malonic acid diethyl ester (140 g, 875 mmol) followed by treatment over 15 minutes with ethyl-3-aminocrotonate (110 g, 850 mmol). The reaction mixture was then heated at 110°C for 20 hours and concentrated. The resultant residue was cooled to 15°C, dissolved in water (800 mL), and stirred for 15 minutes. The mixture was neutralized with a mixture of AcOH:H_2O (1:1) until a pH of 6-7 was achieved. The mixture was then stirred an addition 20 minutes. The resultant solids were collected, washed with petroleum ether (300 mL), and dried under reduced pressure to provide **B17-1** as an off-white solid. Yield: 60.3 g, 35%. ^{1}HNMR (d_6-

DMSO): δ 12.6(s, 1H), 11.38(s, 1H), 5.8(s, 1H), 4.25(q, 2H), 2.14(s, 3H) and 1.25(t, 3H). Mass: (M+1) 198 calculated for $C_9H_{11}NO_4$.

Step 2. Preparation of 2,4-dichloro-6-methyl-nicotinic acid ethyl ester (**B17-2**): A suspension of **B17-1** (36 g, 182.2 mmol) in N,N-bis(2-hydroxyethyl) 2-propanolamine (DEIPA) (36 mL) was cooled to 0°C and slowly treated with $POCl_3$ (250 mL). The resultant clear solution was allowed to warm to 25°C and then heated at 15°C for 20 hours. The reaction mixture was concentrated, and the resultant residue was poured into crushed ice. The chilled mixture was then basified with saturated Na_2CO_3 until a pH of 8 was achieved. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The resultant residue was purified by chromatography (silica gel; 2% EtOAc in petroleum ether as eluting solvent) to provide **B17-2** as a pale yellow solid. Yield: 24 g, 55%. ^{1}HNMR (d_6-DMSO): δ 7.2(s, 1H), 4.45(q, 2H), 2.52(s, 3H) and 1.42(t, 3H). Mass: (M+1) 236 calculated for $C_9H_9Cl_2NO_2$.

Step 3. Preparation of 2-chloro-4-methoxy-6-methyl-nicotinic acid ethyl ester (**B17-3**): A solution of **B17-2** (30 g, 128.2 mmol) in methanol (102 mL) was cooled to 0°C and treated portion-wise over 30 minutes with NaOMe (8.5 g, 157.4 mmol). The reaction mixture was then heated at 60°C for 5 hours. The reaction mixture was cooled to 25°C, filtered, and concentrated. The resultant residue was diluted with DCM (350 mL), filtered through a Celite® bed, and washed with DCM. The combined filtrates were concentrated, and the resultant residue was purified by chromatography (silica gel; 6% EtOAc in petroleum ether as eluting solvent) to provide **B17-3** as a pale yellow solid. Yield: 20.62 g, 70%. ^{1}HNMR($CDCl_3$): δ 6.66(s, 1H), 4.4(q, 2H), 3.95(s, 1H), 3.92(s, 3H), 2.52(s, 3H) and 1.38(t, 3H). Mass: (M+1) 230 calculated $C_{10}H_{12}ClNO_3$.

Step 4. Preparation of 4-methoxy-6-methyl-nicotinic acid ethyl ester (**B17-4**): A mixture of **B17-3** (27 g, 117.3 mmol) and potassium acetate (11.0 g, 112 mmol) in isopropanol (IPA) (500 mL) was charged to a Parr reactor and treated with Pd/C (9.5 g, 70.15 mmol). The contents of the reactor were then hydrogenated at 55 Psi hydrogen pressure and 25°C for 4 hours. The mixture was filtered through a Celite® bed and concentrated. The resultant residue was purified by chromatography (silica gel; 8% EtOAc in petroleum ether as eluting solvent) to provide **B17-4** as a green viscous liquid. Yield: 23 g, 90%. ^{1}HNMR($CDCl_3$): δ 8.84(s, 1H), 6.75(s, 1H), 4.35(q, 2H), 3.98(s, 3H), 2.6(s, 3H) and 1.4(t, 3H). Mass: (M+1) 196 calculated for $C_{10}H_{13}NO_3$.

Step 5. Preparation of 6-methyl-4-oxo-1,4-dihydro-pyridine-3-carboxylic acid hydrochloride (**B17-5**): A suspension of **B17-4** (50 g, 256 mmol) in concentrated HCl (600 mL) was heated at 110°C for 20 hours. The reaction mixture was then concentrated, and the resultant residue was washed in this order with ethanol (150 mL), DCM (2 x 300 mL), and a mixture of DCM:Et_2O (1:1). The resultant solids were collected and dried to provide **B17-5** as an off-white solid. Yield: 40 g. IR (cm^{-1}): 3449, 3095, 2890, 1674, 1647, 1565, 1470, 1428, 1345, 1257, 1186 and 1028. ^{1}HNMR (d_6-DMSO): δ 11.4-12.7 (b, 2H), 8.45(s, 1H), 6.64(s, 1H) and 2.4(s, 3H). Mass: (M+1) 154 calculated for $C_7H_7NO_3$.

Step 6. Preparation of 6-methyl-4-oxo-1,4-dihydro-pyridine-3-carboxylic acid methyl ester (**B17-6**): A solution of **B17-5** (40 g, 261.4 mmol) in methanol (600 mL) was cooled to 0°C and treated drop-wise over 20 minutes with $SOCl_2$ (100 mL). The reaction mixture was allowed to warm to 25°C, heated at 70°C for 20 hours, and concentrated. The resultant residue was washed with ethanol (100 mL), filtered and dried to provide **B17-6** as a gummy solid. Yield: 40 g. ^{1}HNMR ($CDCl_3$): δ 8.8(s, 1H), 6.7(s, 1H), 3.9(s, 3H) and 2.45(s, 3H). Mass: (M+1) 168 calculated for $C_8H_9NO_3$. The product was used in the preparation of **B17-7** below without further purification.

Step 7. Preparation of 6-methyl-4-oxo-1,4-dihydro-pyridine-3-carboxylic acid amide (**B17-7**): A suspension of **B17-6** (40 g, 239.5 mmol) in aqueous NH_3 (800 mL) was heated at 50°C for 20 hours. The reaction mass was then concentrated, and the resultant residue was washed with a mixture of diethyl ether:DCM (8:2) (300 mL). The resultant solids were collected and dried under reduced pressure to provide **B17-7** as an off-white solid. Yield: 40 g. ^{1}HNMR (d_6-DMSO): δ 12.1(b, 1H), 9.4 (s, 1H), 8.3(s, 1H), 7.4(s, 1H), 6.25(s, 1H) and 2.25 (s, 3H). Mass: (M+1) 153 calculated for $C_7H_8N_2O_2$.

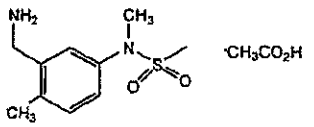
Step 8. Preparation of 4-Chloro-6-methyl-nicotinonitrile (**B17-8**): A suspension of **B17-7** (20 g, 131.5 mmol) in $POCl_3$ (62 mL, 580 mmol) was heated at 110°C for 15 minutes. The mixture was allowed to cool to 25°C and treated portion-wise over 20 minutes with PCl_5 (38.12 g, 183.4 mmol). The mixture was then heated at 110°C for 1 hour and concentrated. The resultant residue was diluted with EtOAc (100 mL), cooled to 10°C, and quenched with aqueous Na_2CO_3 (200 mL). The mixture was then extracted with EtOAc (3 x 250 mL), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The resultant residue was purified by chromatography (silica gel; 4-5% EtOAc in petroleum ether as eluting solvent) to provide **B17-8** as an off-white puffy solid. Yield: 7.5 g, 37%. ^{1}HNMR

($CDCl_3$): δ 8.75(s, 1H), 7.38 (s, 1H), 2.65(s, 3H). Mass: (M+1) 153 calculated for $C_7H_5ClN_2$.

Step 9. Preparation of N-(5-Cyano-2-methyl-pyridin-4-yl)-N-methyl-methanesulfonamide (**B17-9**): A solution of **B17-8** (7 g, 46.8 mmol) in acetonitrile (165 mL) at 25°C was treated sequentially with Cs_2CO_3 (19 g, 58.2 mmol) and $HN(Me)SO_2Me$ (8.9 mL, 95 mmol). The mixture was heated at 60°C for 20 hours and concentrated. The resultant residue was diluted with EtOAc (300 mL) and water (100 mL), and stirred for 10 minutes. The organic layer was collected, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The resultant residue was purified by chromatography (silica gel; DCM as eluting solvent) to provide **B17-9** as a solid. Yield: 9 g, 87%. ^{1}HNMR ($CDCl_3$): δ 8.8(s, 1H), 7.3(d, 1H), 3.4 (s, 3H), 3.18(s, 3H) and 2.65(s, 3H). Mass: (M+1) 226 calculated for $C_9H_{11}N_3O_2S$.

Step 10. A solution of **B17-9** (7.5 g, 33.3 mmol) in EtOH-NH_3 (300 mL) was charged to a Parr reactor and treated with Pd/C (5 g). The contents of the reactor were hydrogenated at 60 Psi hydrogen pressure and 25°C for 4 hours. The mixture was filtered through a Celite® bed and concentrated. The resultant residue was diluted with EtOAc:acetic acid (1.1 eq.) and concentrated. The resultant gummy orange-colored liquid was then diluted with a mixture of ether and EtOAc in a glass flask, and the wall of the flaks was scratched. The resultant solids were collected to provide **B17** as an off-white solid. Yield: 4.4 g, 42%. IR (cm^{-1}): 3484, 3343, 3166, 2975, 1644, 1601, 1560, 1505, 1412, 1313, 1136 and 1058. ^{1}HNMR (d_6-DMSO): δ 8.62(s, 1H), 7.4(s, 1H), 4.7-5.3(broad, 3H), 3.82(s, 2H), 3.14(d, 2H), 2.45(s, 3H) and 1.9(s, 3H). Mass: (M+1) 230 calculated 230 for $C_9H_{15}N_3O_2S$.

Preparation of N-(3-Aminomethyl-4-methyl-phenyl)-N-methyl-methanesulfonamide acetate (**B18**):



Step 1. Preparation of 5-amino-2-methyl-benzonitrile (**B18-1**): A stirred suspension of 2-methyl-5-nitro benzonitrile (20 g, 123.45 mmol) in a mixture of dioxane (640 mL), ethanol (480 mL) and water (160 mL) at 25°C was treated with NH_4Cl (26.4 g, 493.8 mmol) followed by treatment with iron powder (34.4 g, 617.2 mmol). The mixture

was then heated at 80°C for 16 hours. The mixture was filtered through a Celite® bed and concentrated. The resultant residue was diluted with EtOAc (600 mL), washed with water (150 mL) and brine (100 mL), and dried over anhydrous sodium sulfate. The organic solution was then concentrated to provide **B18-1** as an orange solid. Yield: 18.2 g. ^{1}HNMR($CDCl_3$): δ 7.08(d, 1H), 6.84-6.9(m, 1H), 6.75-6.82(m, 1H), 3.65-3.82(m, 2H) and 2.4(s, 3H). Mass: (M+1) 133 calculated for $C_8H_8N_2$. The product was used below to prepare **B18-2** without further purification.

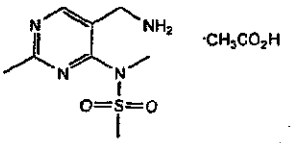
Step 2. Preparation of N-(3-cyano-4-methyl-phenyl)-methanesulfonamide (**B18-2**): A solution of **B18-1** (18 g, 136.36 mmol) in pyridine (150 mL) was cooled to 0°C and treated with mesyl chloride (12.6 mL, 163.63 mmol). The mixture was allowed to warm to 25°C, stirred for 20 hours, and concentrated. The resultant residue was diluted with EtOAc (500 mL), and washed with 2N HCl (50 mL), water (100 mL), and brine (50 mL). The organic solution was then dried over anhydrous sodium sulfate and concentrated to provide **B18-2** as a yellow solid. Yield: 25.1 g, 87.3%. ^{1}HNMR($CDCl_3$): δ 7.5(s, 1H), 7.3-7.45(m, 2H), 7.1-7.25(m, 1H), 3.05(s, 3H) and 2.5(s, 3H). Mass: (M+1) 209 calculated for $C_9H_{10}N_2O_2S$.

Step 3. Preparation of N-(3-cyano-4-methyl-phenyl)-N-methyl-methanesulfonamide (**B18-3**): A solution of **B18-2** (25 g, 119.04 mmol) in a mixture of THF (200 mL) and 40% NaOH solution (200 mL) at 25°C was treated with BTEAC (2.7 g, 11.9 mmol) and stirred vigorously for 20 minutes. The mixture was then treated with methyl iodide (8.89 mL, 142.8 mmol), stirred for 20 hours, and concentrated. The resultant residue was extracted with DCM (500 mL) and washed with water (100 mL) and brine (50 mL). The organic solution was dried over anhydrous sodium sulfate and concentrated. The resultant residue was purified by column chromatography (60-120 mesh silica gel; 40% EtOAc in hexane as eluting solvent) to provide **B18-2** as a white solid. Yield: 26.2 g, 97%. ^{1}HNMR($CDCl_3$): δ 7.55-7.65(m, 1H), 7.5-7.54(m, 1H), 7.3-7.4(m, 1H), 3.34(s, 3H), 2.85(s, 3H) and 2.55(s, 3H). Mass: (M+1) 225 calculated for $C_{10}H_{12}N_2O_2S$.

Step 4. A solution of **B18-3** (28 g, 124.4 mmol) in acetic acid (500 mL) and THF (200 mL) was charged to a Parr reactor and treated with 10% Pd/C (8 g). The contents of the reactor were then hydrogenated at 50 PSi hydrogen pressure and 25°C for 4 hours. The mixture was filtered through a Celite® bed and washed with ethanol (50 mL). The combined filtrates were concentrated, and the resultant residue was azeotroped with EtOAc (3 x 50 mL). The resultant oily residue was dissolved in EtOAc

(200 mL) and maintained at 25°C for 20 hours. The resultant solids were collected and dried to provide **B18** as a white solid. Yield: 2.9 g, 81%. ^{1}HNMR (d_6-DMSO): δ 7.42(s, 1H), 7.15(s, 2H), 5.7-5.98(broad, 3H), 3.72(s, 2H), 3.2(s, 3H), 2.95(s, 3H), 2.25(s, 3H) and 1.86(s, 3H). Mass: (M+1) 229 calculated for $C_{10}H_{16}N_2O_2S$. HPLC Purity: 99.9%.

Preparation of N-(5-Aminomethyl-2-methyl-pyrimidin-4-yl)-N-methyl-methansulfonamide acetate (**B19**):



Step 1. Preparation of 4-hydroxy-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (**B19-1**): A mixture of water (410 mL) and a 50% NaOH solution (115.98 g, 2899 mmol) was cooled to 0°C and treated with 2-methyl 2-thio pseudo urea sulfate (100 g, 359 mmol). The resultant clear solution was treated with a solution of ethoxy methylene malonate (155.38 g, 719 mmol) in ethanol (251 mL) and stirred until the reaction mixture was turbid. The mixture was then allowed to warm to 25°5, and it was allowed to stand at 25°C for 20 hours. The resultant solids were collected, washed with ethanol (2 x 50 mL), and dried under reduced pressure to provide **B19-1** as a pale yellow solid. Yield: 58 g, 75%. ^{1}HNMR (d_6-DMSO): δ 8.25(s, 1H), 4.12(q, 2H), 2.32(s, 3H) and 1.24(t, 3H).

Step 2. Preparation of 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (**B19-2**): Neat $POCl_3$ (120 mL) was cooled to 10°C and treated portion-wise over 4 hours with **B19-1** (50 g, 232 mmol) without exceeding a temperature of 25°C. The mixture was then heated at 65°C. After 3 hours the mixture was cooled to 10°C, poured into crushed ice (350 g), treated drop-wise with water (676 mL) under vigorous stirring. The resultant solids were collected and dried under reduced pressure to provide **B19-2** as a pale yellow solid. Yield: 22 g, 40%. ^{1}HNMR ($CDCl_3$): δ 8.95(s, 1H), 4.44(q, 2H), 2.62(s, 3H) and 1.42 (t, 3H).

Step 3. Preparation of 4-chloro-2-methanesulfonyl-pyrimidine-5-carboxylic acid ethyl ester (**B19-3**): A solution of **B19-2** (40 g, 172 mmol) in methanol (720 mL) was cooled to 0°C and treated with a slurry of oxone (317.9 g, 517 mmol) in distilled water (720 mL). The mixture was allowed to warm to 25°C and stirred at 5 hours. The mixture was filtered, and the solids were washed with DCM (500 mL). The resultant organic layer was collected, and the aqueous layer was extracted with DCM (3 x 200

mL). The combined organic layers were then washed with brine, dried over anhydrous sodium sulfate, and concentrated to provide **B19-2** as a white solid. Yield: 31 g, 68%. IR (cm^{-1}): 3015, 2932, 1734, 1550, 1445, 1391, 1325, 1258, 1222, 1142 and 1067. ^{1}HNMR ($CDCl_3$): δ 9.28(s, 1H), 4.5(q, 2H), 3.4(s, 3H) and 1.45(t, 3H). Mass: (M+1) 265 calculated for $C_8H_9ClN_2O_4S$.

Step 3. Preparation of 4-chloro-2-methyl-pyrimidine-5-carboxylic acid ethyl ester (**B19-3**): A solution of **B19-2** (40 g, 151 mmol) in THF (700 mL) was cooled to 0°C and treated drop-wise over 2 hours with a 3 molar solution of methyl magnesium chloride in THF (54 mL, 166 mmol). The mixture was allowed to warm to 25°C and maintained for at 25°C for 4 hours. The mixture was added to water (500mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (250 mL), dried over anhydrous sodium sulfate, and concentrated to provide **B19-2** as a brown liquid. Yield: 30 g, 98%. IR (cm^{-1}): 2983, 2934, 2868, 1736, 1574, 1523, 1434, 1373, 1269, 1181 and 1070. ^{1}HNMR ($CDCl_3$): δ 9.1(s, 1H), 4.5(q, 2H), 2.74(s, 3H) and 1.5(t, 3H).

Step 3. Preparation of 4-(methanesulfonyl-methyl-amino)-2-methyl-pyrimidine-5-carboxylic acid ethyl ester (**B19-3**): A solution of N-methyl methane sulphonamide (18.2 g, 180 mmol) in acetonitrile (420 mL) was cooled to 0°C and treated with cesium carbonate (68 g, 225 mmol). The mixture was then treated over 2 hours with **B19-2** (30 g, 150 mmol). The mixture was allowed to warm to 25°C, and it was maintained at 25°C for 20 hours. The mixture was then filtered, and the solids were washed with washed with EtOAc (200 mL). The combined filtrates were further diluted with EtOAc (500 mL), washed with water (2 x 500 mL) and brine, and dried over anhydrous sodium sulfate. The organic solution was then concentrated to provide **B19-3** as an orange solid. Yield: 18 g, 44%. ^{1}HNMR (d_6-DMSO): δ 8.94(s, 1H), 4.3(q, 2H), 3.25-3.3(m, 6H), 2.65(s, 3H) and 1.3(t, 3H). Mass: (M+1) 274 calculated for $C_{10}H_{15}N_3O_4S$.

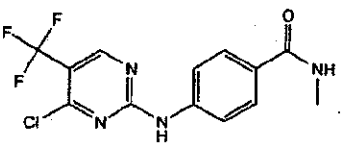
Step 4. Preparation of 4-(methanesulfonyl-methyl-amino)-2-methyl-pyrimidine-5-carboxylic acid amide (**B19-4**): A suspension of **B19-3** (10 g, 36 mmol) in 25% NH_4OH (100 mL) was heated at 32°C for 20 hours. The mixture was concentrated under reduced pressure, and the resultant residue was triturated with EtOAc. The mixture was then filtered and concentrated. The resultant residue was purified by column chromatography (60-120 mesh silica gel; 10% MeOH in $CHCl_3$ as eluting solvent) to provide **B19-4** as a white solid. Yield: 3 g, 33%. ^{1}HNMR (d_6-DMSO): δ 8.75(s, 1H),7.95(s, 1H), 7.7(s, 1H),3.3-3.42(m, 3H), 3.25(s, 3H) and 2.65(s, 3H). Mass: (M+1) 245 calculated for $C_8H_{12}N_4O_3S$.

Step 5. Preparation of N-(5-cyano-2-methyl-pyrimidin-4-yl)-N-methyl-methanesulfonamide (**B19-5**): A solution of **B19-4** (5.2 g, 22.3 mmol) and pyridine (3.36 g, 42.6 mmol) in 1,4 dioxane (78 mL) was cooled to 0°C and treated drop-wise over 10 minutes with TFA (5.8 g, 27.7 mmol). The mixture was allowed to warm to 25°C. After 4 hours the mixture was diluted with EtOAc (100 mL) and washed with water (2 x 200 mL). The aqueous layer was collected and washed with EtOAc (2 x 100 mL). The combined organic layers were then washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The resultant residue was then washed with petroleum ether and dried to provide **B19-5** as a pale yellow solid. Yield: 3.5 g, 76%. ^{1}HNMR ($CDCl_3$): δ 8.84(s, 1H), 3.54(s, 3H), 3.4(s, 3H) and 2.75(s, 3H). Mass: (M-1) 225 calculated for $C_8H_{10}N_4O_2S$.

