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(54) Title: THIOPYRIMIDINE-BASED COMPOUNDS AND USES THEREOF

(57) Abstract: The present invention relates to thiopyrimidine-based compounds that are inhibitors of protein kinases including JAK kinases. In particular, the compounds are selective for JAKl, JAK2 or JAK3 kinases and combinations thereof such as JAKl and JAK2. The kinase inhibitors can be used in the treatment of kinase associated diseases such as immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases and vascular diseases.

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THIOPYRIMIDINE-BASED COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to thiopyrimidine-based compounds that are inhibitors of protein kinases including JAK kinases. In particular, the compounds are selective for JAKl, JAK2 or JAK3 kinases and combinations thereof such as JAKl and JAK2. The kinase inhibitors can be used in the treatment of kinase associated diseases such as immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases; and vascular diseases.

BACKGROUND OF THE INVENTION

JAKs are kinases which phosphorylate a group of proteins called Signal Transduction and Activators of Transcription or STATs. When phosphorylated, STATs dimerize, translocate to the nucleus and activate expression of genes which lead to, amongst other things, cellular proliferation such as proliferation of endothelial cells and smooth muscle cells, and cause hypertrophy of cardiac myocytes.

A review of the JAK/STAT literature offers strong support to the hypothesis that this pathway is important for the recruitment and marshalling of the host immune response to environmental insults, such as viral and bacterial infection. Information accumulated from gene knock-out experiments have underlined the importance of members of the JAK family to the intracellular signalling triggered by a number of important immune regulatory cytokines. The therapeutic possibilities stemming from inhibition (or enhancement) of the JAK/STAT pathway are thus in the sphere of immune modulation, and as such are likely to be promising drugs for the treatment of a range of pathologies in this area. In addition inhibitors of JAKs could be used for immunological and inflammatory diseases including organ transplants, asthma and chronic obstructive pulmonary disease (COPD) as well as autoimmune diseases such as systemic lupus erythematosus, mixed connective tissue disease, scleroderma, autoimmune vasculitides, multiple sclerosis, rheumatoid arthritis, Crohns disease, Type I diabetes and autoimmune thyroid disorders.

The central role played by the JAK family of protein tyrosine kinases in the cytokine dependent regulation of both proliferation and end function of several important cell types indicates that agents capable of inhibiting the JAK kinases are useful in the prevention and chemotherapeutic treatment of disease states dependent on these enzymes. Potent and specific inhibitors of each of the currently known four JAK

family members will provide a means of inhibiting the action of the cytokines that drive immunological and inflammatory diseases, such as those discussed above. Additionally, treatment of hyperproliferative disorders such as cancers including multiple myeloma; prostate, breast and lung cancer; Hodgkin's Lymphoma; B-cell Chronic Lymphocytic Leukemia; metastatic melanoma; glioma; and hepatoma, by JAK inhibitors is indicated. Additionally the use of JAK kinase inhibitors for the treatment of viral diseases and metabolic diseases is indicated.

Potent inhibitors of JAK2, in addition to the above, will also be useful in vascular disease such as hypertension, hypertrophy, cardiac ischemia, heart failure (including systolic heart failure and diastolic heart failure), migraine and related cerebrovascular disorders, stroke, Raynaud's phenomenon, POEMS syndrome, Prinzmetal's angina, vasculitides, such as Takayasu's arteritis and Wegener's granulomatosis, peripheral arterial disease, heart disease and pulmonary arterial hypertension. JAK2 inhibitors will also be useful in myeloproliferatve disorders (MPD) such as polycythemia rubra vera (PCV).

Potent and specific inhibitors of both JAKl and JAK2 will be useful in the treatment of cancers including multiple myeloma; prostate, breast and lung cancer; Hodgkin's Lymphoma; B-cell Chronic Lymphocytic Leukemia; metastatic melanoma; glioma; and hepatoma.

Potent and specific inhibitors of JAK3 will be useful as immunosuppressive agents for, amongst others, organ transplants, and immunological and inflammatory diseases such as asthma and chronic obstructive pulmonary disease as well as autoimmune diseases such as systemic lupus erythematosus, mixed connective tissue disease, scleroderma, autoimmune vasculitides, multiple sclerosis, rheumatoid arthritis, Crohn's disease, Type I diabetes and complications from diabetes, metabolic diseases, and other indications where immunosuppression may be desirable. Furthermore specific inhibitors of JAK3 may find application for therapeutic treatments for proliferative diseases such as leukaemia and lymphoma where JAK3 is hyperactivated.

Although the other members of the JAK family are expressed by essentially all tissues, JAK3 expression appears to be limited to hematopoetic cells. This is consistent with its essential role in signalling through the receptors for IL-2, 1L4, IL-7, IL-9 and IL- 15 by non-covalent association of JAK3 with the gamma chain common to these multichain receptors. Males with X-linked severe combined immunodeficiency (XSCID) have defects in the common cytokine receptor gamma chain (gamma c) gene that encodes a shared, essential component of the receptors of interleukin-2 (IL-2), IL-4, IL-7, IL-9, and IL-1 5. An XSCID syndrome in which patients with either mutated or

severely reduced levels of JAK3 protein has been identified, suggesting that immunosuppression should result from blocking signalling through the JAK3 pathway. Gene Knock out studies in mice have suggested that JAK3 not only plays a critical role in B and T lymphocyte maturation, but that JAK3 is constitutively required to maintain T cell function. Taken together with the biochemical evidence for the involvement of JAK3 in signalling events downstream of the IL-2 and IL-4 receptor, these human and mouse mutation studies suggest that modulation of immune activity through the inhibition of JAK3 could prove useful in the treatment of T- cell and B-cell proliferative disorders such as transplant rejection and autoimmune diseases.

Prolonged immunomodulation through inhibition of JAK3 signalling should have great therapeutic potential for chronic diseases as long as JAK3 inhibition was achieved selectively and not accompanied by inhibition of other kinase-dependent signalling processes. In particular, the high degree of sequence identity held in common by members of the JAK family of kinases raises the possibility that a compound which inhibits JAK3 would also inhibit other members of the family with detrimental long term consequences. For example, prolonged inhibition of JAK2 is likely to lead to erythropenia and thrombocytopenia, since the receptors for both erythropoietin and thrombopoietin use only JAK2 for intracellular transmission of signals.

Compounds of the present invention may also be useful in targeting other kinases of therapeutic relevance, such as the Aurora kinases. The Aurora family of serine/threonine protein kinases are critical for the proper regulation of mitosis. Mammals express three Aurora kinase paralogs, and at least two Aurora kinases (Aurora A and B) are commonly overexpressed in human tumours including breast, lung, colon, ovarian, and pancreatic cancers. The Aurora A gene is amplified in many tumours, indicating that overexpression of Aurora A may confer a selective advantage for the growth of these tumours. Overexpression of Aurora B has also been reported to produce multi-nuclearity and induce aggressive metastasis, suggestion that the overexpression of Aurora kinase B has multiple functions in cancer development. Recent clinical experience and subsequent approvals of kinase inhibitors such as Imatinib, Gefitinib and Erlotinib illustrate that this class of enzymes will be useful for anticancer drug development. Aurora A itself has been identified as a particularly attractive drug target through observations that it can act as an oncogene and transform cells when ectopically expressed. VX-680, a potent inhibitor of Aurora A and B kinases, has been shown to suppress tumour growth in vivo. These findings highlight the desirability of identifying Aurora kinase inhibitors for use in cancer treatment.

Other kinases which may be useful therapeutic targets include CK.2, TBKl, NEK9, LCK , ACKl, p38 kinase, FAK, CAK, CDK4, GSK-3, AbI, PDGF-R, PLKl, PLK2, PLK3, PYK2, c-Kit, NPM-ALK, Flt-3, c-Met, KDR, EGFR, TIE-2, VEGFR-2, VEGFR-3, FMS, HCK, BIk, Bmx, BTK, FIt-I and Flt-4.

Although the inhibition of various types of protein kinases, targeting a range of disease states, is clearly beneficial, it has been to date demonstrated that the identification of a compound which is selective for a protein kinase of interest, and has good "drug like" properties such as high oral bioavailability, is a challenging goal. In addition, it is well established that the predictability of inhibition, or selectivity, in the development of kinase inhibitors is quite low, regardless of the level sequence similarity between the enzymes being targeted.

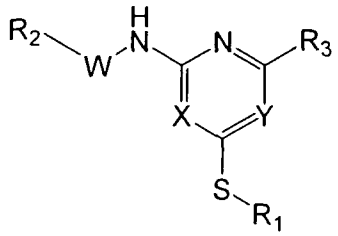
The challenges in developing a therapeutically appropriate JAKl, JAK2 or JAK3 inhibitors or combinations thereof for use in treatment of kinase associated diseases such as immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases; and vascular diseases, include designing a compound with appropriate specificity which also has good drug likeness.

There is therefore a continuing need to design and/or identify compounds which specifically inhibit the JAK family of kinases, and particularly compounds which may preferentially inhibit one or more of the JAK kinases relative to the other JAK kinases. There is a need for such compounds for the treatment of a range of disease states.

SUMMARY OF THE INVENTION

The present inventors have found that a group of thiopyrimidine-based compounds (and analogues thereof such as thiopyridines and thiotriazines), which may include an alkylating group such as a Michael acceptor, are inhibitors of the enzyme Janus Kinase 3.