Step 6. A solution of **B19-5** (5 g, 22 mmol) in 2N methanolic ammonia (350 mL) was charged to a Parr reactor and treated with 10% Pd/C (3.75 g, 35 mmol). The contents of the reactor were then hydrogenated at 48 Psi hydrogen pressure and 25°C for 1 hour. The mixture was filtered through a Celite® bed and washed with methanol (200 mL). The combined filtrates were concentrated, and the resultant residue was diluted with EtOAc (25 mL) and acetic acid (1.3 g, 21 mmol). The mixture was stirred for 30 minutes, and the resultant solids were collected to provide **B19** as a white solid. Yield: 4.2 g, 80%. IR (cm^{-1}): 3433, 3381, 3017, 2930, 1720, 1591, 1555, 1446, 1331, 1148 and 1058. ^{1}HNMR (d_6-DMSO): δ 9.05(s, 1H), 8.5-8.7(broad s, 2H), 4.14(s, 2H), 3.24(s, 3H), 3.15(s, 3H) and 2.66 (s, 3H). HPLC Purity: 99.9%.

4-Chloro-pyrimidine intermediates were prepared by methods similar to that described below for compound **B20**.

Preparation of 4-(4-chloro-5-(trifluoromethyl)pyrimidin-2-ylamino)-N-methylbenzamide (**B20**):

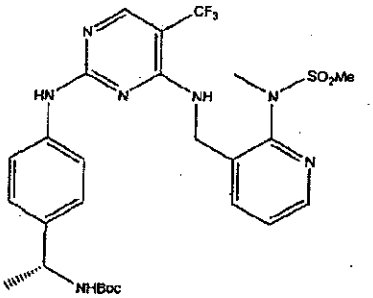


A solution of 2,4-dichloro-5-trifluoromethyl-pyrimidine (8.63 mmol) in 1:1 t-BuOH/DCE (10 mL) was cooled to 5°C, treated with solid $ZnBr_2$ (22.5 mmol), and stirred at 5°C for 30 minutes. The resultant solution was maintained at 5°C and treated first with solid 4-amino-N-methyl-benzamide (7.5 mmol) followed by TEA (16.5 mmol). The resultant white mixture was allowed to warm 25°C, and it was mixed at 25°C for 20

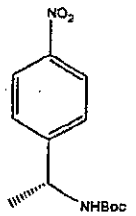
hours. The mixture was adsorbed onto silica gel, and the fraction eluting 0-10% methanol / DCM was collected and concentrated. The resultant residue was triturated with water and filtered to provide **B20**. Yield: 3.0 mmol, 40%. LCMS 2.3 min, MZ+=331.1 ^{1}H NMR (500 MHz, d_6-DMSO) δ ppm 10.89 (s, 1 H), 8.87 (s, 1 H), 8.34 (d, *J*=4.67 Hz, 1 H), 7.73 - 7.89 (m, 3 H), 2.78 (d, *J*=4.67 Hz, 3 H).

Example 1

(R)-tert-butyl 1-(4-(4-((2-(N-methylmethan-5-ylsulfonamido)pyridin-3-yl)methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)ethylcarbamate (1)

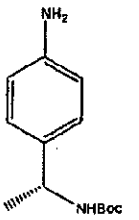


Step 1: Preparation of (R)-tert-butyl 1-(4-nitrophenyl)ethylcarbamate (**C1**).



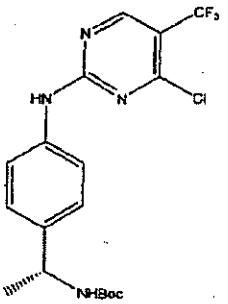
(R)-1-(4-nitrophenyl)ethanamine hydrochloride salt (1.0g, 4.9mmol), tert-butoxycarbonyl (BOC) anhydride (1.18g, 5.43mmol), and 10.0mL of 1M sodium bicarbonate solution were dissolved in DCM (15 mL) and allowed to stir at 25°C for 24h. The organic layer was collected, and the aqueous layer was washed with DCM. The combined organic layers were then washed with water and 0.1N HCl, dried over $MgSO_4$, filtered, and concentrated to provide **C1** as a white solid. Yield: 1.2g, 92%. GC-MS=266. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 8.15 (d, 2H), 7.56 (d, 1H), 7.52 (d, 2H), 4.68 (m, 1H), 1.32 (s, 9H), 1.27 (d, 3H).

Step 2: Preparation of (R)-tert-butyl 1-(4-aminophenyl)ethylcarbamate (**C2**)



A solution of **C1** (1.0g, 3.8mmol) in MeOH (20 mL) was charged to a Parr reactor, and the contents of the reactor were treated with 10% Pd/C (800mg, 0.376mmol). The contents of the reactor were then hydrogenated at 45 Psi hydrogen pressure and 25°C for 4 hours. The contents of the reactor were filtered through Celite® and washed with DCM. The combined filtrates were concentrated to provide **C2** as a sticky orange residue. Yield: 690mg, 78% yield. GC_MS = 236. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 7.07 (d, 1H), 6.88 (d, 2H), 6.43 (d, 2H), 4.85 (s, 2H), 4.40 (m, 1H), 1.31 (s, 9H), 1.18 (d, 3H).

Step 3. Preparation of (R)-tert-butyl 1-(4-(4-chloro-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)ethylcarbamate (**C3**)

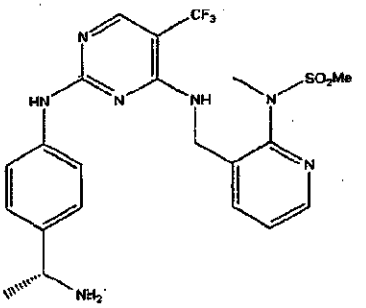


C2 (690mg, 2.92mmol) was dissolved in 10mL DCE:t-BuOH (1:1 vol:vol), and the resultant solution was treated with $ZnBr_2$ (1.97g, 8.76mmol) and 2,4-dichloro-5-(trifluoromethyl)pyrimidine (748mg, 3.45mmol). The resultant mixture was then treated drop-wise with TEA (406ml, 2.92mmol), and the mixture was allowed to stir at 25°C for about 20 hours. The reaction mixture was concentrated, and the resultant residue was treated with EtOAc. The resultant solution was washed with water and brine, and dried over $MgSO_4$. The mixture was then filtered, concentrated, and purified by column chromatography eluting with 22% EtOAc/Heptane. The product-containing eluents were combined and concentrated to provide **C3** as a white solid. Yield: 680mg, 56%. MS-415.2. ^{1}H NMR (500 MHz, DMSO) δ: 10.59 (s, 1H), 8.74 (s, 1H), 7.53 (d, 2H), 7.31 (d, 1H), 7.23 (d, 2H), 4.54 (m, 1H), 1.33 (s, 9H), 1.25 (d, 3H).

Step 4. Compound **C3** (100 mg, 0.24 mmol), **B5** (88.5mg, 0.264mmol), and diethylamine (DIEA) (0.127ml, 0.960mmol) were dissolved in 1,2-dichloroethane (DCE):t-BuOH (1:1vol:vol) (1.2 mL). The resultant solution was heated at 80°C for about 20 hours, cooled to 25°C, treated with EtOAc, and washed with water. The organic phase was collected, and the aqueous phase was washed with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide **1** as a sticky residue. MS^+ 596.8. ^1H NMR (500 MHz, d_6-DMSO) δ: 9.50 (s, 1H), 8.41 (m, 1H), 8.22 (s, 1H), 7.61 (m, 2H), 7.35 (m, 3H), 6.99 (d, 2H), 4.76 (d, 2H), 4.47 (m, 1H), 3.14 (s, 3H), 3.11 (s, 3H), 1.33 (s, 9H), 1.21 (d, 3H). The product was used in the preparation of compound **2** in Example 2 below without further purification.

Example 2

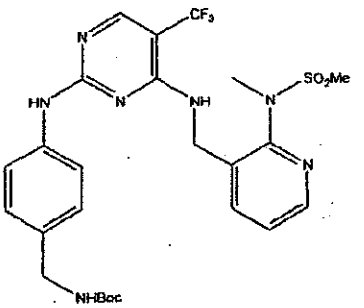
Preparation of (R)-N-(3-((2-(4-(1-aminoethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide hydrochloride (**2**)



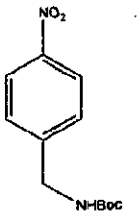
A solution of **1** (143mg, 0.24mmol) in THF (0.3mL) was treated with 4N HCl in dioxane (0.240ml, 0.96mmol), and stirred at 25°C for about 20 hours. The reaction mixture was then triterated with EtOAc and filtered, and the filtrate was concentrated to provide the HCl salt form of **2** as a white solid. Yield: 128mg, 94% yield. MS^+ 494.0. ^1H NMR (500 MHz, d_6-DMSO): δ 10.2 (s, 1H), 8.40 (m, 4H), 8.12 (s, 1H), 7.67 (d, 1H), 7.45 (m, 3H), 7.27 (d, 2H), 4.84 (d, 2H), 4.28 (m, 1H), 3.16 (s, 3H), 3.14 (s, 3H), 1.45 (d, 3H). FAK IC_{50}: <0.000595 μM (Table 1, Example 354)

Example 3

Preparation of tert-butyl 4-(4-((2-(N-methylmethan-5-ylsulfonamido)pyridin-3-yl)methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)benzylcarbamate (**3**)

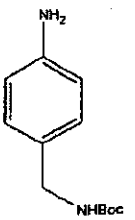


Step 1: Preparation of tert-butyl 4-nitrobenzylcarbamate (**C4**).



A stirred solution of (4-nitrophenyl)methanamine hydrochloride (10g, 53.0mmol) in THF (150mL) and water (13mL) was cooled to 0°C and treated with BOC anhydride (11.6g, 53.0mmol) and DIEA (27.7mL, 159mmol). The reaction mixture was stirred for about 20 hours as it was allowed to warm to 25°C. The mixture was then concentrated, and the resultant residue was dissolved in EtOAc. The resultant solution was washed with 1N HCl, saturated sodium bicarbonate, and brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated to provide **C4** as an off white solid. Yield: 14.0g, 99%. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.16 (d, 2H), 7.55 (t, 1H), 7.46 (d, 2H), 4.21 (d, 2H), 1.36 (s, 9H).

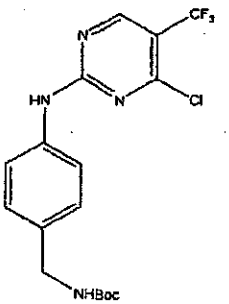
Step 2. Preparation of tert-butyl 4-aminobenzylcarbamate (**C5**)



C4 (7.0g, 27.7mmol) was dissolved in dioxane (325mL), ethanol (240mL), and water (160mL). The resultant solution was then treated with Fe(0) powder (7.12g, 127.4mmol) and ammonium chloride (5.33g, 99.7mmol), and the resultant mixture was stirred at 70°C for 4 hours. The reaction mixture was cooled to 25°C, filtered through Celite®, and washed with EtOAc. The organic solvents were evaporated, and the resultant aqueous residue was extracted with EtOAc. The combined organic layers

were dried over $MgSO_4$, filtered, and concentrated to provide **C5** as a yellow solid. Yield: 6.52g, 99% yield. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 7.146 (t, 1H), 6.87 (d, 2H), 6.48 (d, 2H), 4.95 (s, 2H), 3.92 (d, 2H), 1.38 (s, 9H).

Step 3. Tert-butyl 4-(4-chloro-5-(trifluoromethyl)pyrimidin-2-ylamino)benzylcarbamate (**C6**)

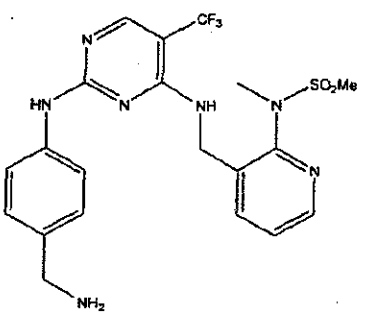


Compound **C6** was prepared as a white solid in a manner similar to that described in Step 3 of Example 1 except that **C5** (1.30g, 5.86mmol) was used instead of **C2**. Yield: 1.37g, 49%. MS$^-$ 401.1. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 10.6 (s, 1H), 8.75 (s, 1H), 7.56 (d, 2H), 7.34 (t, 1H), 7.18 (d, 2H), 4.05 (d, 2H), 1.36 (s, 9H).

Step 4. Compound **3** was prepared as a white solid in a manner similar to that described in Step 4 of Example 1 except that **C6** (1.2g, 2.98mmol) was used instead of **C3**, and the resultant crude product was purified by column chromatography, eluting with 45-55% EtOAc/Heptane. Yield: 1.17g, 68%. MS$^+$ 582.3. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 9.57 (s, 1H), 8.42 (s, 1H), 8.58 (s, 1H), 7.64 (m, 2H), 7.35 (m, 4H), 6.94 (d, 2H), 4.80 (d, 2H), 3.98 (d, 2H), 3.16 (s, 3H), 3.14 (s, 3H), 1.39 (s, 9H).

Example 4

Preparation of N-(3-((2-(4-(aminomethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide (**4**)

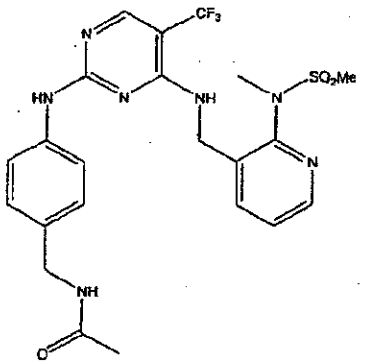


The HCl salt form of **4** was prepared as a white solid in a manner similar to that described for preparing **2** in Example 2 except that **3** (1.0g, 1.72mmol) was used instead of **1**.

The salt form of **4** was dissolved in DCM, and was washed with saturated sodium bicarbonate. The organic phase was then dried over Na_2SO_4, filtered, and concentrated to provide the free-base form of **4** as a foamy white solid. Yield: 904mg, 99%. MS^+ 482. ^1H NMR (500 MHz, d_6-DMSO) δ: 9.50 (s, 1H), 8.44 (d, 1H), 8.25 (s, 1H), 7.66 (d, 1H), 7.57 (t, 1H), 7.38 (m, 3H), 7.04 (d, 2H), 4.80 (d, 2H), 3.58 (d, 2H), 3.17 (s, 3H), 3.13 (s, 3H). FAK IC_{50}: 0.00059 μM (Table 1, Example 104)

Example 5

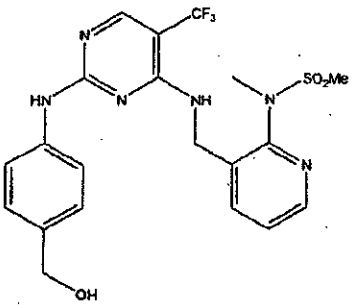
Preparation of N-(4-(4-((2-(N-methylmethan-5-ylsulfonamido)pyridin-3-yl)methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)benzyl)acetamide (**5**)



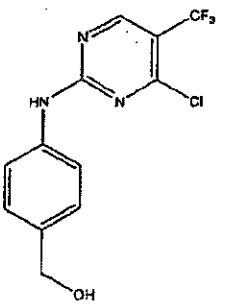
The free-base form of **4** (80mg, 0.166mmol), acetic anhydride (0.019ml, 0.199mmol), and DIEA (0.043ml, 0.249mmol) were dissolved in THF (0.5ml) and stirred at 25°C for 24 hours. The reaction mixture was then treated with EtOAc and washed with 1N NaOH. The resultant organic layer was dried over $MgSO_4$, filtered, and concentrated to provide **5** as a white solid. Yield: 63mg, 73%. MS^+ 524.5. ^1H NMR (500 MHz, d_6-DMSO) δ: 9.55 (s, 1H), 8.44 (d, 1H), 8.25 (s, 1H), 8.22 (t, 1H), 7.60 (m, 2H), 7.38 (m, 3H), 6.96 (d, 2H), 4.80 (d, 2H), 4.11 (d, 2H), 3.16 (s, 3H), 3.13 (s, 3H), 1.85 (s, 3H). FAK IC_{50}: 0.0006 μM

Example 6

Preparation of N-(3-((2-(4-(hydroxymethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide (6)



Step 1. Preparation of (4-(4-chloro-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)methanol (C7):



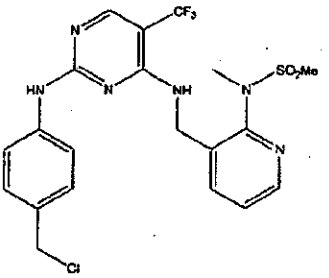
Step 1. C7 was prepared in a manner similar to that described in for making C3 in Step 3 of Example 1 except that 4-aminobenzyl alcohol (2.4g, 19mmol) was used instead of C2. When the reaction was complete the reaction mixture was concentrated and dissolved in EtOA. The resultant solution was washed with water, brine, dried over $MgSO_4$, and concentrated. The resultant tan solid was triterated with ether and a small amount of EtOAc, filtered and concentrated to provide C7 as a tan solid. Yield: 2.98g, 50%. MS^+ 304.1. ^1H NMR (500 MHz, d_6-DMSO) δ: 10.61 (s, 1H), 8.76 (s, 1H), 7.59 (d, 2H), 7.26 (d, 2H), 5.10 (bs, 1H), 4.43 (s, 2H).

Step 2. Compound 6 was prepared in a manner similar to that described for making compound 1 in Step 4 of Example 1, except that C7 (2.5g, 8.2mmol) was used instead C3. When the reaction was complete the reaction mixture was concentrated and dissolved in EtOA. The resultant solution was washed with water, brine, and dried over $MgSO_4$, and concentrated. The resultant solid was triterated with hot EtOAc, and the mixture was cooled to 0°C and filtered to provide 6 as a white solid. Yield: 2.94g, 74%. MS^+ 483.4. ^1H NMR (500 MHz, d_6-DMSO) δ: 9.50 (s, 1H), 8.41 (d, 1H), 8.22 (s,

1H), 7.62 (d, 1H), 7.55 (t, 1H), 7.36 (m, 3H), 6.99 (d, 2H), 4.98 (t, 1H), 4.76 (d, 2H), 4.32 (d, 2H), 3.13 (s, 3H), 3.11 (s, 3H). FAK IC_{50}: <0.000595 μM (Table 1, Example 319)

Example 7

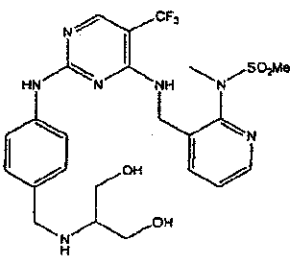
Preparation of N-(3-((2-(4-(chloromethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide (7)



A suspension of 6 (800mg, 1.66mmol) in DCM (5mL) was cooled to 0°C and treated with a solution of thionyl chloride (0.266ml, 3.65mmol) in DCM (2.0 mL). The reaction mixture was allowed to warm to 25°C and stirred at 25°C for 20 hours. The reaction mixture was then treated with DCM and washed with water (2x). The aqueous layer was collected and washed with DCM. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated to provide 7 as a white solid. Yield: 668mg, 80%. ^1H NMR (500 MHz, d_6-DMSO) δ: 6.68 (s, 1H), 8.45 (d, 1H), 8.28 (s, 1H), 7.64 (m, 2H), 7.42 (m, 3H), 7.14 (d, 2H), 4.82 (d, 2H), 4.66 (s, 2H), 3.17 (s, 3H), 3.15 (s, 3H). FAK IC_{50}: 0.00155 μM (Table 1, Example 348)

Example 8

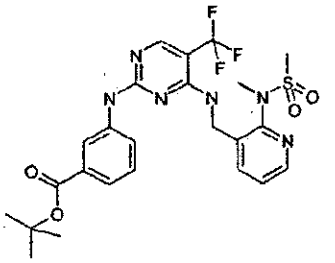
Preparation of N-(3-((2-(4-((1,3-dihydroxypropan-2-ylamino)methyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide (8)



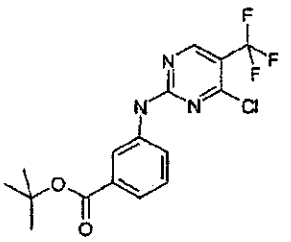
A mixture of 7 (100mg, 0.200mmol), 2-amino-1,3-propanediol (90.9mg, 0.998mmol), sodium hydroxide (7.98mg, 0.200mmol) and 2-propanol (0.5mL) was heated to reflux. After 30 minutes the mixture was cooled, treated with DCM, and washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated. The resultant residue was then purified by column chromatography (silica gel; eluting with 6% MeOH/DCM with NH_4OH), and the eluents containing the product were combined and concentrated to provide **8** as a white solid. Yield: 60.9mg, 55%. MS^+ 556.2. ^1H NMR (500 MHz, d_6-DMSO) δ: 9.48 (s, 1H), 8.41 (s, 1H), 8.21 (s, 1H), 7.59 (m, 2H), 7.34 (m, 3H), 6.99 (d, 2H), 4.75 (d, 2H), 4.35 (t, 2H), 3.58 (s, 2H), 3.34 (m, 4H), 3.12 (s, 3H), 3.09 (s, 3H), 2.45 (m, 1H). FAK IC_{50}: <0.000595 μM (Table 1, Example 389)

Example 9

Preparation of tert-butyl 3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoate (**9**)



Step 1. Preparation of tert-butyl 3-({4-chloro-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoate (**C8**)



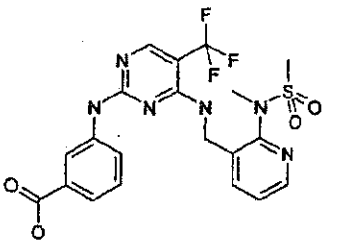
A solution of pyrimidine (24.8 g, 115 mmol) in tert-butanol (150 mL) and DCE (150 mL) was treated with $ZnBr_2$ (25.8 g, 115 mmol), and the resultant mixture was stirred at 25°C until all the $ZnBr_2$ dissolved. The resultant solution was cooled to 0° C and treated drop-wise with aniline (22.13 g, 115 mmol). The resultant brown mixture was then treated drop-wise with DIEA (40.1 mL, 230 mmol). The mixture was allowed

to warm to 25°C and stirred for 16 hours under N_2 atmosphere. The mixture was concentrated, and the resultant residue was suspended in MeOH. The resultant white solids were collected to provide **C8** as a white solid. Yield: 22.7 grams, 53%. APCI m/z 371.8/373.8 (M^-); ^{1}H NMR (d_6-DMSO) δ: 10.84 (bs, 1 H), 8.85 (s, 1 h), 8.37 (bs, 1 H), 7.92 (d, *J = 7.8 Hz.*, 1 h), 7.62 (d, *J = 7.8 Hz.*, 1 H), 7.48 (t, *J = 7.8 Hz.*, 1 H), 1.56 (s, 9 H) ppm.