Accordingly, in a first aspect, the present invention provides a compound of the general formula I:



I

or salts, isomers and/or prodrugs thereof, wherein:

X and Y are independently selected from N and CR_3;

each R_3 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxy!, halogen, nitro, substituted or unsubstituted amino, cyano, nitro, trifluoromethyi, methoxy, trifluoromethoxy, aryl and substituted or unsubstituted 5 or 6 membered heterocyclyl containing I to 2 N atoms;

Rι is selected from hydrogen, C_{1-6}alkyl, C^alkylCN, C_{3-8}cycloalkyl, C_{1-6}alkylenecycloalkyl, aryl, C_{1-6}alkylenearyl, heterocyclyl and C_{1-6}alkyleneheterocyclyl, wherein C_{1-6}alkyl, C_{3-8}cycloalkyl, heterocyclyl and aryl may be optionally substituted with 1 to 3 substituents selected from R or R_9;

R_9 is independently selected from halogen, substituted or unsubstituted C_{1-6}alkyl, OH, (O), OCN, substituted or unsubstituted OC_{1-6}alkyl, CN, CF_3, CF_2CN, SCN, $SO_2NR_5R_6$, SR_7, CHO, CO_2R_7, COR^7, $CONR_5R_6$, $CONR_5R_7$, NR_5COR_7, NO_2, NR_5R_6, NR_5CN, $CH(CN)NR_5R_6$, $NR_5SO_2R_7$, $COCF_3$, $COCH_2F$, NR_5COCOR_7, NR_5COOR_7, $NR_5CONR_6R_7$, heterocyclyl and COheterocyclyl, wherein each heterocyclyl may be optionally substituted with 1 to 4 substituents selected from NH_2, CN, OH, CO_2R_7, CH_2CN and 5 membered N-containing heterocyclyl;

R is C_{1-6}alkyleneR_9, OC_{1-6}alkyleneR_9 (except when R_9 is NR_5R_6 or OC_{1-6}alkyl, then R is OC_{2-6}alkyleneR_9); or

R_9 and R together with the groups to which they are attached form a substituted or unsubstituted 5 or 6 membered N-containing heterocyclyl;

R_5 and R_6 are each independently selected from H, C_{1-6}alkyl, Q^alkylCN, C_{3-8}cycloalkyl, aryl, heterocyclyl, C^alkylene, cycloalkyl, substituted or unsubstituted C_{1-6}alkylene, SO_2C_{1-6}alkyl and C_{1-6}alkylene heterocyclyl; or

R_5 and R_6 together with the nitrogen to which they are attached form a 4-8 membered ring having 1 to 3 heteroatoms independently selected from NR_8, O, $S(0)_m$ wherein m is O, 1 or 2 and wherein the ring may be optionally substituted with C_{1-6}alkyl or NR_5R_6;

R_8 is selected from H, C_{1-6}alkyl, C_{2-6}alkylene0H, C_{2-6}alkyleneNR $_5R_6$, C_{3-8}cycloalkyl, aryl, heterocyclyl, C_{1-6}alkylenecycloalkyl, C_{1-6}alkylenearyl, C_{1-6}alkyleneheterocyclyl and C_{1-6}alkyleneCN,

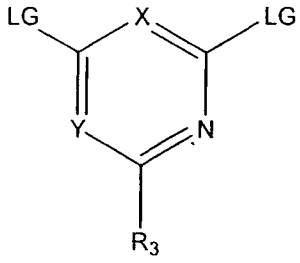
R_7 is selected from H, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted OC_{1-6}alkyl, substituted or unsubstituted SCi^alkyl, CNOH, C_{1-6}alkyleneCN, substituted or unsubstituted C_{3-8}cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, C^alkylenecycloalkyl, C_{1-6}alkylenearyl, C_{1-6}alkyleneheterocyclyI, C^alkenyl, C_{2-6}alkynyl, NR_5R_6, C_{1-6}alkyleneNR$_5$R6 and C_{1-6}alkylene0R $_5$;

W is absent, CO. SO_2 or C_{1-6}alkylene;

R_2 is selected from H, Q^alkyl, C_{3-8}cycloalkyl, aryl and heterocyclyl, each of which may be optionally substituted with 1 to 4 substituents selected from R and R_9; and wherein each alkenyl and alkynyl may be optionally substituted with 1 to 3 subsituents independently selected from C_{1-6}alkyl, CO_2R_7, $CONR_5R_6$, aryl, heterocyclyl, C_{1-6}alklene OH and C_{1-6}alkyleneNH$_2$;

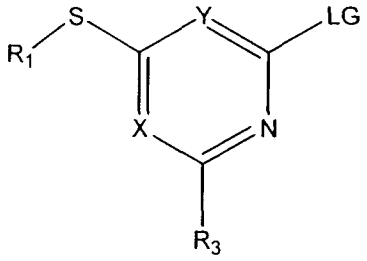
In a second aspect, there is provided a process for the preparation of the compound of formula I defined above which comprises the steps of:

(a) adding S-R_1 wherein R_1 is as defined in formula I above to a compound of formula II



II

wherein X, Y and R3 are as defined in formula I above and LG is a leaving group to prepare a compound of formula III



III

wherein X, Y, LG, Ri and R_3 are as defined above; and

(b) coupling the compound of formula III with a source OfNH-W-R_2 wherein W and R_2 are as defined in formula I above.

The compounds of formula I are kinase inhibitors, preferably JAK inhibitors, more preferably JAK.2 or JAK3 inhibitors. These compounds are useful in the treatment of a kinase associated disease, preferably a JAK kinase associated disease such as immunological and inflammatory diseases; hyperproliferative diseases including myeloproliferative diseases; vascular diseases such as pulmonary arterial hypertension (PAH); viral diseases and metabolic diseases.

In a third aspect, there is provided a kinase inhibitor comprising the compound

formula I defined above.

There is also provided use of the compound of formula I defined above as a kinase inhibitor.

There is further provided the compound of formula I defined above for use as a kinase inhibitor.

The compounds of formula I preferably act as selective JAK2 inhibitors, selective JAK3 inhibitors or selective JAKl and JAK2 inhibitors.

The compound of formula I may also be administered in the form of a pharmaceutical composition together with a pharmaceutically acceptable carrier.

In a fourth aspect, there is provided a pharmaceutical composition comprising the compound of formula I defined above and a pharmaceutically acceptable carrier.

In one embodiment, the pharmaceutical composition also comprises one or more additional therapeutic agents.

The compound of formula I may be contained within or attached to an implant, such as a drug eluting stent. For example, when the compound is used for the treatment of PAH, the compound may be contained within or attached to a pulmonary artery stent, which may act locally, or be released from the stent into the pulmonary circulation where the compound exerts its therapeutic activity in the pulmonary vasculature.

In a fifth aspect, there is provided an implant which comprises the compound of formula I defined above.

In a sixth aspect, there is provided a method for the treatment of a kinase associated disease such as immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases; and vascular diseases which comprises administering a therapeutically effective amount of the compound of formula I or a pharmaceutical composition defined above to a subject in need thereof.

There is also provided use of the compound of formula I or a pharmaceutical composition as defined above in the manufacture of a medicament for the treatment of a kinase associated disease such as immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases; and vascular diseases.

There is further provided use of the compound of formula I or a pharmaceutical composition as defined above in the treatment of a kinase associated disease such as immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases; and vascular diseases.

There is still further provided the compound of formula I or a pharmaceutical composition defined above for use in the treatment of a kinase associated disease such as immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases; and vascular diseases.

In a seventh aspect, there is provided a method for suppressing the immune system of a subject which comprises administering a therapeutically effective amount of the compound of formula 1or a pharmaceutical composition defined above to the subject in need thereof.

There is also provided use of the compound of formula I or a pharmaceutical composition as defined above in the manufacture of a medicament for suppressing the immune system of a subject.

There is further provided use of the compound of formula 1or a pharmaceutical composition as defined about in suppressing the immune system of a subject.

There is still further provided the compound of formula I or a pharmaceutical composition defined above for use in suppressing the immune system of a subject.

In an eighth aspect, there is provided a method of inhibiting a kinase in a cell comprising contacting the cell with the compound of formula I defined above.

BRIEF DESCRIPTION OF THE FIGURES

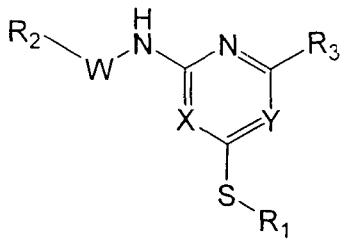
Figure 1 shows the amino acid sequence alignment of selected JAK Kinases.

Figure 2 shows a model of the JAK3 kinase ATP binding pocket displaying the Cysteine residue.

DETAILED DESCRIPTION

The present invention relates to compounds of formula I that inhibit kinases, in particular JAK kinases such as JAK2 or JAK3 kinases and are useful in the treatment of kinase associated diseases such as immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases; and vascular diseases.

Accordingly, in a first aspect, the present invention provides a compound of the general formula I:



I

or salts, isomers and/or prodrugs thereof, wherein:

X and Y are independently selected from N and CR_3;

each R3 is independently selected from hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, hydroxyl, halogen, nitro, substituted or unsubstituted amino, cyano, nitro, trifluoromethyl, methoxy, trifluoromethoxy, aryl and substituted or unsubstituted 5 or 6 membered heterocyclyl containing 1 to 2 N atoms;

Ri is selected from hydrogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylCN, $C_{3\text{-}8}$ cycloalkyl, Ci-$_6$alkylenecycloalkyl, aryl, $C_{1\text{-}6}$alkylenearyl, heterocyclyl and Ci-$_6$alkyleneheterocyclyl, wherein Ci.$_6$alkyl, C3-scycloalkyl, heterocyclyl and aryl may be optionally substituted with 1 to 3 substituents selected from R or R_9;