Step 2. A solution of tert-butanol (20.0 mL), DCE (20.0 mL) and DIEA (3.13 mL, 18.0 mmol) was treated with **C8** (5.60 g, 15.0 mmol) and **B5** (5.02 g, 15.0 mmol), and the resulting mixture was stirred at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was cooled to 25°C and concentrated. The resultant residue was partitioned between EtOAc and 1 N sodium hydroxide, and the organic phase was collected. The aqueous layer was extracted with EtOAc, and the combined organic phases were dried over $MgSO_4$ and filtered. The resultant filtrate was concentrated under reduced pressure, and the resultant residue was triturated with hot EtOAc to provide **9** as a white solid. Yield: 7.83 grams, 95%. LC/MS (standard) 25° = 3.0 min., m/z 553.6 (MH^+). HPLC (FAK1) 25° = 8.14 min. ^{1}H NMR (d_6-DMSO) δ: 9.75 (bs, 1 H), 8.44 (d, *J = 5.2 Hz.*, 1 H), 8.29 (s, 1 H), 8.05 (bs, 1 H), 7.82 (d, *J = 7.8 Hz.*, 1 H), 7.60 (t, *J = 5.7 Hz.*, 1 H), 7.44 – 7.40 (m, 2 H), 7.17 (t, *J = 5.7 Hz*, 1 H), 4.82 (d, *J = 5.7 Hz.*, 2 H), 3.16 (s, 3 H), 3.13 (s, 3 H), 1.51 (s, 9 H) ppm. FAK IC_{50}: 0.0006 μM

Example 10

Preparation of 3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoic acid trifluoroacetic acid salt (**10**)

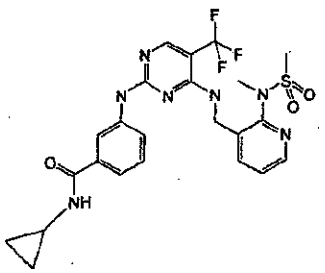


A solution of **9** (7.83g, 14.1mmol) in DCE (30.0mL) was cooled to 0°C and treated slowly with TFA (45.0mL). The resultant orange-brown solution was allowed to slowly warm to 25°C under an N_2 atmosphere and stirred for 4 hours. The mixture was then concentrated, and the resultant residue was treated with EtOAc. The resultant white solids were collected by filtration and washed with EtOAc to provide the trifluoroacetate

salt form of **10**. Yield: 7.24grams, 84%. APCI m/z 496.8 (MH^+), HPLC (FAK1) 25° = 5.29 min., ^1H NMR (d_6-DMSO) δ: 9.82 (bs, 1 H), 8.44 (d, *J = 5.2 Hz.*, 1 H), 8.29 (s, 1 H), 8.08 (bs, 1 H), 7.79 (d, *J = 7.8 Hz.*, 1 H), 7.60 – 7.38 (m, 4 H), 7.17 (t, *J = 5.7 Hz*, 1 H), 4.82 (d, *J = 5.7 Hz.*, 2 H), 3.16 (s, 3 H), 3.13 (s, 3 H) ppm. FAK IC_{50}: 0.0006 μM

Example 11

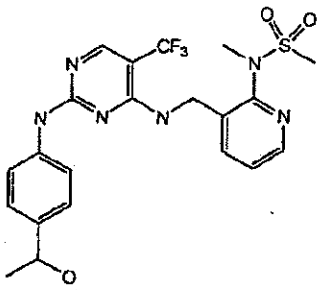
Preparation of N-cyclopropyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**11**)



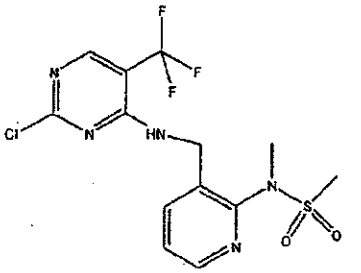
A polymer supported carbodiimide (PS-CDI) (0.326mmol) was allowed to swell in acetonitrile (volume of 500μL). The resultant suspension was treated with **10** (100mg, 0.164mmol) and DIEA (29μL, 0.164mmol). The resultant solution was then treated with cyclopropylamine (19μL, 0.164mmol). The resultant suspension was then mixed on a shaker plate for 16 hours. The mixture was then filtered, and the solids washed with 10% MeOH in chloroform. The combined filtrates were concentrated under reduced pressure, and the resultant residue was purified over silica (99:1:0.1 $CHCl_3$:CH_3OH:NH_4OH) to provide **11** as a white foam. Yield: 14.3mg, 16%. LC Ret. Time (standard) = 2.1 min., m/z 536.2 (MH^+); ^1H NMR (CD_3OD) δ: 8.42 (d, J = 7.8 Hz., 1 H), 8.20 (s, 1 h), 7.97 (t, J = 7.8 Hz., 1 H), 7.81 (d, J = 7.8 Hz., 1 H), 1.68 (d, J = 7.8 Hz., 1 H), 7.39 – 7.34 (m, 2 H), 7.26 (t, J = 7.8 Hz., 1 H), 4.94 (s, 2 H), 3.23 (s, 3 H), 3.14 (s, 3 H), 2.82 (m, 1 H), 0.79 (m, 2 h), 0.60 (m, 2 H) ppm. FAK IC_{50}: 0.00186 μM

Example 12

Preparation of N-(3-((2-(4-(1-hydroxyethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide (**12**)



Step 1. N-(3-((2-chloro-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide (**C9**)



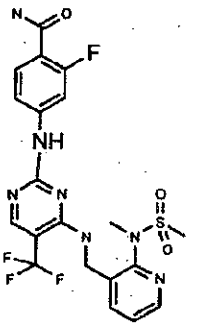
A solution of **B5** and trifluoroethanol (120mL) was treated with triethylamine (TEA) (16.6mL) and stirred at 25°C for 1 hour. In a separate reaction flask, a solution of 2,4-dichloro-5-trifluoromethylpyrimidine (13.2g, 60.8mmol) and trifluoroethanol (120mL) was cooled to -45°C. The cold 2,4-dichloro-5-trifluoromethylpyrimidine solution was then treated drop-wise with the solution containing **B5** and stirred at -45°C for 2 hours. The mixture was allowed to warm to 25°C, and it was stirred at 25°C for about 20 hours. The reaction mixture was then concentrated and cooled to 0°C. The resultant white mixture was diluted with EtOAc (15ml), and the solids collected by filtration. The white solids were then washed with water and EtOAc to provide **C9**. Yield: 0.7g, 45%. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 3.07 (s, 3H), 3.29(s, 3H), 4.68 (d, 2H), 7.39 (m, 1H), 7.72 (d, 1H), 8.40 (s, 1H), 8.50 (t, 1H); ESI-MS: 396.0 (MH^+).

Step 2. A solution of **C9** (0.253 mmol) and anhydrous DMSO (0.5 ml) was treated with 1-(4-aminophenyl)ethanol (0.277 mmol) followed by potassium phosphate dibasic (0.746mmol). The mixture was stirred at 100°C for 1.5 days, and treated with additional 1-(4-aminophenyl)ethanol (0.583mmol). The mixture was stirred at 100°C for 15 hours and concentrated. The resultant residue was purified first by column chromatography (silica gel; 10% (NH_4OH/MeOH)/CH_2Cl_2) followed by preparatory thin layer chromatography developed in 5% MeOH/CH2Cl2 to provide **12**. Yield: 13.6 mg,

10.8%. ^{1}H NMR(CD_3OD) δ: 8.39(d, 1H), 8.13(s, 1H), 7.73(d, 1H), 7.33(m, 3H), 7.14(d, 2H), 4.87(s, 2H), 4.72(q, 1H), 3.17(s, 3H), 3.10(s, 3H), 1.37(d, 3H). MS: m/z 497(MH^+).

Example 13

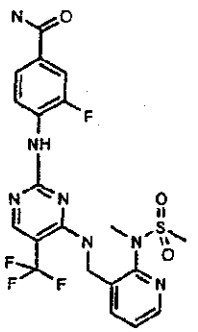
Preparation of 2-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide formic acid salt (**13**)



A mixture of 4-amino-2-fluorobenzamide (1.5 eq., 189 µM) in 2-propanol (1.0 mL) was treated with **C9** (1 equiv., 130uM) followed by trifluoroacetic acid (2.7 equiv., 341µM) and stirred in a sealed vial at 100°C for about 20 hours. The mixture was then cooled to 25°C, treated with DMSO, filtered, and purified on a Shimadzu using a reverse phase Symmetry C-8 column and eluting with 20-80%B for 10min at 40ml/min (A:0.1% formic acid in water, B: 0.1% formic acid in acetonitrile to provide the formic acid salt of **13** as a cream colored solid. Yield: 17.5mg, 27%. LC-MS M+1 = 514. NMR (d_6-DMSO) δ: 3.13 (6H, s), 4.81 (2H, s), 7.30-7.40 (6H, m), 7.41-7.73 (2H, m), 8.3 (1H, s), 8.41 (1H, s), 9.96 (1H, s). FAK IC_{50}: <0.000595 µM (Table 1, Example 320)

Example 14

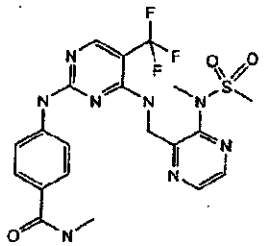
Preparation of 3-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide formic acid salt (**14**)



Compound **14** was prepared in a manner similar to that described Example 13 for the preparation of **13** except that 4-amino-3-fluorobenzamide (1.5 equ/189μM) was used instead of 4-amino-2-fluorobenzamide to provide the formic acid salt of **14** as a cream colored solid. Yield: 26mg, 37%. LC-MS M+1 = 514. NMR (d_6-DMSO) δ: 2.98 (3H, s), 3.09 (3H, s), 4.65 (2H, s), 7.35-7.66 (7H, m), 7.87 (1H, s), 8.23 (1H, s), 8.38 (1H, s), 9.19 (1H, s). FAK IC_{50}: <0.000595 μM (Table 1, Example 322)

Example 15

Preparation of 4-(4-{[(3-methanesulfonyl-methyl-amino)-pyrazin-2-ylmethyl]-amino}-5-(trifluoromethyl)-pyrimidin-2-ylamino)-N-methyl-benzamide (**15**)

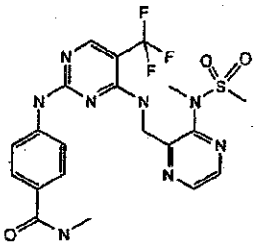


Step 1. A suspension of **B20** (0.3 mmol), **B2** (0.3 mmol), and diisopropylethyl amine (0.9 mmol) in 1:1 (v:v) DCE/tBuOH was mixed at 80°C for 9 hours. The mixture was allowed to cool to 25°C, and it was mixed at 25°C for 20 hours. The mixture was then treated with 9:1 (v:v) ether/ethanol. The solids were collected and washed with water to provide **15**. Yield: 0.23 mmol, 78%. HPLC (KDC 10_90) 3.526 min. ^{1}H NMR (500 MHz, d_6-DMSO) δ ppm 9.83 (s, 1 H), 8.69 (d, *J*=2.59 Hz, 1 H), 8.58 (d, *J*=2.59 Hz, 1 H), 8.31 (s, 1 H), 8.20 (d, *J*=4.67 Hz, 1 H), 7.58 - 7.70 (m, 3 H), 7.41 (t, *J*=5.18 Hz, 1

H), 5.00 (d, *J*=5.18 Hz, 2 H), 3.23 (s, 3 H), 3.20 (s, 3 H), 2.75 (d, *J*=4.15 Hz, 3 H). FAK IC_{50}: <0.000595 μM (Table 1, Example 317)

Example 15A

Preparation of 4-(4-{[(3-methanesulfonyl-methyl-amino)-pyrazin-2-ylmethyl]-amino}-5-(trifluoromethyl)-pyrimidin-2-ylamino)-N-methyl-benzamide hydrochloride salt (**15A**)



Step 1. A suspension of **B20** (26.3 mmol), **B2** (28.9 mmol) and diisopropylethyl amine (105 mmol) was mixed in 1:1 DCE:tBuOH (80 mL) and heated to 88 °C in a sealed flask for 1.5 hour. The mixture turned green and a solid precipitated. The suspension was diluted with Et2O/EtOH (10:1) and filtered to obtain 10.1 g of a white solid (75%). 8 g of this product was slurried in 400 mL of MeOH and to the mixture was added 18mL 4.0M HCl in dioxane. This was stirred at room temperature for 1 hour, then it was filtered to obtain **15A** as an off-white solid HCl salt (~quant yield). 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (d, *J*=3.74 Hz, 3 H), 3.18 (m, 6 H), 5.01 (d, *J*=4.98 Hz, 2 H), 7.52 (d, 2 H), 7.67 (d, *J*=8.72 Hz, 2 H), 7.98 (br. s., 1 H), 8.29 (d, *J*=4.15 Hz, 1 H), 8.42 (s, 1 H), 8.59 (d, 1 H), 8.68 (d, 1 H), 10.38 (s, 1 H). ESI-MS: 511.1 (MH^+), 509.2 $(M-H)^-$. FAK IC_{50}: 0.00179 μM (Table 1, Example 318)

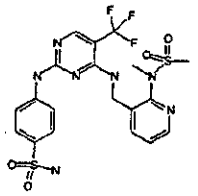
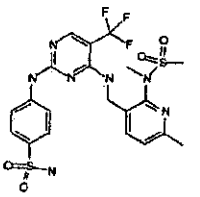
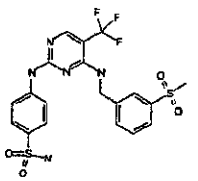
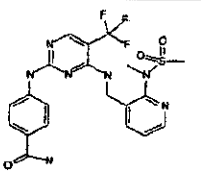
Examples 16-415

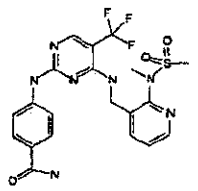
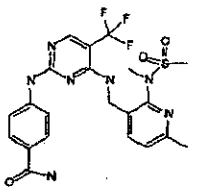
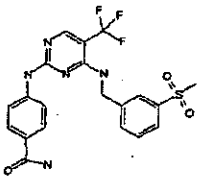
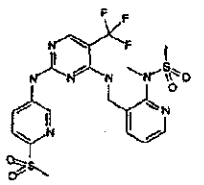
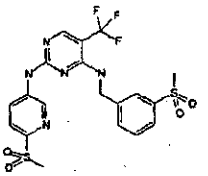
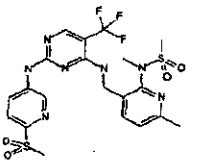
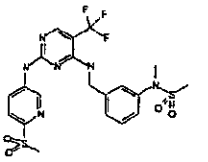
Compounds **16-415** in Examples 16-415 (see Table 1) were prepared by the methods described above in the Detailed Description of the Invention and as described in Examples 1-15A. The amines used in these reactions were obtained commercially and used as received, prepared as described above for compounds **B1-B20** or in Examples 1-15A above, or prepared by common synthetic methods for amines known to those skilled in the art. Unless otherwise noted, compounds having chiral centers were prepared as racemic mixtures.

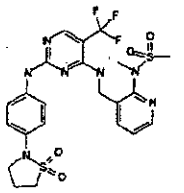
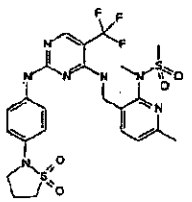
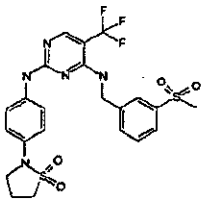
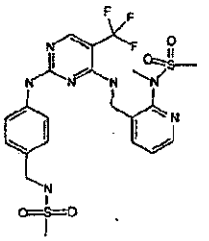
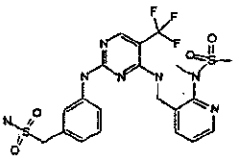
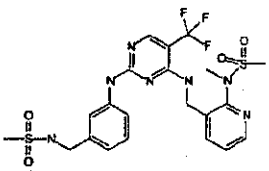
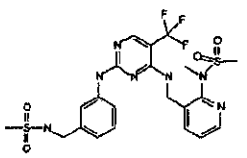
Table 1 also contains biological kinase inhibition (IC50 values) for compounds **16-415.**

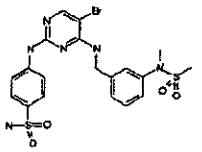
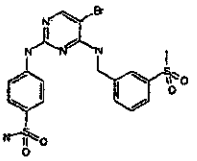
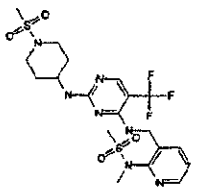
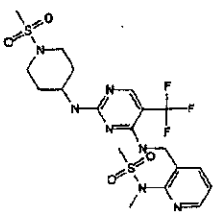
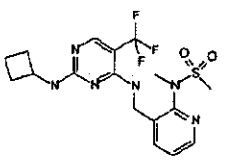
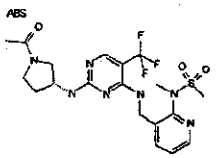
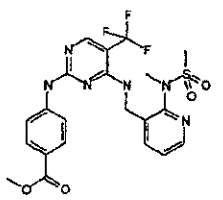
The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

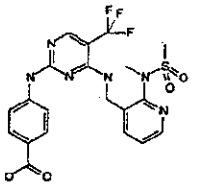
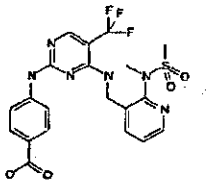
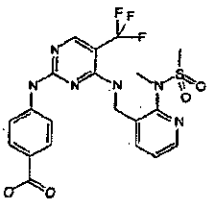
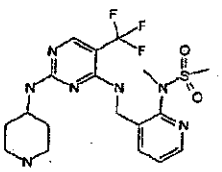
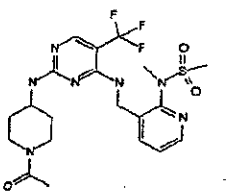
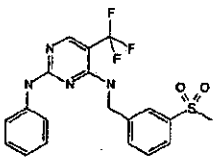
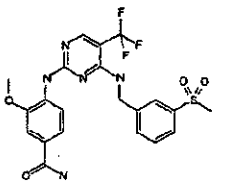
Table 1. IC50 values against FAK kinase.