R9 is independently selected from halogen, substituted or unsubstituted $C_{1\text{-}6}$alkyl, OH, (O), OCN, substituted or unsubstituted OC,.$_6$alkyl, CN, CF_3,CF_2CN, SCN, $SO_2NR_5R_6$, SR_7, CHO, CO_2R_7, COR^7, $CONR_5R_6$, $CONR_5R_7$, NR_5COR_7, NO_2, NR_5R_6, NR_5CN, CH(CN)NR_5R_6, $NR_5SO_2R_7$, $COCF_3$, $COCH_2F$, NR_5COCOR_7, NR_5COOR_7,$NR_5CONR«R_7$, heterocyclyl and COheterocyclyl, wherein each heterocyclyl may be optionally substituted with 1 to 4 substituents selected from NH_2, CN, OH, CO_2R_7, CH_2CN and 5 membered N-containing heterocyclyl;

R is Ci-$_6$alkyleneRg, $OC_{1\text{-}6}$alkyleneR$_9$ (except when R_9 is NR_5R_6 or $OC_{1\text{-}6}$aIkyl, then R is $OC_{2\text{-}6}$alkyleneR$_9$); or

R_9 and R together with the groups to which they are attached form a substituted or unsubstituted 5 or 6 membered N-containing heterocyclyl;

R_5 and R_6 are each independently selected from H, Ci.$_6$alkyl, $C_{1\text{-}6}$alkylCN, C3-8cyc!oalkyl, aryl, heterocyclyl, Ci_$_6$alkylene, cycloalkyl, substituted or unsubstituted $C_{1\text{-}6}$alkylene, $SO_2C_{1\text{-}6}$alkyl and Ci_$_6$alkylene heterocyclyl; or

R_5 and R_6 together with the nitrogen to which they are attached form a 4-8 membered ring having 1 to 3 heteroatoms independently selected from NR_8, O, S(0)$_m$ wherein m is O, 1 or 2 and wherein the ring may be optionally substituted with $C_{1\text{-}6}$alkyl or NR_5R_6;

R_8 is selected from H, C,.$_6$alkyl, $C_{2\text{-}6}$alkylene0H, C^alkyleneNRsR^ C3.scycloalkyl, aryl, heterocyclyl, $C_{1\text{-}6}$alkylenecycloalkyl, $C_{1\text{-}6}$alkylenearyl, Ci-$_6$alkyleneheterocyclyl and $C_{1\text{-}6}$alkyleneCN,

R_7 is selected from H, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted OC_{1-6}alkyl, substituted or unsubstituted $SC_{)-6}$alkyl, CNOH, C_{1-6}alkyleneCN, substituted or unsubstituted C_{3-}gcycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl,C_{1-6}alkylenecycloalkyl,C_{1-6}alkylenearyl, C_{1-6}alkyleneheterocyclyl, C_{2-6}alkenyl, C_{2-6}alkynyl, NR_5R_6, C_{1-6}alkyleneNR$_5$R$_6$ and C_{1-6}alkylene0R5;

W is absent, CO, SO_2 or C_{1-6}alkylene;

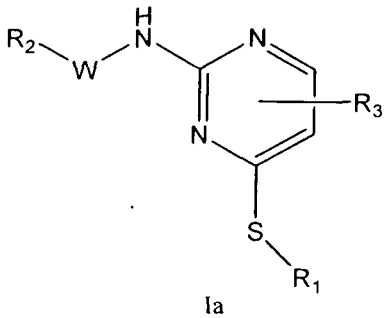
R_2 is selected from H, C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl and heterocyclyl, each of which may be optionally substituted with 1 to 4 substituents selected from R and R_9; and wherein each alkenyl and alkynyl may be optionally substituted with 1 to 3 subsituents independently selected from Ci_{-6}alkyl, CO_2R_7, CONR$_5$R$_6$, aryl, heterocyclyl, Ci_{-6}alklene OH and C_{1-6}alkyleneNH$_2$;

In one embodiment, the compound of formula I selectively inhibits JAK 3 with respect to JAK 1 or JAK 2. The term "selectively inhibits" is defined to mean that the apparent IC_{5O} of the compound for JAK 3 is more than ten-fold lower (i.e. more potent) than the IC_{50} for JAK 1 or JAK 2.

The compounds of formula I which inhibit JAK3 may either reversibly or irreversibly inhibit JAK 3. Generally, the strength of binding of reversible inhibitors of an enzyme is measured by the IC_{5O} value which is a reflection of the equilibrium constant of the interaction between the inhibitor and the active site of the enzyme. Irreversible inhibitors display an apparent IC_{50} because once the inhibitor is bound it will not leave the active site and the measured IC_{50} will therefore improve (i.e. number will decrease) over time.

In the compounds of formula I, X is preferably N and Y is preferably CR_3 wherein R_3 is as defined above.

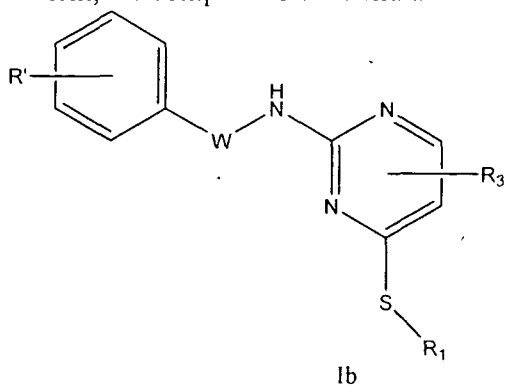
Thus, in one embodiment, the compounds of formula I have the formula Ia



Ia

wherein W, Ri, R_2 and R_3 are as defined above.

In another embodiment, the compounds of formula I and Ia have the formula Ib

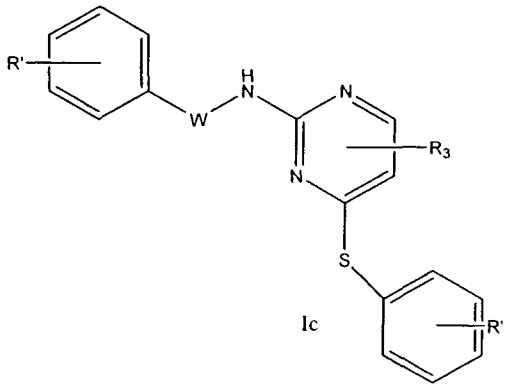


Ib

wherein W, R_1 and R_3 are as defined above; and

R' is H, R or R9 as defined above.

In a further embodiment, the compounds of formula I, Ia and Ib have the formula Ic



Ic

wherein W, R_3 and R' are as defined above.

W is preferably absent, CO or Ci-6alkylene.

Ri is preferably aryl such as phenyl; heterocyclyl such as a N-containing heterocyclyls for example indolinyl; C_{1-6}alkyl; or aryl substituted with one or more substituents selected from NR_5R_6, NR_5COR_7, CN, OC_{1-6}alkyl, OH, CO_2R_7, $CONR_5R_7$, $CONR_5R_6$, $NR_5CO_2R_7$, substituted or unsubstituted C_{1-6}alkyl, SR_7, CHO, substituted or unsubstituted heterocyclyl such as thiomorpholin-3-one, tetrazole pyrrolidine-2,5-dione, CF_3, OCN and COR_7 wherein R_5 to R_7 are as defined above .

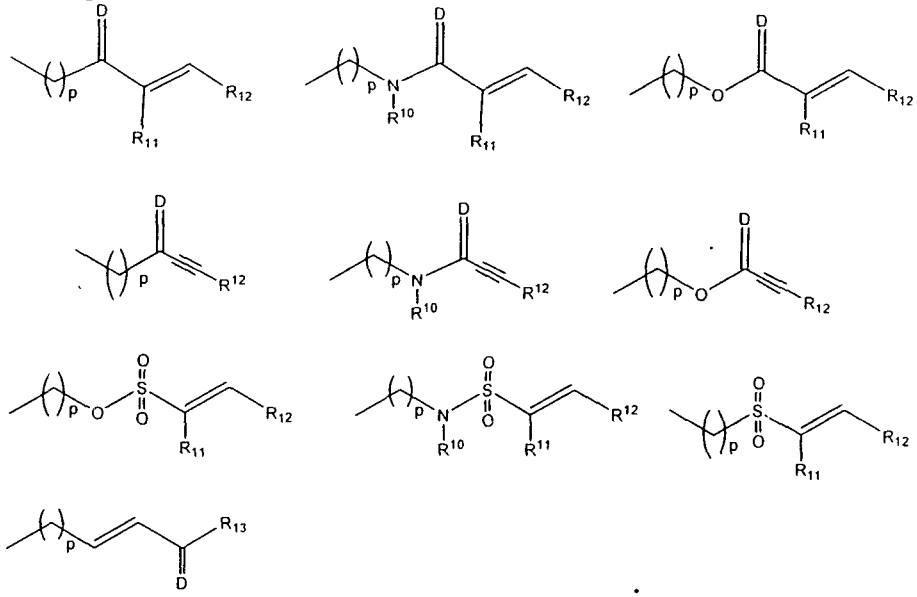
R_2 is preferably aryl such as phenyl; imidazolyl; methylene dioxy phenyl; or aryl substituted with one or more substituents selected from an N-containing 5 or 6 membered heterocyclyl such as morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl or 1,3-thiazolidine 1,1-dioxide; substituted or unsubstituted OC_{1-6}alkyl such as methoxy; NR_5COR_7 wherein R_5 is H and R_7 is C^alkyl, C_2-6alkenyI, C_{2-6}alkynyl or CN; NH_2;

halo such as chloro or fluoro; CO_2R_7; $SO_2NR_5R_6$; NO_2; $NHSO_2Me$; $CHOHCF_3CH_3$; CH_2NHSO_2Me; OH and SH wherein R_5 to R_7 are as defined above.

R_3 is preferably H; C_{1-6}alkyl; halo such as bromo, fluoro or iodo; C^alkenyi; amino which may be substituted with C_{2-6}alkenyl; cyano; nitro; methoxy; aryl such as phenyl; or 5 or 6 membered heterocyclyl containing 1 or 2 N atoms such as pyrazolyl, 1,2,3,6-tetrahydropyridine and pyridinyl, wherein the heterocyclyl may be substituted with trimethylcarboxy.