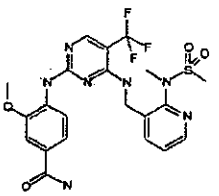
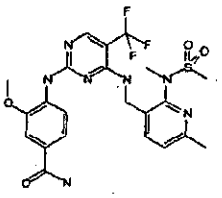
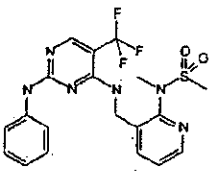
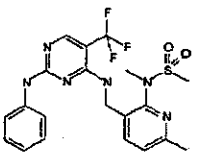
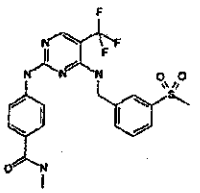
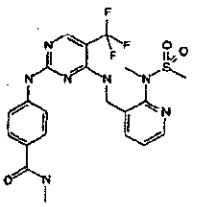
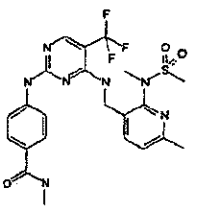
Ex.	Structure	Compound Name	FAK IC50, μM
16		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzenesulfon-amide (**16**)	0.00409
17		4-({4-[({6-methyl-2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzene-sulfonamide (**17**)	0.00126
18		4-{[4-{[3-(methylsulfonyl)benzyl]amino}-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzene-sulfonamide (**18**)	0.0132
19		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**19**)	0.0034

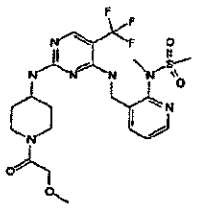
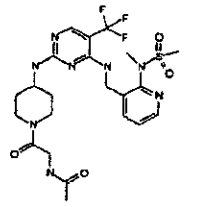
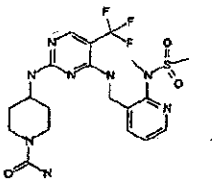
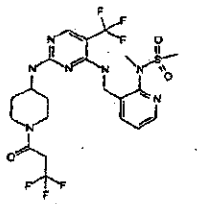
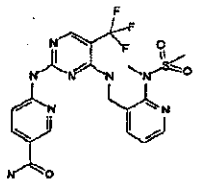
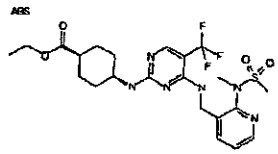
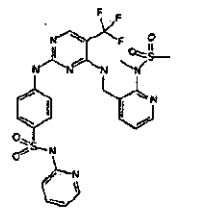
Ex.	Structure	Compound Name	FAK IC50, μM
20		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**20**), hydrochloride salt	0.0006
21		4-({4-[({6-methyl-2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**21**)	0.001
22		4-{[4-{[3-(methylsulfonyl)benzyl]amino}-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**22**)	0.00356
23		N-methyl-N-[3-({[2-{[6-(methylsulfonyl)pyridin-3-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**23**)	0.0686
24		N-4-[3-(methylsulfonyl)benzyl]-N-2-[6-(methylsulfonyl)pyridin-3-yl]-5-(trifluoromethyl)-pyrimidine-2,4-diamine (**24**)	0.337
25		N-methyl-N-[6-methyl-3-({[2-{[6-(methylsulfonyl)pyridin-3-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**25**)	0.0129
26		N-methyl-N-[3-({[2-{[6-(methylsulfonyl)pyridin-3-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide (**26**)	0.154

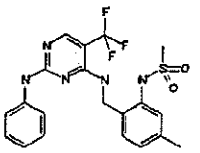
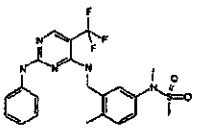
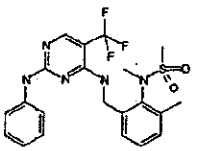
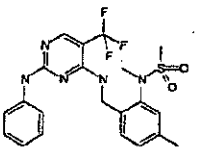
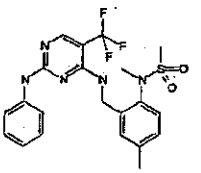
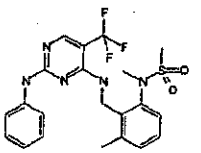
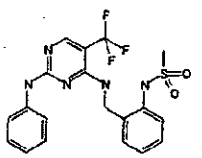
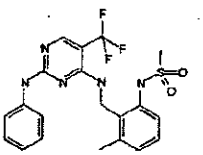
Ex.	Structure	Compound Name	FAK IC50, μM
27		N-[3-({[2-{[4-(1,1-dioxidoisothiazolidin-2-yl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**27**)	0.00138
28		N-[3-({[2-{[4-(1,1-dioxidoisothiazolidin-2-yl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-6-methylpyridin-2-yl]-N-methylmethanesulfonamide (**28**)	0.00201
29		N~2~-[4-(1,1-dioxidoisothiazolidin-2-yl)phenyl]-N~4~-[3-(methylsulfonyl)benzyl]-5-(trifluoromethyl)pyrimidine-2,4-diamine (**29**)	0.00209
30		N-methyl-N-{3-[({2-[(4-{[(methylsulfonyl)amino]methyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**30**)	0.00072
31		N-[3-({[2-({3-[(aminosulfonyl)methyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**31**)	0.00222
32		N-methyl-N-{3-[({2-[(3-{[(methylsulfonyl)amino]methyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**32**)	
33		N-methyl-N-{3-[({2-[(3-{[(methylsulfonyl)amino]methyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**33**), hydrochloride salt	0.00133

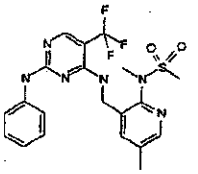
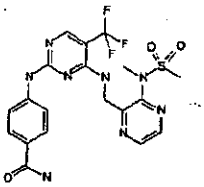
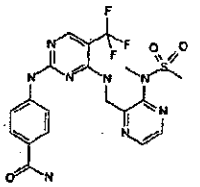
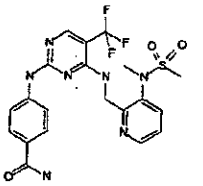
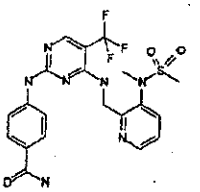
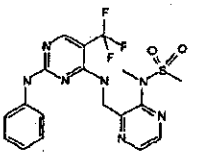
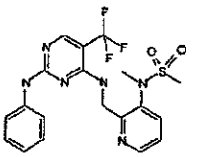
Ex.	Structure	Compound Name	FAK IC50, μM
34		4-{[5-bromo-4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)pyrimidin-2-yl]amino}benzenesulfonamide (**34**)	0.0156
35		4-[(5-bromo-4-{[3-(methylsulfonyl)benzyl]amino}pyrimidin-2-yl)amino]benzene-sulfonamide (**35**)	0.0176
36		N-methyl-N-[3-({[2-{[1-(methylsulfonyl)piperidin-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**36**)	0.188
37		N-methyl-N-[3-({[2-{[1-(methylsulfonyl)piperidin-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**37**), trifluoroacetic acid salt	
38		N-[3-({[2-(cyclobutylamino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**38**)	0.497
39		N-[3-({[2-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**39**)	1
40		methyl 4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoate (**40**)	0.00059

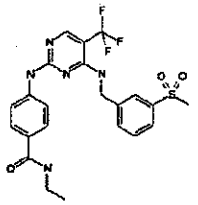
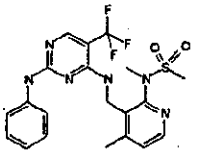
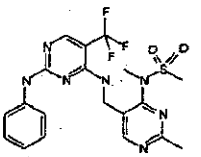
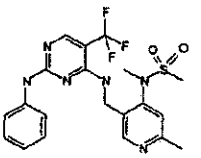
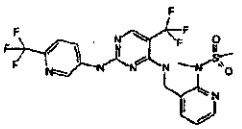
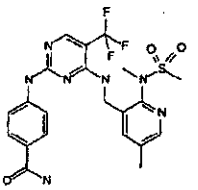
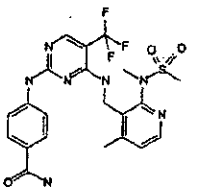
Ex.	Structure	Compound Name	FAK IC50, μM
41		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoic acid (**41**)	
42		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoic acid (**42**), sodium salt	0.188
43		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoic acid (**43**), trifluoroacetic acid salt	0.0006
44		N-methyl-N-[3-({[2-(piperidin-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**44**)	0.188
45		N-{3-[({2-[(1-acetylpiperidin-4-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**45**)	0.188
46		N-4-[3-(methylsulfonyl)benzyl]-N-2-phenyl-5-(trifluoromethyl)pyrimidine-2,4-diamine (**46**)	0.00102
47		3-methoxy-4-{[4-{[3-(methylsulfonyl)benzyl]amino}-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**47**)	0.00059

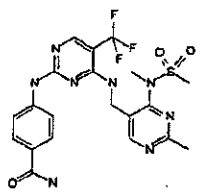
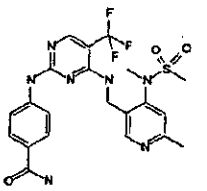
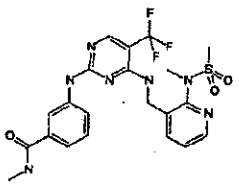
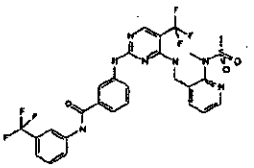
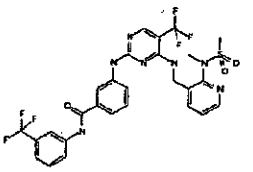
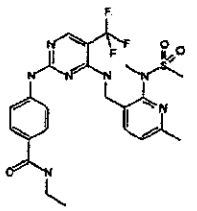
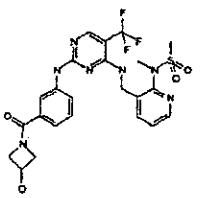
Ex.	Structure	Compound Name	FAK IC50, μM
48		3-methoxy-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**48**)	0.00059
49		3-methoxy-4-({4-[({6-methyl-2-[methyl(methylsulfonyl)-amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**49**)	0.00059
50		N-[3-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**50**)	0.00059
51		N-[3-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-6-methylpyridin-2-yl]-N-methylmethanesulfonamide (**51**)	0.00059
52		N-methyl-4-{[4-{[3-(methylsulfonyl)benzyl]amino}-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**52**)	0.00195
53		N-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**53**)	0.00059
54		N-methyl-4-({4-[({6-methyl-2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**54**)	0.00059

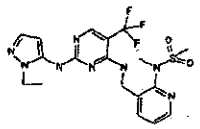
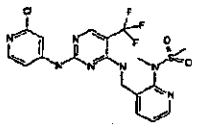
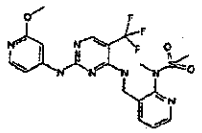
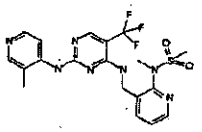
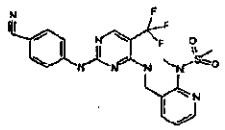
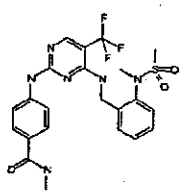
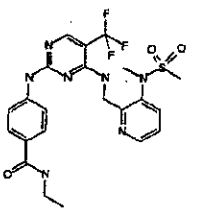
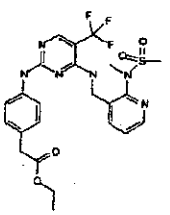
Ex.	Structure	Compound Name	FAK IC50, μM
55		N-[3-({[2-{[1-(methoxyacetyl)piperidin-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**55**)	0.188
56		N-{2-[4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)piperidin-1-yl]-2-oxoethyl}acetamide (**56**)	0.188
57		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)piperidine-1-carboxamide (**57**)	0.188
58		N-methyl-N-[3-({[5-(trifluoromethyl)-2-{[1-(3,3,3-trifluoropropanoyl)piperidin-4-yl]amino}pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**58**)	0.165
59		6-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)nicotinamide (**59**)	0.00893
60		ethyl cis-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)cyclohexanecarboxylate (**60**)	0.188
61		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-pyridin-2-ylbenzenesulfonamide (**61**)	0.00102

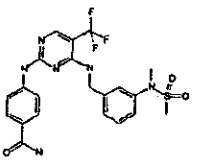
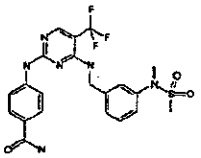
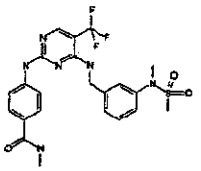
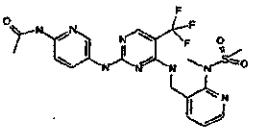
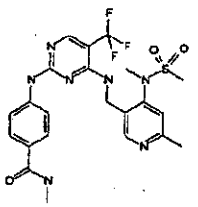
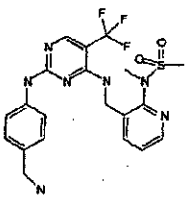
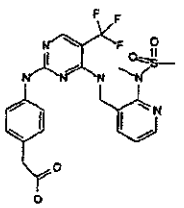
Ex.	Structure	Compound Name	FAK IC50, μM
62		N-[2-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-5-methylphenyl]methanesulfonamide (**62**)	0.0103
63		N-[3-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-4-methylphenyl]-N-methylmethanesulfonamide (**63**)	0.0006
64		N-[2-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-6-methylphenyl]-N-methylmethanesulfonamide (**64**)	0.0006
65		N-[2-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-5-methylphenyl]-N-methylmethanesulfonamide (**65**)	0.0006
66		N-[2-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-4-methylphenyl]-N-methylmethanesulfonamide (**66**)	0.0006
67		N-[2-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-3-methylphenyl]-N-methylmethanesulfonamide (**67**)	0.0006
68		N-[2-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide (**68**)	0.00059
69		N-[2-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-3-methylphenyl]methane-sulfonamide (**69**)	0.0006

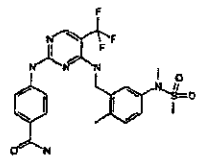
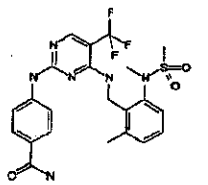
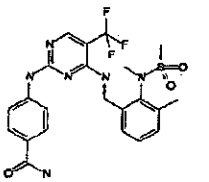
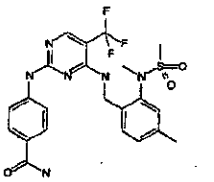
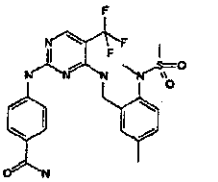
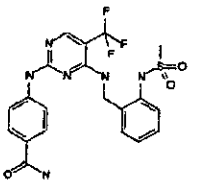
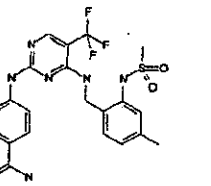
Ex.	Structure	Compound Name	FAK IC50, μM
70		N-[3-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-5-methylpyridin-2-yl]-N-methylmethanesulfonamide (**70**)	0.0006
71		4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**71**)	0.0006
72		4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**72**), hydrochloride salt	
73		4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**73**)	0.0006
74		4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**74**), hydrochloride salt	
75		N-[3-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyrazin-2-yl]-N-methylmethane-sulfonamide (**75**)	0.0006
76		N-[2-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-3-yl]-N-methylmethane-sulfonamide (**76**)	0.093

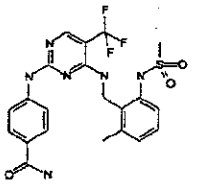
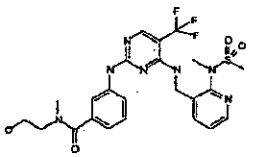
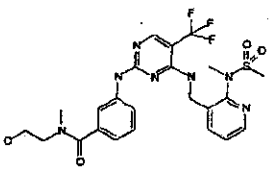
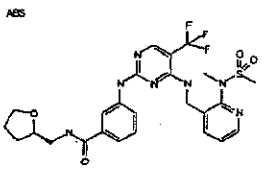
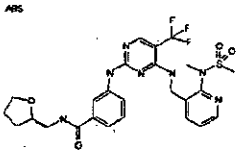
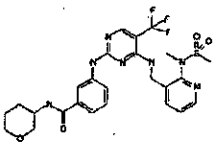
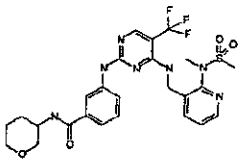
Ex.	Structure	Compound Name	FAK IC50, μM
77		N-ethyl-4-{[4-{[3-(methylsulfonyl)benzyl]amino}-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**77**)	0.0006
78		N-[3-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-4-methylpyridin-2-yl]-N-methylmethanesulfonamide (**78**)	0.0006
79		N-[5-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-2-methylpyrimidin-4-yl]-N-methylmethanesulfonamide (**79**)	0.00262
80		N-[5-({[2-anilino-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)-2-methylpyridin-4-yl]-N-methylmethanesulfonamide (**80**)	0.00059
81		N-methyl-N-[3-({[5-(trifluoromethyl)-2-{[6-(trifluoromethyl)pyridin-3-yl]amino}pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**81**)	0.0158
82		4-({4-[({5-methyl-2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**82**)	0.0006
83		4-({4-[({4-methyl-2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**83**)	0.0006

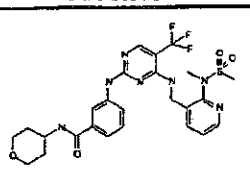
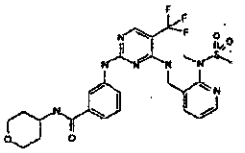
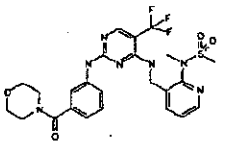
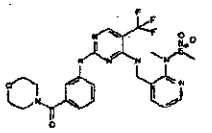
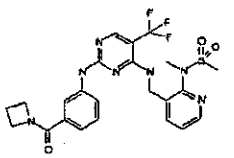
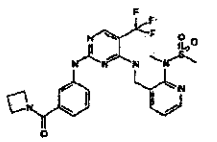
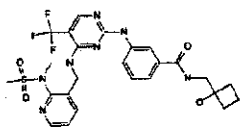
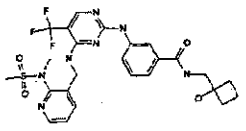
Ex.	Structure	Compound Name	FAK IC50, μM
84		4-({4-[({2-methyl-4-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**84**)	0.00171
85		4-({4-[({6-methyl-4-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**85**)	0.00084
86		N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**86**)	0.00161
87		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-[3-(trifluoromethyl)phenyl]benzamide (**87**)	
88		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-[3-(trifluoromethyl)phenyl]benzamide (**88**), hydrochloride salt	0.0215
89		N-ethyl-4-({4-[({6-methyl-2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**89**)	0.0006
90		N-[3-({[2-({3-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**90**)	0.00072

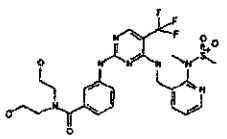
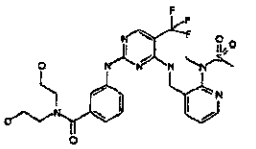
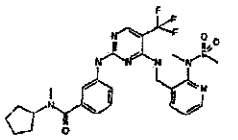
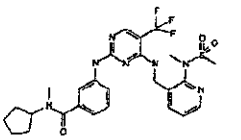
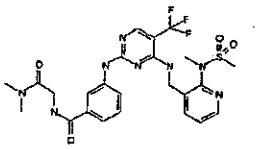
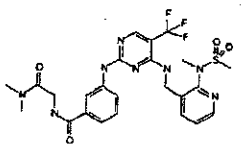
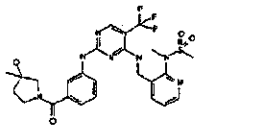
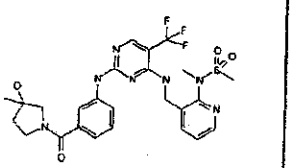
Ex.	Structure	Compound Name	FAK IC50, μM
91		N-{3-[({2-[(1-ethyl-1H-pyrazol-5-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**91**)	0.188
92		N-{3-[({2-[(2-chloropyridin-4-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**92**)	0.00192
93		N-{3-[({2-[(2-methoxypyridin-4-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**93**)	0.0006
94		N-methyl-N-{3-[({2-[(3-methylpyridin-4-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**94**)	0.00801
95		N-{3-[({2-[(4-cyanophenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**95**)	0.0006
96		N-methyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**96**)	0.00059
97		N-ethyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**97**)	0.00059
98		ethyl [4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]acetate (**98**)	0.00059

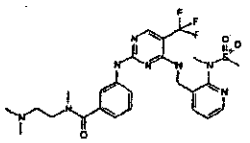
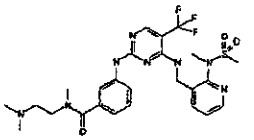
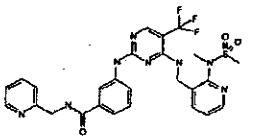
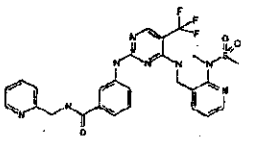
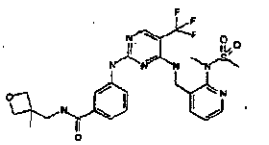
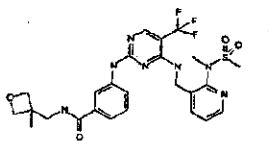
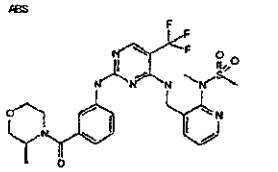
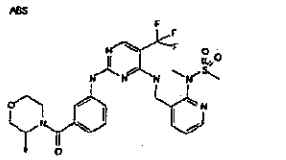
Ex.	Structure	Compound Name	FAK IC50, μM
99		4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**99**)	0.00038
100		4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**100**), hydrochloride salt	
101		N-methyl-4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**101**)	0.00059
102		N-[5-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)pyridin-2-yl]acetamide (**102**)	0.00233
103		N-methyl-4-({4-[({6-methyl-4-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**103**)	0.00059
104		N-[3-({[2-{[4-(aminomethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**104**)	0.00059
105		[4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]acetic acid (**105**)	0.00094

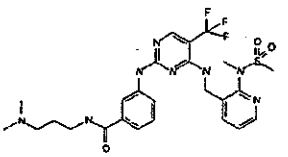
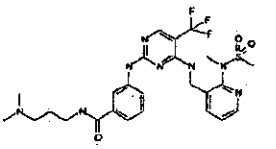
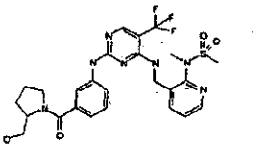
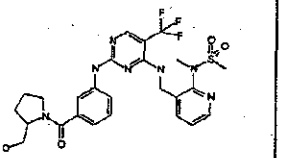
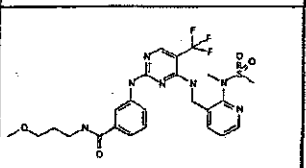
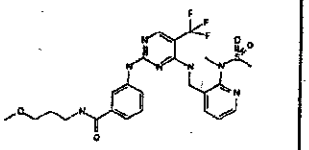
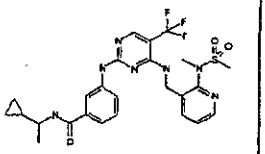
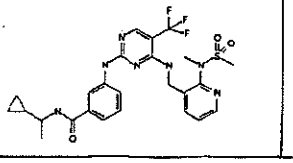
Ex.	Structure	Compound Name	FAK IC50, μM
106		4-{[4-({2-methyl-5-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**106**)	0.00096
107		4-{[4-({2-methyl-6-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**107**)	0.00059
108		4-{[4-({3-methyl-2-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**108**)	0.0006
109		4-{[4-({4-methyl-2-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**109**)	0.0006
110		4-{[4-({5-methyl-2-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**110**)	0.0006
111		4-{[4-({2-[(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**111**)	0.0006
112		4-{[4-({4-methyl-2-[(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**112**)	0.0006

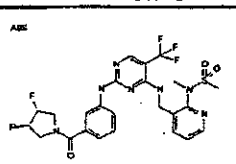
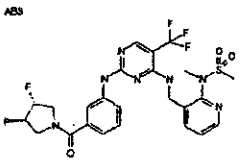
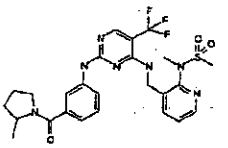
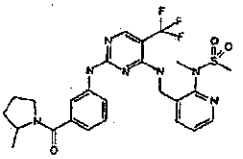
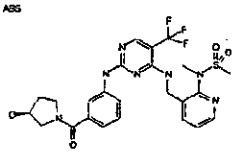
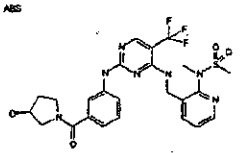
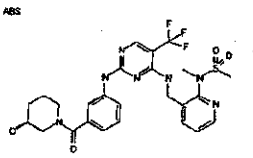
Ex.	Structure	Compound Name	FAK IC50, μM
113		4-{[4-({2-methyl-6-[(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**113**)	0.0006
114		N-(2-hydroxyethyl)-N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**114**)	
115		N-(2-hydroxyethyl)-N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**115**), trifluoroacetic acid salt	0.00088
116		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-[(2R)-tetrahydrofuran-2-ylmethyl]benzamide (**116**)	
117		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-[(2R)-tetrahydrofuran-2-ylmethyl]benzamide (**117**), trifluoroacetic acid salt	0.00147
118		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(tetrahydro-2H-pyran-3-yl)benzamide (**118**)	
119		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(tetrahydro-2H-pyran-3-yl)benzamide (**119**), trifluoroacetic acid salt	0.00114

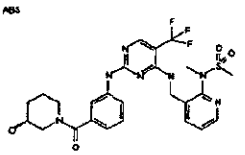
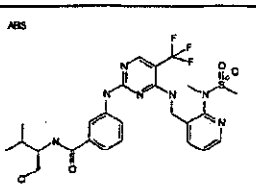
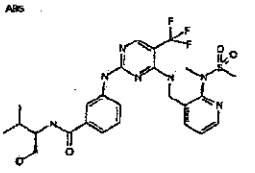
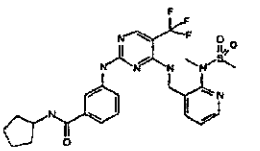
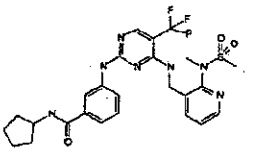
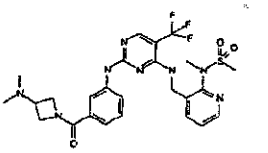
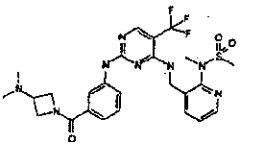
Ex.	Structure	Compound Name	FAK IC50, μM
120		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(tetrahydro-2H-pyran-4-yl)benzamide (**120**)	
121		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(tetrahydro-2H-pyran-4-yl)benzamide (**121**), *trifluoroacetic* acid salt	0.00094
122		N-methyl-N-[3-({[2-{[3-(morpholin-4-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**122**)	
123		N-methyl-N-[3-({[2-{[3-(morpholin-4-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**123**), trifluoroacetic acid salt	0.00215
124		N-[3-({[2-{[3-(azetidin-1-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**124**)	
125		N-[3-({[2-{[3-(azetidin-1-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethanesulfon-amide (**125**), trifluoroacetic acid salt	0.00127
126		N-[(1-hydroxycyclobutyl)methyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**126**)	
127		N-[(1-hydroxycyclobutyl)methyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**127**), trifluoroacetic acid salt	0.00211

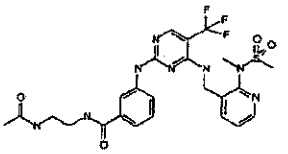
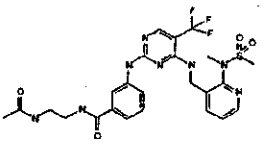
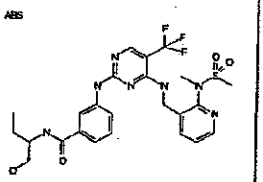
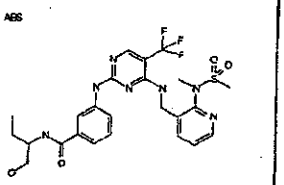
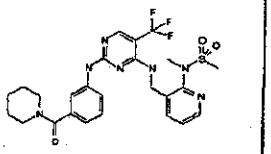
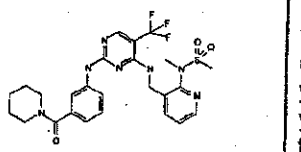
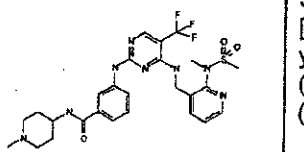
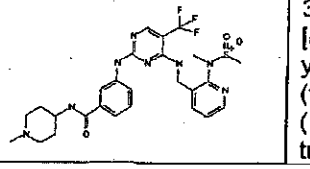
Ex.	Structure	Compound Name	FAK IC50, μM
128		N,N-bis(2-hydroxyethyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**128**)	
129		N,N-bis(2-hydroxyethyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**129**), trifluoroacetic acid salt	0.00076
130		N-cyclopentyl-N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**130**)	
131		N-cyclopentyl-N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**131**), trifluoroacetic acid salt	0.0108
132		N-[2-(dimethylamino)-2-oxoethyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**132**)	
133		N-[2-(dimethylamino)-2-oxoethyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**133**), trifluoroacetic acid salt	0.00195
134		N-[3-({[2-({3-[(3-hydroxy-3-methylpyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**134**)	
135		N-[3-({[2-({3-[(3-hydroxy-3-methylpyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**135**), trifluoroacetic acid salt	0.00333

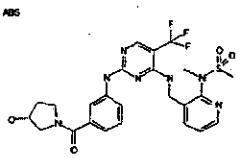
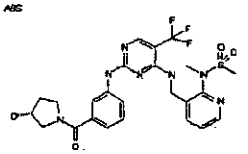
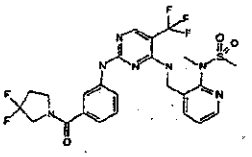
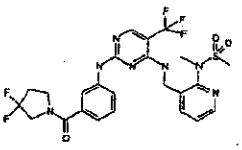
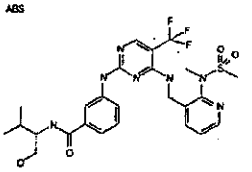
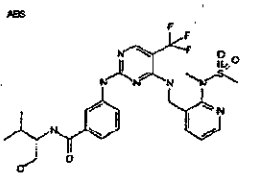
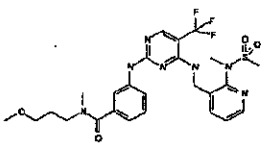
Ex.	Structure	Compound Name	FAK IC50, μM
136		N-[2-(dimethylamino)ethyl]-N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**136**)	
137		N-[2-(dimethylamino)ethyl]-N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**137**), trifluoroacetic acid salt	0.00433
138		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(pyridin-2-ylmethyl)benzamide (**138**)	
139		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(pyridin-2-ylmethyl)benzamide (**139**), trifluoroacetic acid salt	0.00191
140		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-[(3-methyloxetan-3-yl)methyl]benzamide (**140**)	
141		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-[(3-methyloxetan-3-yl)methyl]benzamide (**141**), trifluoroacetic acid salt	0.00084
142		N-methyl-N-{3-[({2-[(3-{[(3S)-3-methylmorpholin-4-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**142**)	
143		N-methyl-N-{3-[({2-[(3-{[(3S)-3-methylmorpholin-4-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**143**), trifluoroacetic acid salt	0.0024

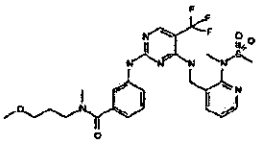
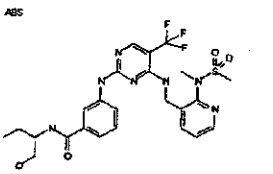
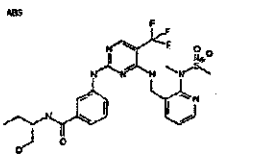
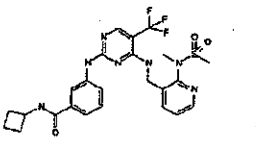
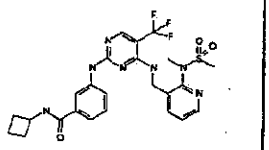
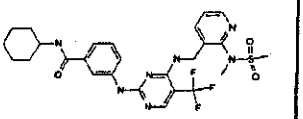
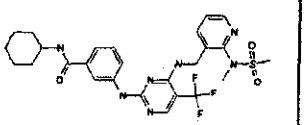
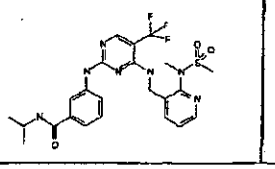
Ex.	Structure	Compound Name	FAK IC50, μM
144		N-[3-(dimethylamino)propyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**144**)	
145		N-[3-(dimethylamino)propyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**145**), trifluoroacetic acid salt	0.00254
146		N-{3-[({2-[(3-{[2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**146**)	
147		N-{3-[({2-[(3-{[2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**147**), trifluoroacetic acid salt	0.00474
148		N-(3-methoxypropyl)-3-({4-[({2-[methyl(methylsulfonyl)-amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**148**)	
149		N-(3-methoxypropyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**149**), trifluoroacetic acid salt	0.00151
150		N-(1-cyclopropylethyl)-3-({4-[({2-[methyl(methylsulfonyl)-amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**150**)	
151		N-(1-cyclopropylethyl)-3-({4-[({2-[methyl(methylsulfonyl)-amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**151**), trifluoroacetic acid salt	0.00524

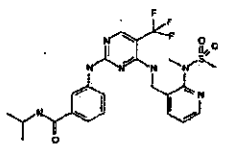
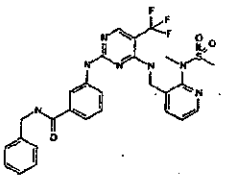
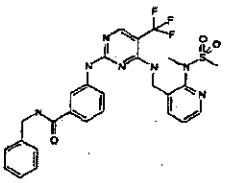
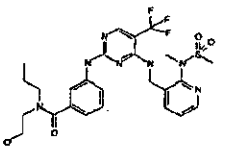
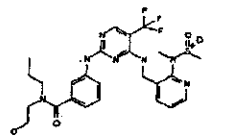
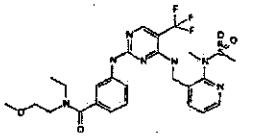
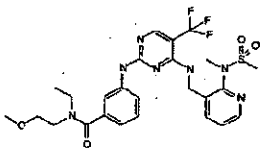
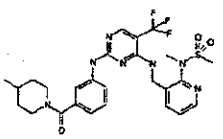
Ex.	Structure	Compound Name	FAK IC50, μM
152		N-{3-[({2-[(3-{[(3R,4R)-3,4-difluoropyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**152**)	
153		N-{3-[({2-[(3-{[(3R,4R)-3,4-difluoropyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**153**), trifluoroacetic acid salt	0.00335
154		N-methyl-N-[3-({[2-({3-[(2-methylpyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**154**)	
155		N-methyl-N-[3-({[2-({3-[(2-methylpyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**155**), trifluoroacetic acid salt	0.00975
156		N-{3-[({2-[(3-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**156**)	
157		N-{3-[({2-[(3-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**157**), trifluoroacetic acid salt	0.00424
158		N-{3-[({2-[(3-{[(3S)-3-hydroxypiperidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**158**)	

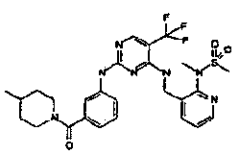
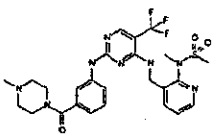
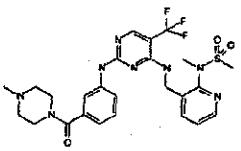
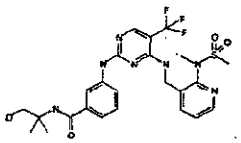
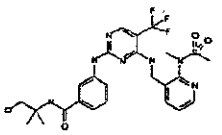
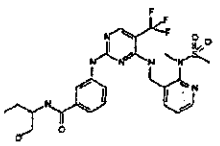
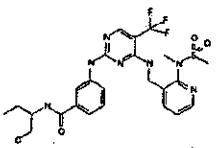
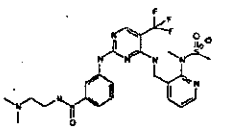
Ex.	Structure	Compound Name	FAK IC50, μM
159		N-{3-[({2-[(3-{[(3S)-3-hydroxypiperidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**159**), trifluoroacetic acid salt	0.00614
160		N-[(1R)-1-(hydroxymethyl)-2-methylpropyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**160**)	
161		N-[(1R)-1-(hydroxymethyl)-2-methylpropyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**161**), trifluoroacetic acid salt	0.00374
162		N-cyclopentyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**162**)	
163		N-cyclopentyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**163**), trifluoroacetic acid salt	0.0051
164		N-{3-[({2-[(3-{[3-(dimethylamino)azetidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**164**)	
165		N-{3-[({2-[(3-{[3-(dimethylamino)azetidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**165**), trifluoroacetic acid salt	0.00493

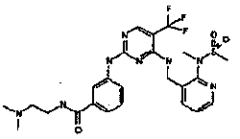
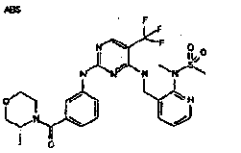
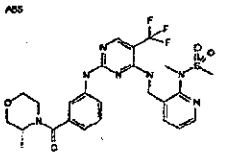
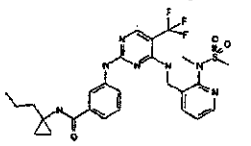
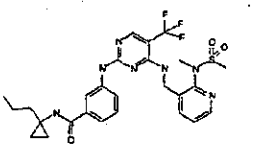
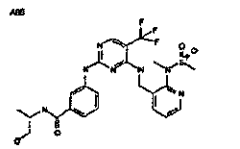
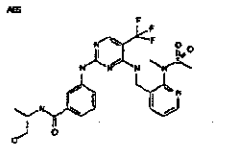
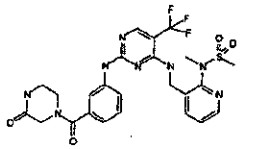
Ex.	Structure	Compound Name	FAK IC50, μM
166		N-[2-(acetylamino)ethyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**166**)	
167		N-[2-(acetylamino)ethyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**167**), trifluoroacetic acid salt	0.00344
168		N-[(1R)-1-(hydroxymethyl)propyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**168**)	
169		N-[(1R)-1-(hydroxymethyl)propyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**169**), trifluoroacetic acid salt	0.00247
170		N-methyl-N-[3-({[2-{[3-(piperidin-1-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**170**)	
171		N-methyl-N-[3-({[2-{[3-(piperidin-1-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**171**), trifluoroacetic acid salt	0.00791
172		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(1-methylpiperidin-4-yl)benzamide (**172**)	
173		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(1-methylpiperidin-4-yl)benzamide (**173**), trifluoroacetic acid salt	0.00096

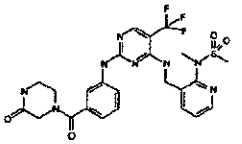
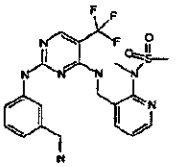
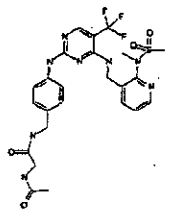
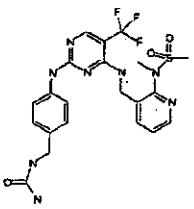
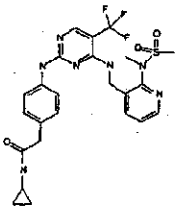
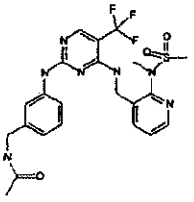
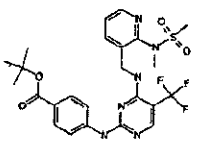
Ex.	Structure	Compound Name	FAK IC50, μM
174		N-{3-[({2-[(3-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**174**)	
175		N-{3-[({2-[(3-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl) pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methyl-methanesulfonamide (**175**), trifluoroacetic acid salt	0.00408
176		N-[3-({[2-({3-[(3,3-difluoropyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**176**)	
177		N-[3-({[2-({3-[(3,3-difluoropyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl) pyrimidin-4-yl]amino} methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**177**), trifluoroacetic acid salt	0.00593
178		N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**178**)	
179		N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**179**), trifluoroacetic acid salt	0.00109
180		N-(3-methoxypropyl)-N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**180**)	

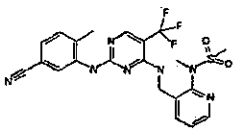
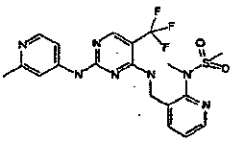
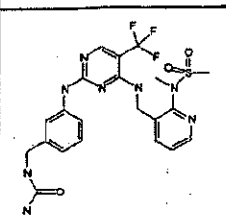
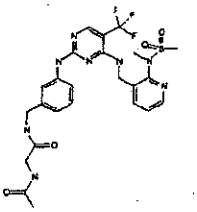
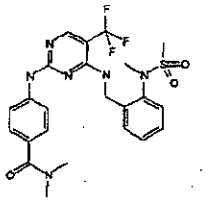
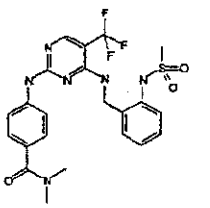
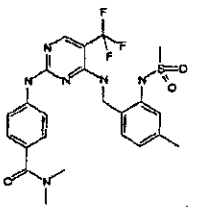
Ex.	Structure	Compound Name	FAK IC50, μM
181		N-(3-methoxypropyl)-N-methyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**181**), trifluoroacetic acid salt	0.00918
182		N-[(1S)-1-(hydroxymethyl)propyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**182**)	
183		N-[(1S)-1-(hydroxymethyl)propyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**183**), trifluoroacetic acid salt	0.00196
184		N-cyclobutyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**184**)	
185		N-cyclobutyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**185**), trifluoroacetic acid salt	0.00217
186		N-cyclohexyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**186**)	
187		N-cyclohexyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**187**), trifluoroacetic acid salt	0.00584
188		N-isopropyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**188**)	