Where the compounds of formulae I and Ia inhibit JAK3 kinases, a substituent of one of R_1 and R_2 is preferably selected from groups that can react reversibly or irreversibly with a thiol moiety such as the thiol groups of the Cys963 residue of JAK.3. Similarly, where the compounds of formulae Ib inhibit JAK3 kinases, one of R' and a substituent of R_2 is preferably selected from groups that can react reversibly or irreversibly with a thiol moiety such as the thiol groups of the Cys963 residue of JAK3. Additionally where the compounds of formulae Ic inhibit JAK3 kinases, one of the R' substituents is preferably selected from groups that can react reversibly or irreversibly with a thiol moiety such as the thiol groups of the Cys963 residue of JAK3. Examples of such groups include Michael acceptors.

Michael acceptors are α,β-unsaturated carbonyl or thiocarbonyl compounds and selected examples are shown below.



wherein

D is O or N;

Rio is selected from H and substituted or unsubstituted C_{1-4}alkyl;

Rn and R_{i2} are independently selected from H, substituted or unsubstituted C_{1-4}alky!. C_{1-4}alkylNR$_{14}$R$_{15}$, C_{1-4}alkylOR^8, substituted or unsubstituted aryl or may be joined to form a substituted or unsubstituted 5 to 8 membered ring optionally containing one or more heteroatoms selected from O, S, SO_2 and NRi_0;

R_{13} is selected from OH, OC_{1-4}alkyl, $NR,_4Ri_5$;

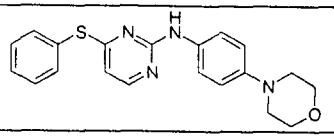
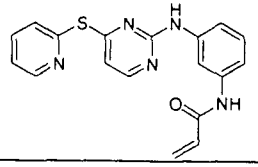
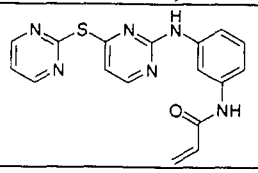
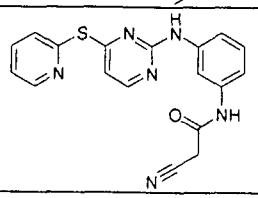
p is Oto 4; and

R_{14} and R_{15} are independently selected from H, substituted or unsubstituted C_{1-4}alkyl or may be joined to form a substituted 3-8 membered ring optionally containing one or more heteroatoms selected from O, S, SO_2 and NRi_0.

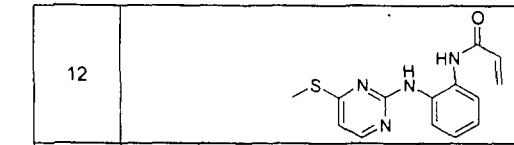
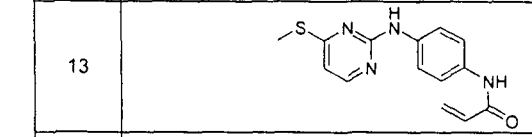
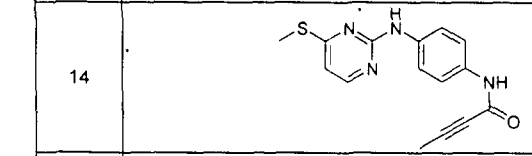
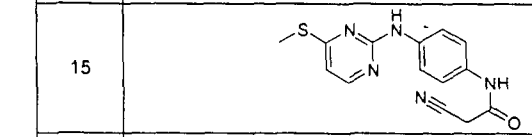
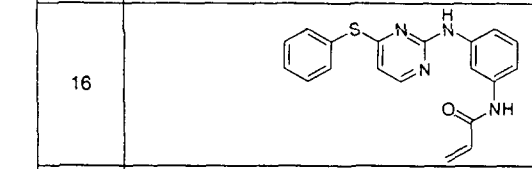
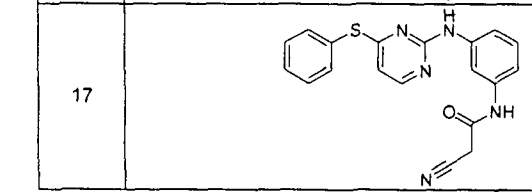
Other groups which can undergo reversible or irreversible reaction with thiol moieties include, ketones, aldehydes, α-acyloxy ketones, α-phenoxy ketones, halomethyl ketones, maleimides, nitriles, 1,2,4-thiadiazoles, 2-vinyl oxazoles, 2-alkynyl-oxazoles, keto-oxazoles, cyclic disulfides, epoxides and O-acyl hydroxamates.