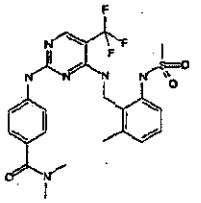
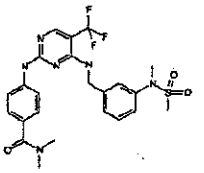
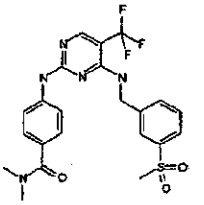
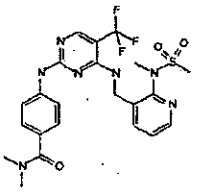
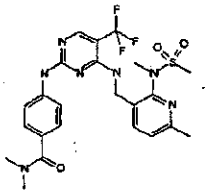
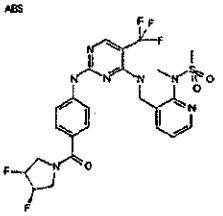
Ex.	Structure	Compound Name	FAK IC50, μM
189		N-isopropyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**189**), trifluoroacetic acid salt	0.0043
190		N-benzyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**190**)	
191		N-benzyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**191**), trifluoroacetic acid salt	0.0055
192		N-(2-hydroxyethyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-propylbenzamide (**192**)	
193		N-(2-hydroxyethyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-propylbenzamide (**193**), trifluoroacetic acid salt	0.0011
194		N-ethyl-N-(2-methoxyethyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**194**)	
195		N-ethyl-N-(2-methoxyethyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**195**), trifluoroacetic acid salt	0.00681
196		N-methyl-N-[3-({[2-({3-[(4-methylpiperidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**196**)	

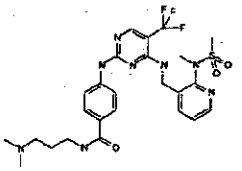
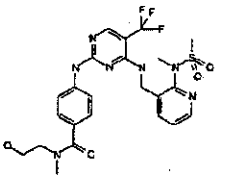
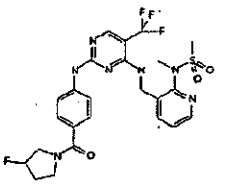
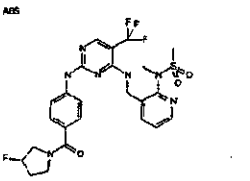
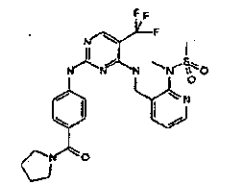
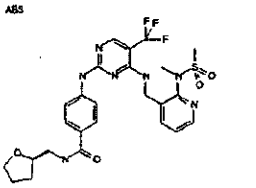
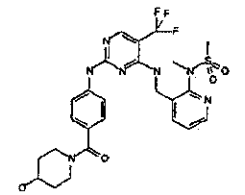
Ex.	Structure	Compound Name	FAK IC50, μM
197		N-methyl-N-[3-({[2-({3-[(4-methylpiperidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**197**), trifluoroacetic acid salt	0.00447
198		N-methyl-N-[3-({[2-({3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**198**)	
199		N-methyl-N-[3-({[2-({3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**199**), trifluoroacetic acid salt	0.00256
200		N-(2-hydroxy-1,1-dimethylethyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**200**)	
201		N-(2-hydroxy-1,1-dimethylethyl)-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**201**), trifluoroacetic acid salt	0.00164
202		N-[1-(hydroxymethyl)propyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**202**)	
203		N-[1-(hydroxymethyl)propyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**203**), trifluoroacetic acid salt	0.00113
204		N-[2-(dimethylamino)ethyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**204**)	

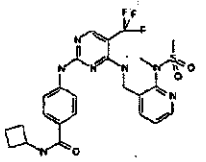
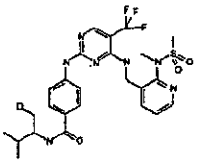
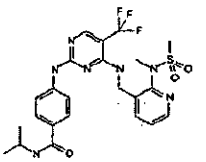
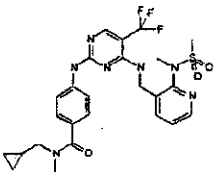
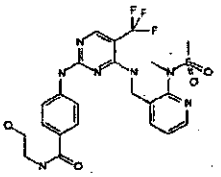
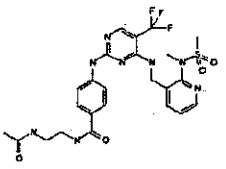
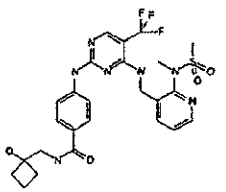
Ex.	Structure	Compound Name	FAK IC50, μM
205		N-[2-(dimethylamino)ethyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**205**), trifluoroacetic acid salt	0.0032
206		N-methyl-N-{3-[({2-[(3-{[(3R)-3-methylmorpholin-4-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**206**)	
207		N-methyl-N-{3-[({2-[(3-{[(3R)-3-methylmorpholin-4-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**207**), trifluoroacetic acid salt	0.00278
208		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(1-propylcyclopropyl)benzamide (**208**)	
209		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(1-propylcyclopropyl)benzamide (**209**), trifluoroacetic acid salt	0.00368
210		N-[(1S)-2-hydroxy-1-methylethyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**210**)	
211		N-[(1S)-2-hydroxy-1-methylethyl]-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**211**), trifluoroacetic acid salt	0.00106
212		N-methyl-N-[3-({[2-({3-[(3-oxopiperazin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**212**)	

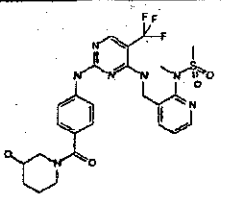
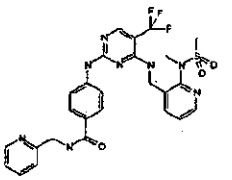
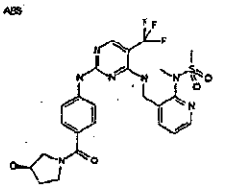
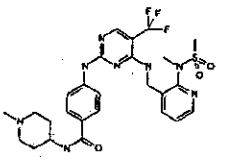
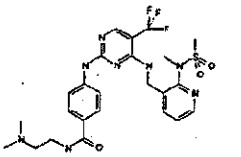
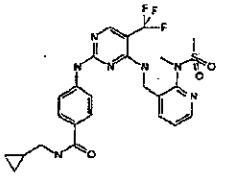
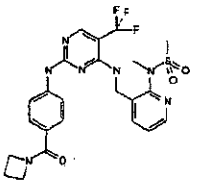
Ex.	Structure	Compound Name	FAK IC50, μM
213		N-methyl-N-[3-({[2-({3-[(3-oxopiperazin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**213**), trifluoroacetic acid salt	0.00288
214		N-[3-({[2-{[3-(aminomethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**214**)	0.0007
215		N~2~-acetyl-N-[4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzyl]glycinamide (**215**)	0.0006
216		N-{3-[({2-[(4-{[(aminocarbonyl)amino]-methyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**216**)	0.0006
217		N-cyclopropyl-2-[4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]acetamide (**217**)	0.0006
218		N-[3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzyl]acetamide (**218**)	0.0006
219		tert-butyl 4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoate (**219**)	0.0006

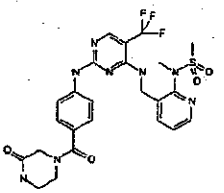
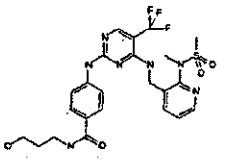
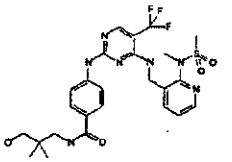
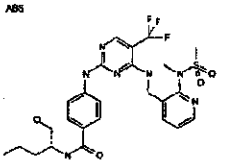
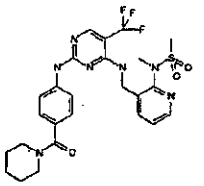
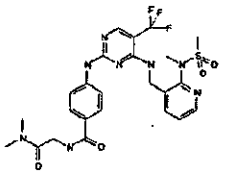
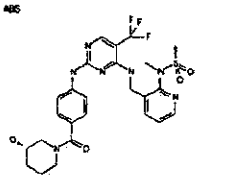
Ex.	Structure	Compound Name	FAK IC50, μM
220		N-{3-[({2-[(5-cyano-2-methylphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**220**)	0.0006
221		N-methyl-N-{3-[({2-[(2-methylpyridin-4-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**221**)	0.188
222		N-{3-[({2-[(3-{[(aminocarbonyl)amino]-methyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide (**222**)	0.0006
223		N-2-acetyl-N-[3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzyl]glycinamide (**223**)	0.0006
224		N,N-dimethyl-4-{[4-({2-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**224**)	0.0006
225		N,N-dimethyl-4-{[4-({2-[(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**225**)	0.00098
226		N,N-dimethyl-4-{[4-({4-methyl-2-[(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**226**)	0.00292

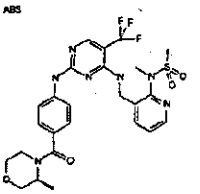
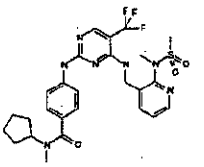
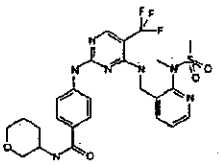
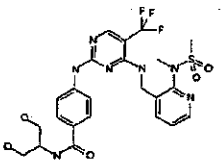
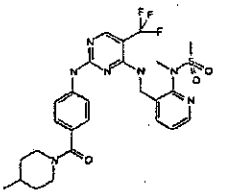
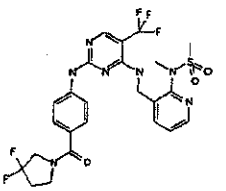
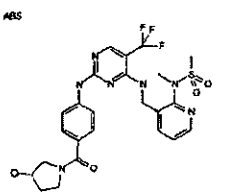
Ex.	Structure	Compound Name	FAK IC50, μM
227		N,N-dimethyl-4-{[4-({2-methyl-6-[(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**227**)	0.00343
228		N,N-dimethyl-4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**228**)	0.00219
229		N,N-dimethyl-4-{[4-{[3-(methylsulfonyl)benzyl]amino}-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**229**)	0.00493
230		N,N-dimethyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**230**)	0.00238
231		N,N-dimethyl-4-({4-[({6-methyl-2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**231**)	0.0006
232		N-{3-[({2-[(4-{[(3R,4R)-3,4-difluoropyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**232**)	0.00262

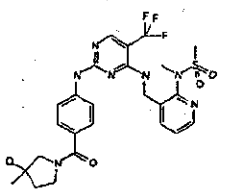
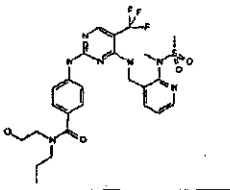
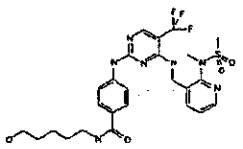
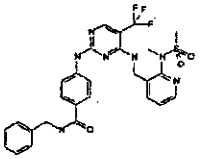
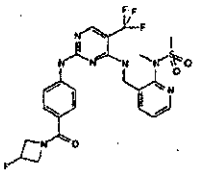
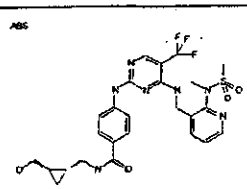
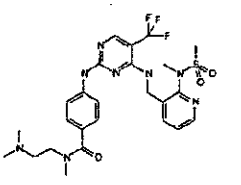
Ex.	Structure	Compound Name	FAK IC50, μM
233		N-[3-(dimethylamino)propyl]-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**233**)	0.00133
234		N-(2-hydroxyethyl)-N-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**234**)	0.00232
235		N-[3-({[2-({4-[(3-fluoropyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**235**)	0.0006
236		N-{3-[({2-[(4-{[(3S)-3-fluoropyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**236**)	0.00141
237		N-methyl-N-[3-({[2-{[4-(pyrrolidin-1-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**237**)	0.00205
238		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-[(2R)-tetrahydrofuran-2-ylmethyl]benzamide (**238**)	0.00125
239		N-[3-({[2-({4-[(4-hydroxypiperidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**239**)	0.0006

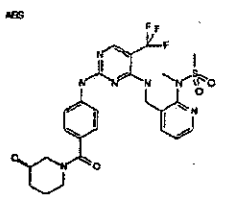
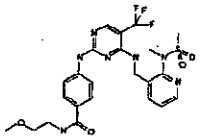
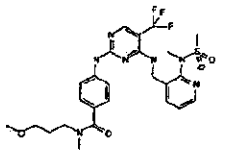
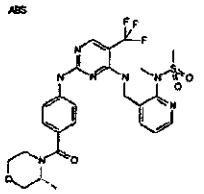
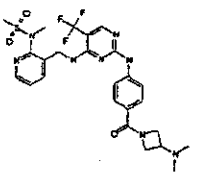
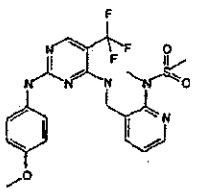
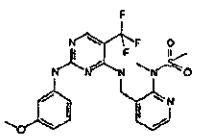
Ex.	Structure	Compound Name	FAK IC50, μM
240		N-cyclobutyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**240**)	0.00069
241		N-[1-(hydroxymethyl)-2-methylpropyl]-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**241**)	0.0006
242		N-isopropyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**242**)	0.001
243		N-(cyclopropylmethyl)-N-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**243**)	0.0021
244		N-(2-hydroxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**244**)	0.00111
245		N-[2-(acetylamino)ethyl]-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**245**)	0.00262
246		N-[(1-hydroxycyclobutyl)methyl]-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**246**)	0.0006

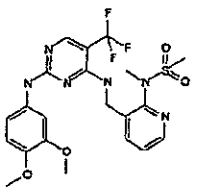
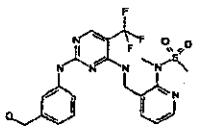
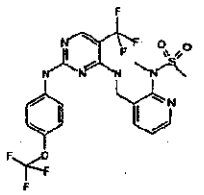
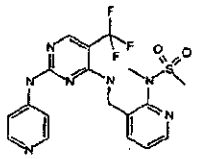
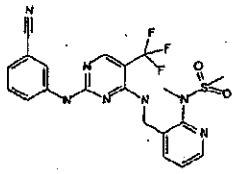
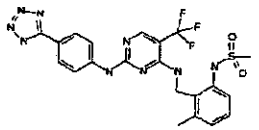
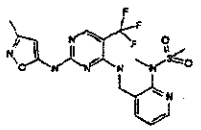
Ex.	Structure	Compound Name	FAK IC50, μM
247		N-[3-({[2-({4-[(3-hydroxypiperidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**247**)	0.00063
248		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(pyridin-2-ylmethyl)benzamide (**248**)	0.00935
249		N-{3-[({2-[(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**249**)	0.00191
250		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(1-methylpiperidin-4-yl)benzamide (**250**)	0.00069
251		N-[2-(dimethylamino)ethyl]-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**251**)	0.00121
252		N-(cyclopropylmethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**252**)	0.00148
253		N-[3-({[2-{[4-(azetidin-1-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**253**)	0.0006

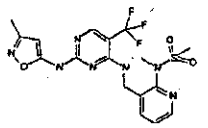
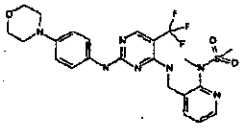
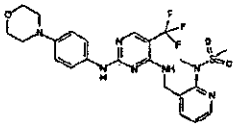
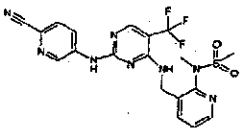
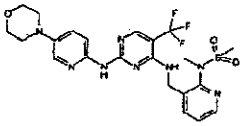
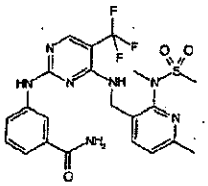
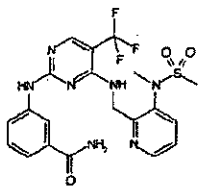
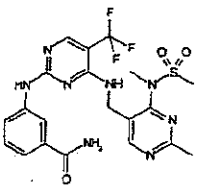
Ex.	Structure	Compound Name	FAK IC50, μM
254		N-methyl-N-[3-({[2-({4-[(3-oxopiperazin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**254**)	0.00133
255		N-(3-hydroxypropyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**255**)	0.00082
256		N-(3-hydroxy-2,2-dimethylpropyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**256**)	0.00157
257		N-[(1R)-1-(hydroxymethyl)butyl]-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**257**)	0.0058
258		N-methyl-N-[3-({[2-{[4-(piperidin-1-ylcarbonyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**258**)	0.00179
259		N-[2-(dimethylamino)-2-oxoethyl]-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**259**)	0.00157
260		N-{3-[({2-[(4-{[(3S)-3-hydroxypiperidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide (**260**)	0.0023

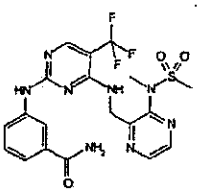
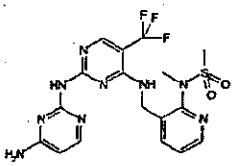
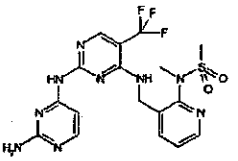
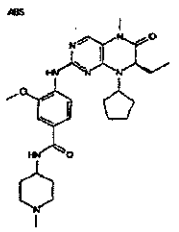
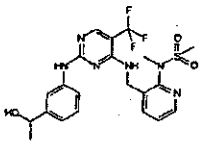
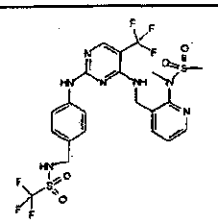
Ex.	Structure	Compound Name	FAK IC50, μM
261		N-methyl-N-{3-[({2-[(4-[[(3S)-3-methylmorpholin-4-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**261**)	0.00113
262		N-cyclopentyl-N-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**262**)	0.0058
263		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-(tetrahydro-2H-pyran-3-yl)benzamide (**263**)	0.00081
264		N-[2-hydroxy-1-(hydroxymethyl)ethyl]-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**264**)	0.0046
265		N-methyl-N-[3-({[2-({4-[(4-methylpiperidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**265**)	0.0006
266		N-[3-({[2-({4-[(3,3-difluoropyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**266**)	0.0006
267		N-{3-[({2-[(4-[[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**267**)	0.00115

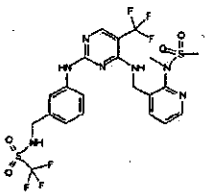
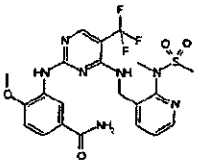
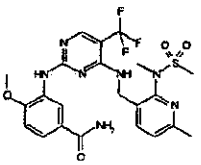
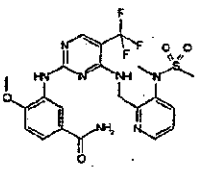
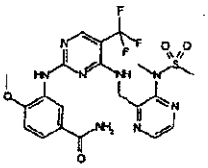
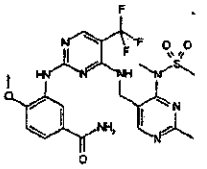
Ex.	Structure	Compound Name	FAK IC50, μM
268		N-[3-({[2-({4-[(3-hydroxy-3-methylpyrrolidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**268**)	0.00262
269		N-(2-hydroxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-propylbenzamide (**269**)	0.00869
270		N-(5-hydroxypentyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**270**)	0.00099
271		N-benzyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**271**)	0.00114
272		N-[3-({[2-({4-[(3-fluoroazetidin-1-yl)carbonyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**272**)	0.00264
273		N-{[(1R,2R)-2-(hydroxymethyl)cyclopropyl]methyl}-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**273**)	0.00269
274		N-[2-(dimethylamino)ethyl]-N-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**274**)	0.00466

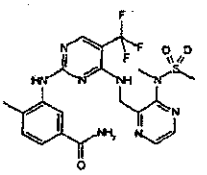
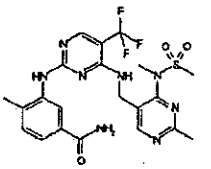
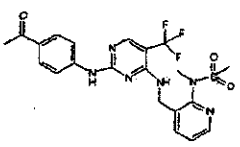
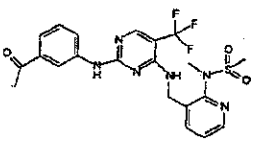
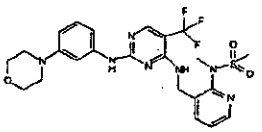
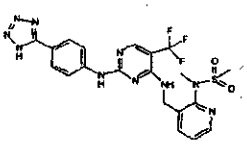
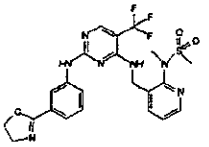
Ex.	Structure	Compound Name	FAK IC50, μM
275		N-{3-[({2-[(4-[[(3R)-3-hydroxypiperidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**275**)	0.00236
276		N-(2-methoxyethyl)-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**276**)	0.0006
277		N-(3-methoxypropyl)-N-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**277**)	0.00236
278		N-methyl-N-{3-[({2-[(4-[[(3R)-3-methylmorpholin-4-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**278**)	0.00664
279		N-{3-[({2-[(4-[[3-(dimethylamino)azetidin-1-yl]carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**279**)	0.00397
280		N-{3-[({2-[(4-methoxyphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**280**)	0.0006
281		N-{3-[({2-[(3-methoxyphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**281**)	0.0006

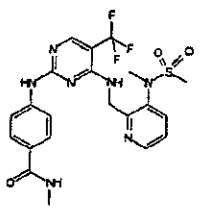
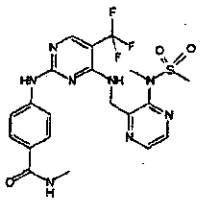
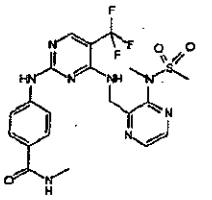
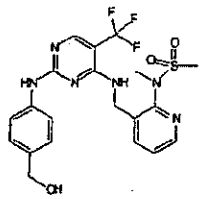
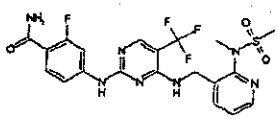
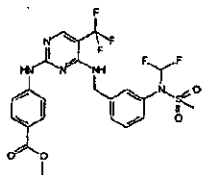
Ex.	Structure	Compound Name	FAK IC50, μM
282		N-{3-[({2-[(3,4-dimethoxyphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**282**)	0.0006
283		N-[3-({[2-{[3-(hydroxymethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**283**)	0.0006
284		N-methyl-N-[3-({[2-{[4-(trifluoromethoxy)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**284**)	0.00183
285		N-methyl-N-[3-({[2-(pyridin-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**285**)	0.00127
286		N-{3-[({2-[(3-cyanophenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide (**286**)	0.00164
287		N-[3-methyl-2-({[2-{[4-(1H-tetrazol-5-yl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide (**287**)	0.00195
288		N-methyl-N-{3-[({2-[(3-methylisoxazol-5-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**288**)	

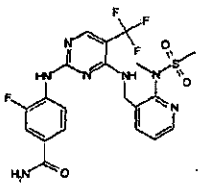
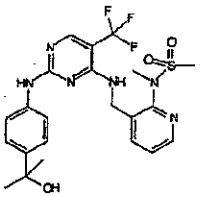
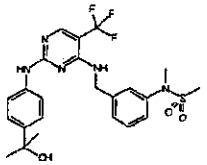
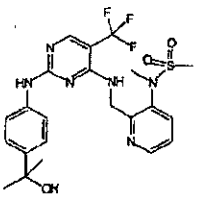
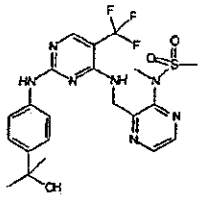
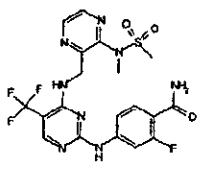
Ex.	Structure	Compound Name	FAK IC50, μM
289		N-methyl-N-{3-[({2-[(3-methylisoxazol-5-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**289**), formic acid salt	0.0182
290		N-methyl-N-{3-[({2-[(4-morpholin-4-ylphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**290**)	
291		N-methyl-N-{3-[({2-[(4-morpholin-4-ylphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**291**), *hydrochloride salt*	<0.000595
292		N-{3-[({2-[(6-cyanopyridin-3-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**292**), trifluoroacetic acid salt	0.0233
293		N-methyl-N-{3-[({2-[(5-morpholin-4-ylpyridin-2-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**293**), trifluoroacetic acid salt	<0.000595 (n=2)
294		3-({4-[({6-methyl-2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**294**)	<0.000595
295		3-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**295**)	0.00133
296		3-({4-[({2-methyl-4-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**296**)	0.00389

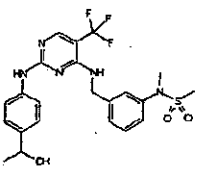
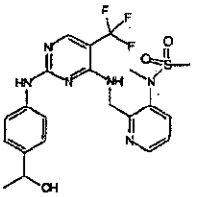
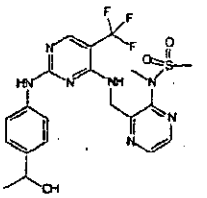
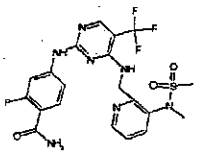
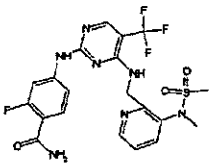
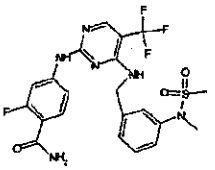
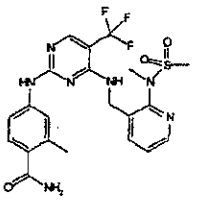
Ex.	Structure	Compound Name	FAK IC50, μM
297		3-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**297**)	0.00226
298		N-{3-[({2-[(4-aminopyrimidin-2-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**298**)	0.0328
299		N-{3-[({2-[(2-aminopyrimidin-4-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**299**)	>0.188
300		4-{[(7R)-8-cyclopentyl-7-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-yl]amino}-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (**300**)	0.121
301		N-[3-({[2-{[3-(1-hydroxyethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**301**)	<0.000595
302		1,1,1-trifluoro-N-[4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzyl]methanesulfonamide (**302**)	0.00100

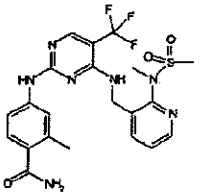
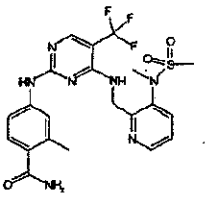
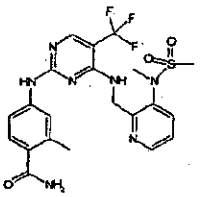
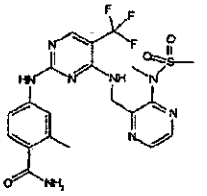
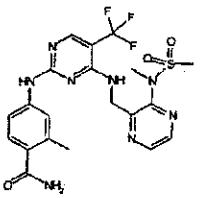
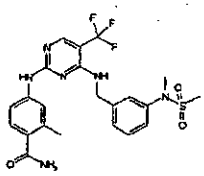
Ex.	Structure	Compound Name	FAK IC50, μM
303		1,1,1-trifluoro-N-[3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzyl]methanesulfonamide (**303**)	0.000727
304		4-methoxy-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**304**)	0.000777
305		4-methoxy-3-({4-[({6-methyl-2-[methyl(methylsulfonyl)-amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**305**)	0.000646
306		4-methoxy-3-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**306**)	0.000696
307		4-methoxy-3-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**307**)	0.00111
308		4-methoxy-3-({4-[({2-methyl-4-[methyl(methylsulfonyl)-amino]pyrimidin-5-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**308**)	0.00350

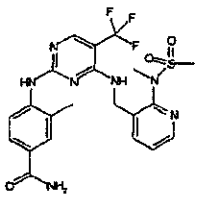
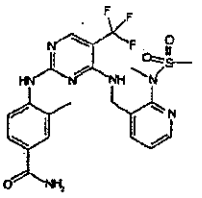
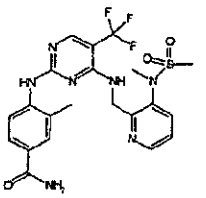
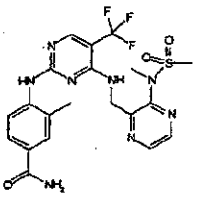
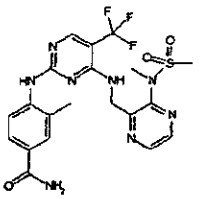
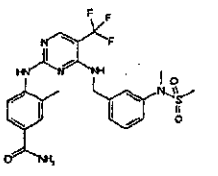
Ex.	Structure	Compound Name	FAK IC50, μM
309		4-methyl-3-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**309**)	0.00351
310		4-methyl-3-({4-[({2-methyl-4-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**310**)	0.00504
311		N-{3-[({2-[(4-acetylphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**311**)	0.00100
312		N-{3-[({2-[(3-acetylphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**312**)	0.00126
313		N-methyl-N-{3-[({2-[(3-morpholin-4-ylphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}methanesulfonamide (**313**)	0.00202
314		N-methyl-N-[3-({[2-{[4-(1H-tetrazol-5-yl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**314**)	<0.000595
315		N-[3-({[2-{[3-(4,5-dihydro-1,3-oxazol-2-yl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**315**)	0.000914

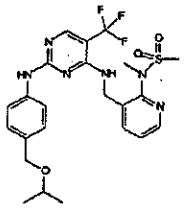
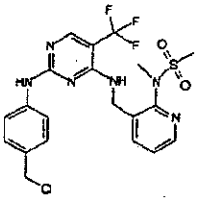
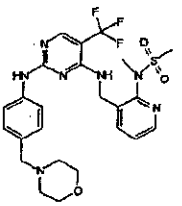
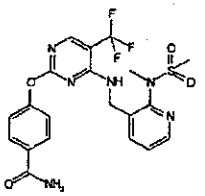
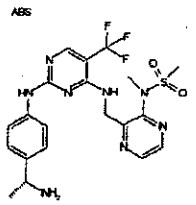
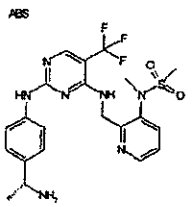
Ex.	Structure	Compound Name	FAK IC50, μM
316		N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**316**)	0.000965
317		N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**317**)	<0.000595
318		N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**318**), hydrochloride salt	0.00179
319		N-[3-({[2-{[4-(hydroxymethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**319**)	<0.000595
320		2-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**320**), formic acid salt	<0.000595
321		4-{[4-({3-[(difluoromethyl)(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzoate (**321**)	0.119 (0.0159-0.883 n=2)

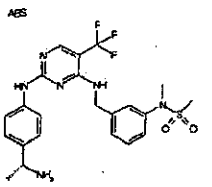
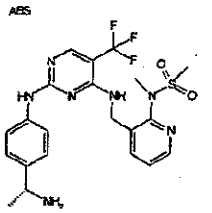
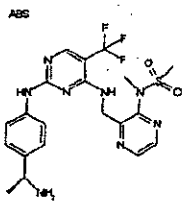
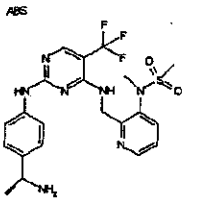
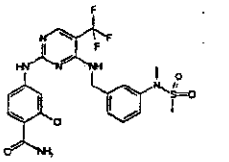
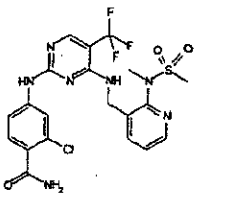
Ex.	Structure	Compound Name	FAK IC50, μM
322		3-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**322**), formic acid salt	<0.000595
323		N-[3-({[2-{[4-(1-hydroxy-1-methylethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**323**)	0.00150
324		N-[3-({[2-{[4-(1-hydroxy-1-methylethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide (**324**)	0.00187
325		N-[2-({[2-{[4-(1-hydroxy-1-methylethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-3-yl]-N-methylmethane-sulfonamide (**325**)	0.00266
326		N-[3-({[2-{[4-(1-hydroxy-1-methylethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyrazin-2-yl]-N-methylmethane-sulfonamide (**326**)	0.00162
327		2-fluoro-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**327**), formic acid salt	0.00169

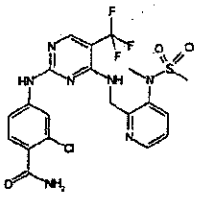
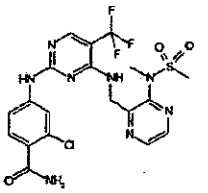
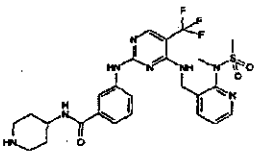
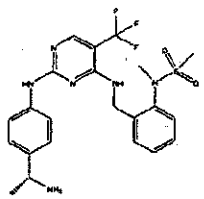
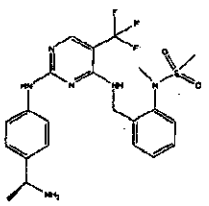
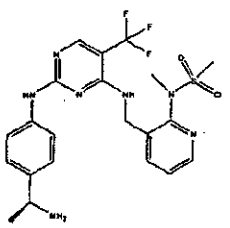
Ex.	Structure	Compound Name	FAK IC50, μM
328		N-[3-({[2-{[4-(1-hydroxyethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide (**328**)	0.000619
329		N-[2-({[2-{[4-(1-hydroxyethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-3-yl]-N-methylmethane-sulfonamide (**329**)	0.000914
330		N-[3-({[2-{[4-(1-hydroxyethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyrazin-2-yl]-N-methylmethane-sulfonamide (**330**)	0.000750
331		2-fluoro-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**331**), hydrochloride salt	0.00177
332		2-fluoro-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**332**), formic acid salt	0.000863
333		2-fluoro-4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**333**)	0.00214
334		2-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**334**)	<0.000595 (n=2)

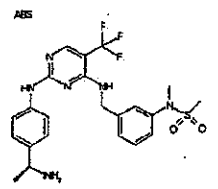
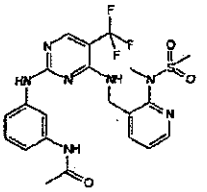
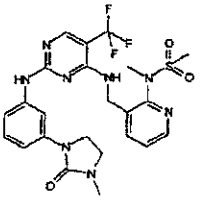
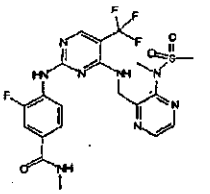
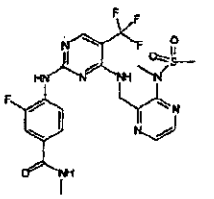
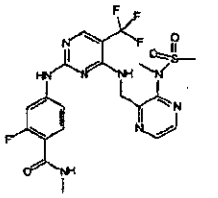
Ex.	Structure	Compound Name	FAK IC50, μM
335		2-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**335**), hydrochloride salt	<0.000595 (n=2)
336		2-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**336**)	<0.000595
337		2-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**337**), hydrochloride salt	<0.000595
338		2-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**338**)	<0.000595
339		2-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**339**), hydrochloride salt	<0.000595
340		2-methyl-4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**340**)	<0.000595

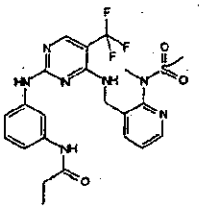
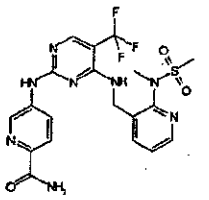
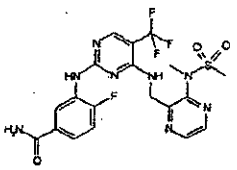
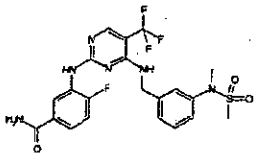
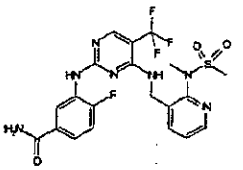
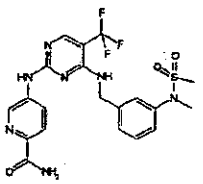
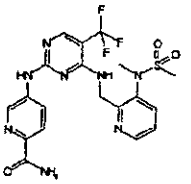
Ex.	Structure	Compound Name	FAK IC50, μM
341		3-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**341**)	<0.000595
342		3-methyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**342**), hydrochloride salt	0.00103
343		3-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**343**)	0.000993
344		3-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**344**)	0.000900
345		3-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**345**), hydrochloride salt	0.000981
346		3-methyl-4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**346**)	0.000886

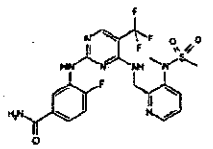
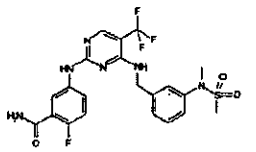
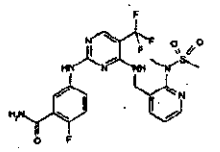
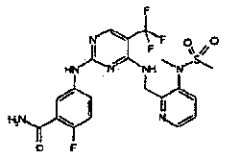
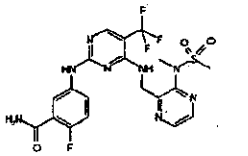
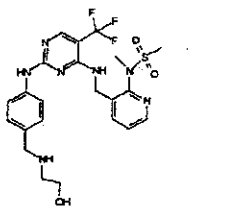
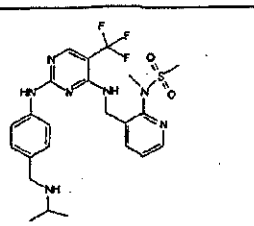
Ex.	Structure	Compound Name	FAK IC50, μM
347		N-[3-({[2-{[4-(isopropoxymethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**347**)	0.00215
348		N-[3-({[2-{[4-(chloromethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**348**)	0.00155
349		N-methyl-N-[3-({[2-{[4-(morpholin-4-ylmethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**349**)	<0.000595
350		4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}oxy)benzamide (**350**)	0.0637
351		N-[3-({[2-({4-[(1R)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyrazin-2-yl]-N-methylmethane-sulfonamide (**351**), hydrochloride salt	0.000616
352		N-[2-({[2-({4-[(1R)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-3-yl]-N-methylmethane-sulfonamide (**352**), hydrochloride salt	<0.000595

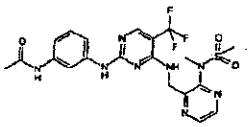
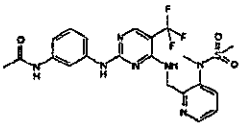
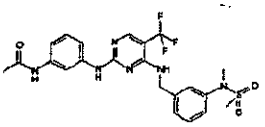
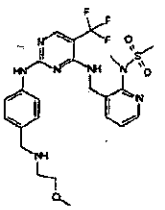
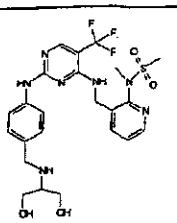
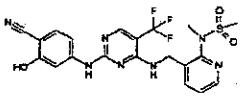
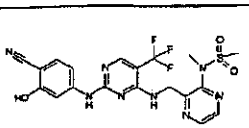
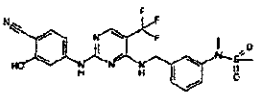
Ex.	Structure	Compound Name	FAK IC50, μM
353		N-[3-({[2-({4-[(1R)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide (**353**), hydrochloride salt	<0.000595
354		N-[3-({[2-({4-[(1R)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**354**), hydrochloride salt	<0.000595
355		N-[3-({[2-({4-[(1S)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyrazin-2-yl]-N-methylmethane-sulfonamide (**355**), hydrochloride salt	<0.000595
356		N-[2-({[2-({4-[(1S)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-3-yl]-N-methylmethane-sulfonamide (**356**), hydrochloride salt	0.000593
357		2-chloro-4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**357**)	0.00147
358		2-chloro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**358**)	<0.000595

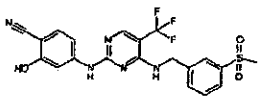
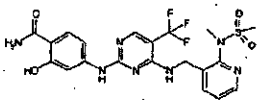
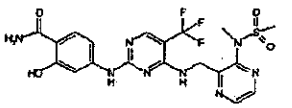
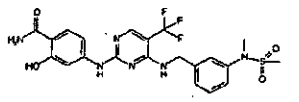
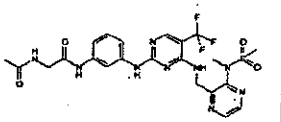
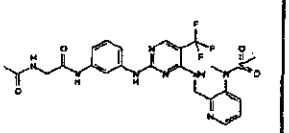
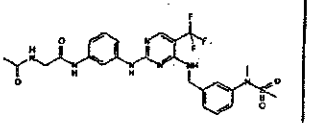
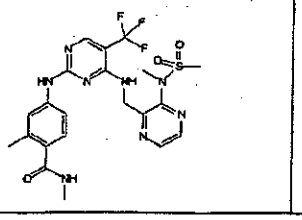
Ex.	Structure	Compound Name	FAK IC50, μM
359		2-chloro-4-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**359**)	<0.000595
360		2-chloro-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**360**)	<0.000595
361		3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)-N-piperidin-4-ylbenzamide (**361**), *hydrochloride salt*	0.00870
362		N-[2-({[2-({4-[(1R)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide (**362**), hydrochloride salt	<0.000595
363		N-[2-({[2-({4-[(1S)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide (**363**), hydrochloride salt	<0.000595
364		N-[3-({[2-({4-[(1S)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**364**), hydrochloride salt	0.000644

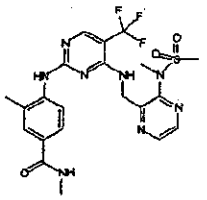
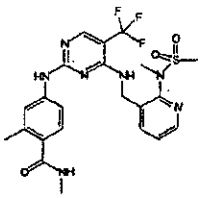
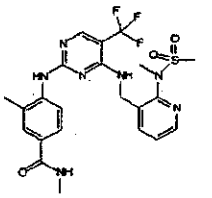
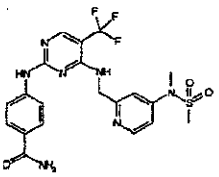
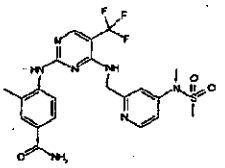
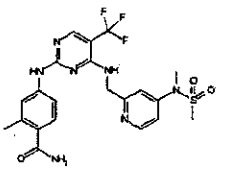
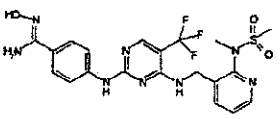
Ex.	Structure	Compound Name	FAK IC50, μM
365		N-[3-({[2-({4-[(1S)-1-aminoethyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]-N-methylmethanesulfonamide (**365**), hydrochloride salt	0.000976
366		N-[3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]acetamide (**366**)	<0.000595
367		N-methyl-N-[3-({[2-{[3-(3-methyl-2-oxoimidazolidin-1-yl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**367**)	0.00164
368		3-fluoro-N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**368**)	<0.000595
369		3-fluoro-N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**369**), hydrochloride salt	0.00149
370		2-fluoro-N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**370**)	0.000600

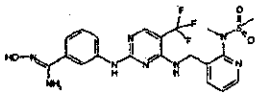
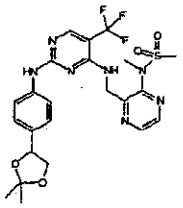
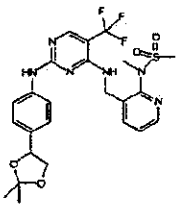
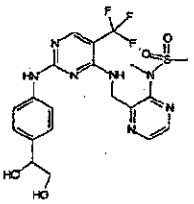
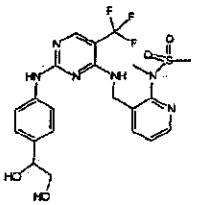
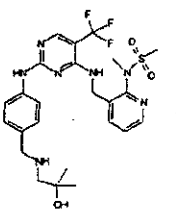
Ex.	Structure	Compound Name	FAK IC50, μM
371		N-[3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]propanamide (**371**)	0.00194
372		5-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)pyridine-2-carboxamide (**372**), formic acid salt	0.00400
373		4-fluoro-3-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**373**)	0.00749
374		4-fluoro-3-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**374**)	0.0155
375		4-fluoro-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**375**)	0.00629
376		5-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}pyridine-2-carboxamide (**376**), formic acid salt	0.00615
377		5-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)pyridine-2-carboxamide (377), formic acid salt	0.0153

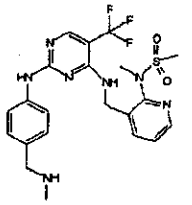
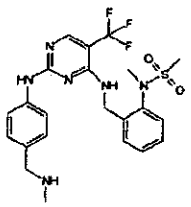
Ex.	Structure	Compound Name	FAK IC50, μM
378		4-fluoro-3-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**378**)	0.00194
379		2-fluoro-5-[[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**379**), hydrochloride salt	0.00478
380		2-fluoro-5-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**380**), hydrochloride salt	0.00160
381		2-fluoro-5-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**381**), hydrochloride salt	0.00455
382		2-fluoro-5-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**382**), hydrochloride salt	0.0107
383		N-{3-[({2-[(4-{[(2-hydroxyethyl)amino]methyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**383**)	<0.000595
384		N-[3-({[2-({4-[(isopropylamino)methyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**384**)	<0.000595

Ex.	Structure	Compound Name	FAK IC50, μM
385		N-[3-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]acetamide (**385**)	0.00144
386		N-[3-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]acetamide (**386**)	0.00165
387		N-(3-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)acetamide (**387**)	0.00295
388		N-{3-[({2-[(4-{[(2-methoxyethyl)amino]methyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**388**)	<0.000595
389		N-[3-({[2-{[4-({[2-hydroxy-1-(hydroxymethyl)ethyl]amino}methyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**389**)	<0.000595
390		N-{3-[({2-[(4-cyano-3-hydroxyphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethane-sulfonamide (**390**)	0.000746
391		N-{3-[({2-[(4-cyano-3-hydroxyphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyrazin-2-yl}-N-methylmethane-sulfonamide (**391**), hydrochloride salt	0.00124
392		N-{3-[({2-[(4-cyano-3-hydroxyphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]phenyl}-N-methylmethanesulfonamide (**392**)	0.00451

Ex.	Structure	Compound Name	FAK IC50, μM
393		2-hydroxy-4-{[4-{[3-(methylsulfonyl)benzyl]amino}-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzonitrile (**393**)	0.00741
394		2-hydroxy-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**394**), formic acid salt	<0.000595
395		2-hydroxy-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**395**), formic acid salt	0.000849
396		2-hydroxy-4-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}benzamide (**396**), formic acid salt	0.00313
397		N-2-acetyl-N-[3-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]glycinamide (**397**)	0.00151
398		N~2~-acetyl-N-[3-({4-[({3-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl]glycinamide (**398**)	0.00218
399		N-2-acetyl-N-(3-{[4-({3-[methyl(methylsulfonyl)amino]benzyl}amino)-5-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)glycinamide (**399**)	0.00557
400		N,2-dimethyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**400**), hydrochloride salt	0.000660

Ex.	Structure	Compound Name	FAK IC50, μM
401		N,3-dimethyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**401**), hydrochloride salt	0.00117
402		N,2-dimethyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**402**), hydrochloride salt	<0.000595
403		N,3-dimethyl-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**403**), hydrochloride salt	0.00109
404		4-({4-[({4-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**404**), formic acid salt	0.00207
405		3-methyl-4-({4-[({4-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**405**), formic acid salt	0.0173
406		2-methyl-4-({4-[({4-[methyl(methylsulfonyl)amino]pyridin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide (**406**), formic acid salt	0.000784
407		N'-hydroxy-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzenecarboximidamide (**407**), formic acid salt	<0.000595

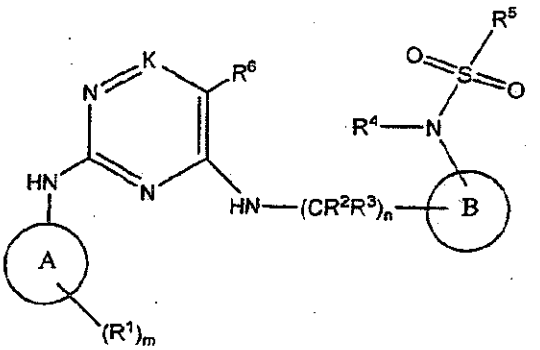
Ex.	Structure	Compound Name	FAK IC50, μM
408		N'-hydroxy-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzenecarboxiimidamide (**408**), formic acid salt	0.00229
409		N-[3-({[2-{[4-(2,2-dimethyl-1,3-dioxolan-4-yl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyrazin-2-yl]-N-methylmethane-sulfonamide (**409**)	0.00475
410		N-[3-({[2-{[4-(2,2-dimethyl-1,3-dioxolan-4-yl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**410**)	0.00119
411		N-[3-({[2-{[4-(1,2-dihydroxyethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyrazin-2-yl]-N-methylmethane-sulfonamide (**411**), hydrochloride salt	0.000941
412		N-[3-({[2-{[4-(1,2-dihydroxyethyl)phenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]-N-methylmethane-sulfonamide (**412**), hydrochloride salt	<0.000595
413		N-{3-[({2-[(4-{[(2-hydroxy-2-methylpropyl)amino]methyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)methyl]pyridin-2-yl}-N-methylmethanesulfonamide (**413**)	<0.000595

Ex.	Structure	Compound Name	FAK IC50, μM
414		N-methyl-N-[3-({[2-({4-[(methylamino)methyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)pyridin-2-yl]methanesulfonamide (**414**), hydrochloride salt	<0.000595
415		N-methyl-N-[2-({[2-({4-[(methylamino)methyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]amino}methyl)phenyl]methanesulfonamide (**415**), hydrochloride salt	<0.000595

Claims

We claim:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof; wherein

A is a ring moiety selected from the group consisting of a:

(a) 4- to 7-membered carbocyclyl,

(b) 4- to 7-membered heterocyclyl,

(c) phenyl, and

(d) 5- to 6-membered heteroaryl ring,

wherein each of said 4- to 7-membered carbocyclyl and 4- to 7-membered heterocyclyl of said A group may optionally contain one or two olefinic bonds; and wherein one or two carbon ring atoms in each of said 4- to 7-membered carbocyclyl and 4- to 7-membered heterocyclic of said A group may independently optionally be replaced with one or two moieties independently selected from the group consisting of -C(O)-, -C(S)- and -C(=NR^4)-;

B is phenyl or a 5- to 6-membered heteroaryl;

K is CH, C(NH_2) or N;

each R^1 is independently selected from the group consisting of -H, halo, -CF_3, -CN, -NO_2, -NR^7R^8, -$NR^7C(NR^7R^8)(=CR^9)$, -$CR^7(NR^7R^8)(=NR^7)$, -$NR^7C(NR^7R^8)(=NR^7)$, -$NR^7C(O)R^9$, -$C(O)NR^7R^8$, -$C(O)R^9$, -$C(O)C(O)R^9$, -$C(O)OR^{10}$, -$OC(O)R^9$, -OR^{10}, -$OC(O)OR^{10}$, -$S(O)_jR^{11}$, -$S(O)(=NR^7)R^8$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl,

-(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^1 is optionally independently substituted by one to three R^{12} groups;

R^2 and R^3 are each independently selected from the group consisting of –H, -halo, -OR^{10}, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^2 and R^3 is optionally substituted by one to three R^{12} groups;

R^4 and R^5 are each independently selected from the group consisting of –H, -NR^7R^8, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_{10})aryl and -(C_1-C_9)heteroaryl moieties of said R^4 and R^5 is optionally substituted by one to three R^{12} groups;

R^6 is selected from the group consisting of –halo, -NR^7R^8, -OR^{10}, -$C(O)R^9$, -CO_2R^{10}, -$CONR^7R^8$, -$S(O)_jR^{11}$, -$NR^7CONR^7R^8$, and -$NR^8SO_2R^{11}$, -NO_2, -CN, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_2-C_6)perfluorinated alkyl, -(C_2-C_6)perfluorinated alkenyl, -(C_3-C_6)perfluorinated alkynyl, -(C_3-C_7)cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, -(C_1-C_9)heteroaryl, -(C_6-C_{10})perfluorinated aryl, and -(C_1-C_9)perfluorinated heteroaryl; and wherein each of said -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_1-C_9)heterocyclyl, -(C_1-C_{10})heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl moieties of said R^6 is optionally substituted by one to three R^{12} groups;

R^7 and R^8 are each independently selected from the group consisting of -H, $-OR^{10}$, $-S(O)_jR^{11}$, $-NO_2$, $-(C_1-C_8)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^7 and R^8 is optionally substituted by one to three R^{12} groups;

each R^9 is independently selected from the group consisting of -H, -halo, $-NR^{13}R^{14}$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^9 is optionally substituted by one to three R^{12} groups;

each R^{10} is independently selected from the group consisting of -H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^{10} is optionally substituted by one to three R^{12} groups;

each R^{11} is independently selected from the group consisting of -H, $-NR^{13}R^{14}$, $-C(O)R^{13}$, $-CF_3$, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_6-C_{10})$bicycloalkyl, $-(C_6-C_{10})$bicycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, $-(C_4-C_9)$heterocycloalkenyl, $-(C_6-C_9)$heterobicycloalkyl, $-(C_6-C_9)$heterobicycloalkenyl $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$heteroaryl; and wherein each of the foregoing $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_2-C_9)$heterocycloalkyl, (C_4-C_9)heterocycloalkenyl, $-(C_6-C_{10})$aryl and $-(C_1-C_9)$heteroaryl moieties of said R^{11} is optionally substituted by one to three R^{12} groups;

each R^{12} is independently selected from the group consisting of -H, -OR^{13}, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$OC(O)OR^{13}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, -$NR^{13}C(NR^{13}R^{14})(=NR^{13})$, -$NR^{13}C(NR^{13}R^{14})(=N\text{-}C(O)R^{13})$, -$NR^{13}C(O)R^{14}$, -$NR^{13}S(O)_jR^{13}$, -$S(O)_jR^{13}$, -$CF_3$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_6$-$C_{10}$)bicycloalkyl, -($C_6$-$C_{10}$)bicycloalkenyl, -($C_2$-$C_9$)heterocycloalkyl, -($C_4$-$C_9$)heterocycloalkenyl, -($C_6$-$C_9$)heterobicycloalkyl, -($C_6$-$C_9$)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{12} is optionally independently substituted by *one to three groups selected from the group consisting of* -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -$C(O)R^{15}$, -$C(O)NR^{15}R^{16}$, -$S(O)_jR^{15}$, and -$S(O)_jNR^{15}R^{16}$, -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{13} and R^{14} are each independently selected from the group consisting of –H, -$NR^{15}C(O)R^{16}$, -CF_3, -CN, -$S(O)_jR^{15}$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said R^{13} and R^{14} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

R^{15} and R^{16} are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-

C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl, -(C_6-C_9)heterobicycloalkenyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl of said $R^{15}$and R^{16} is optionally independently substituted by one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$;

wherein one or two carbon ring atoms in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkenyl in said R^1-R^{14} groups may optionally and independently be replaced with -C(O)- or -C(S)-;

wherein two groups attached to the same tetravalent carbon atom in each of the aforementioned -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_6-C_{10})bicycloalkyl, -(C_6-C_{10})bicycloalkenyl, -(C_2-C_9)heterocycloalkyl, -(C_4-C_9)heterocycloalkenyl, -(C_6-C_9)heterobicycloalkyl and -(C_6-C_9)heterobicycloalkeny of said R^1 to R^{14} groups may optionally join to form a ring system selected from the group consisting of a -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl; and wherein

j is an integer from 0 to 2;

n is an integer from 1 to 3; and

m is an integer from 0 to 3.

2. The compound of claim 1 wherein A is a phenyl.

3. The compound of claim 1 wherein A is a 5- to 6-membered heteroaryl.

4. The compound of any one of the preceding claims wherein each R^1 is independently selected from the group consisting of -H, halo, -CF_3, -CN, -NO_2, -NR^7R^8, -$NR^7C(NR^7R^8)(=CR^9)$, -$CR^7(NR^7R^8)(=NR^7)$, -$NR^7C(NR^7R^8)(=NR^7)$, -$NR^7C(O)R^9$, -$C(O)NR^7R^8$, -$C(O)R^9$, -$C(O)C(O)R^9$, -$C(O)OR^{10}$, -$OC(O)R^9$, -OR^{10}, -$OC(O)OR^{10}$, -$S(O)_jR^{11}$, and -$S(O)(=NR^7)R^8$.

5. The compound of any one of claims 1 to 4, wherein R^1 is -$C(O)R^9$.

6. The compound of claim 5 wherein R^1 is -$C(O)R^9$ and R^9 is selected from the group consisting of –$NR^{13}R^{14}$, -(C_1-C_6)alkyl and -(C_3-C_{10})cycloalkyl; wherein each of said -(C_1-C_6)alkyl, and -(C_3-C_{10})cycloalkyl of said R^9 group is optionally substituted by one to three R^{12} groups; and wherein two groups attached to the same tetravalent carbon atom of said -(C_1-C_6)alkyl and -(C_3-C_{10})cycloalkyl of said R^9 may optionally join to form a ring

system selected from the group consisting of a -(C_3-C_{10})cycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_2-C_9)heterocycloalkyl, and -(C_4-C_9)heterocycloalkenyl.

7. The compound of claim 6 wherein R^1 is -C(O)R^9 and R^9 is -$NR^{13}R^{14}$.

8. The compound of claim 7 wherein R^1 is -C(O)R^9, R^9 is -$NR^{13}R^{14}$, and R^{13} and R^{14} are each independently selected from the group consisting of –H and -(C_1-C_6)alkyl; and wherein said -(C_1-C_6)alkyl of said R^{13} and R^{14} groups is optionally independently substituted with one to three groups selected from the group consisting of -halo, -CF_3, -CN, -NO_2, -OH, -O((C_1-C_6)alkyl), -C(O)((C_1-C_6)alkyl), -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocycloalkyl, -SH, -S((C_1-C_6)alkyl), -NH_2, -NH((C_1-C_6)alkyl) and -N((C_1-C_6)alkyl)$_2$.

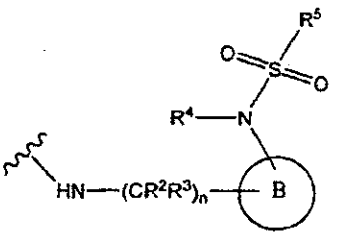
9. The compound of any one of the preceding claims wherein R^2 and R^3 are each independently selected from the group consisting of –H, -halo, and -OR^{10}.

10. The compound of any one of claims 1 to 8 wherein R^2 and R^3 are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl moieties of said R^2 and R^3 is optionally independently substituted by one to three R^{12} groups.

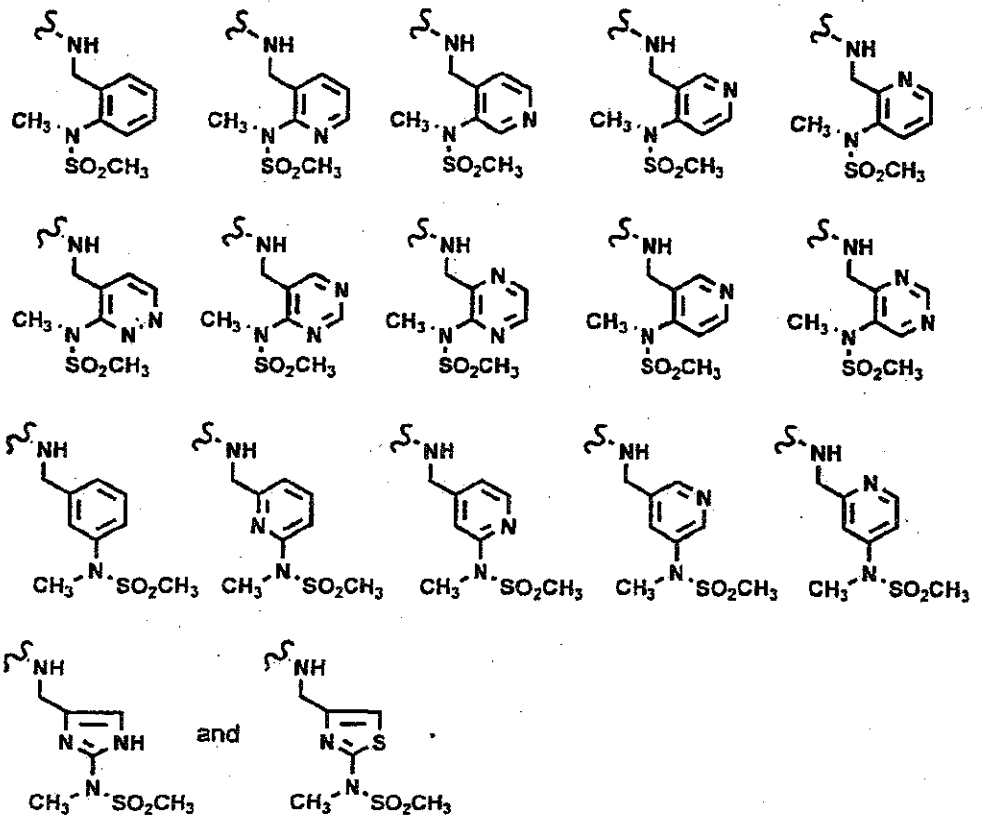
11. The compound of any one of the preceding claims wherein R^4 and R^5 are each independently selected from the group consisting of –H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl; and wherein each of the foregoing -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl moieties of said R^4 and R^5 is optionally independently substituted by one to three R^{12} groups.

12. The compound of any one of the preceding claims wherein R^6 is -CF_3, K is CH, m is 1, and n is 1.

13. The compound of claim 1 wherein the moiety



represents a moiety selected from the group consisting of:



14. A compound of claim 1 which is selected from the group consisting of (R)-N-(3-((2-(4-(1-aminoethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide;

N-(3-((2-(4-(aminomethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide;

N-[4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzyl]acetamide;

N-(3-((2-(4-(hydroxymethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide; and

N-(3-((2-(4-(chloromethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide; or a pharmaceutically acceptable salt thereof.

15. A compound of claim 1 which is selected from the group consisting of N-(3-((2-(4-((1,3-dihydroxypropan-2-ylamino)methyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethane-sulfonamide; or a pharmaceutically acceptable salt thereof.

tert-butyl 3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoate;

3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzoic acid;

N-cyclopropyl-3-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; and

N-(3-((2-(4-(1-hydroxyethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide; or a pharmaceutically acceptable salt thereof.

16. A compound of claim 1 which is selected from the group consisting of

2-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide;

3-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; and

N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide; or a pharmaceutically acceptable salt thereof.

17. A compound of claim 1 which is selected from the group consisting of

2-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide formate; 3-fluoro-4-({4-[({2-[methyl(methylsulfonyl)amino]pyridin-3-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide formate; and

N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride.

18. Use of an amount of compound of any one of claims 1 to 17 that is effective in treating cancer in the manufacture of a medicament for the treatment of cancer.

19. The use according to claim 18 wherein said cancer is selected from the group consisting of lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer

of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.

20. A pharmaceutical composition comprising a compound of any one of claims 1 to 17 and a pharmaceutically acceptable carrier.

21. A compound which is N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a compound of claim 21 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

23. A compound which is N-methyl-4-({4-[({3-[methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride.

24. A pharmaceutical composition comprising a compound of claim 23 and a pharmaceutically acceptable carrier.