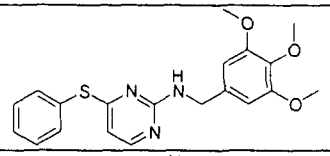
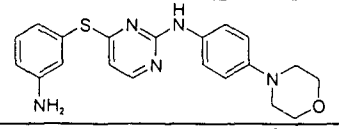
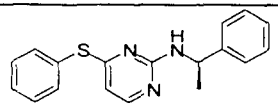
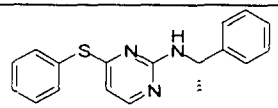
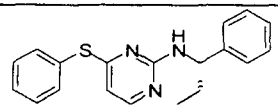
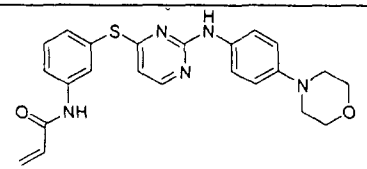
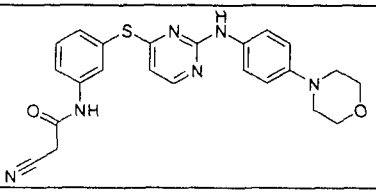
Examples of compounds of formula I include, but are not limited to, the following:

Table 1

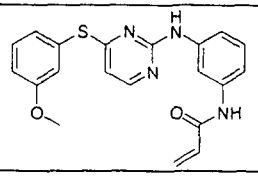
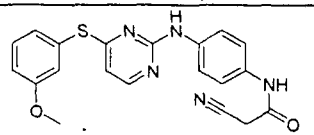
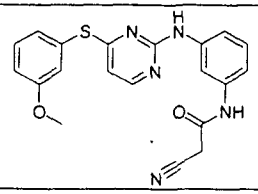
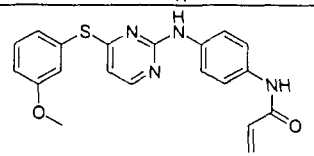
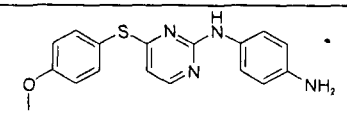
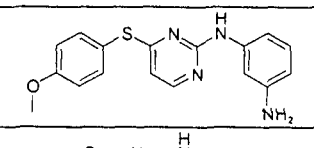
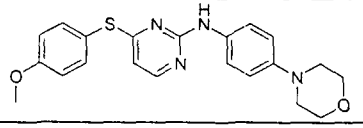
Compound number	Structure	Exact mass	Name	LCMS method	retention time (min)	Observed m/z	^{1}H NMR
1		364 14	N-(4-morpholinophenyl)-4-(phenylthio)pyrimidin-2-amine	C	7 3	m/z 365 1 [M+H]+	^{1}H NMR ($CDCl_3$) δ 3 08 (m, 4H) 3 86 (m, 4H), 6 25 (d, *J*=5 35Hz, 1H), 6 79 (d, *J*=8 94Hz, 2H), 6 95 (br s, 1H), 7 30 (d, *J*=8 93Hz, 2H), 7 46-7 50 (m, 3H), 7 62 (dd, *J*=7 04, 1 64Hz, 2H), 8 01(d *J*=5 35Hz, 1H)
2		349 10	N-(3-(4-(pyridin-2-ylthio)pyrimidin-2-ylamino)phenyl)acrylamide	B	7 7	m/z 349 3 M+	^{1}H NMR ($CDCl_3$) δ 5 74 (dd, *J*=10 13, 1 26Hz 1H), 6 19-6 28 (m, 1H), 6 42 (dd, *J*=16 79 1 21Hz, 1H), 6 64 (d, *J*=5 29Hz, 1H), 7 10-7 19 (m, 2H), 7 24 (br s 1H), 7 30-7 34 (m, 1H), 7 39 (br s, 1H), 7 69-7 75 (m, 3H), 8 14 (d, *J*=5 25Hz, 1H), 8 66-8 68 (m, 1H)
3		350 09	N-(3-(4-(pyrimidin-2-ylthio)pyrimidin-2-ylao)phenyl)acrylamide	C	5 8	m/z 351 0 [M+H]+	
4		362 09	2-cyano-N-(3-(4-(pyridin-2-ylthio)pyrimidin-2-ylao)phenyl)acetamide	C	5 9	m/z 363 0 [M+H]+	

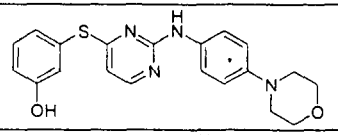
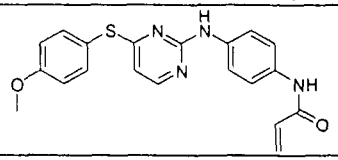
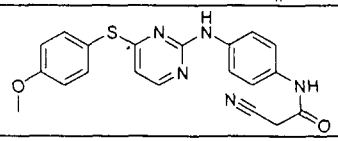
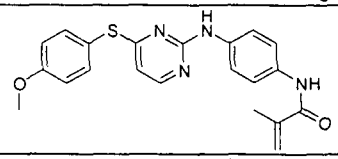
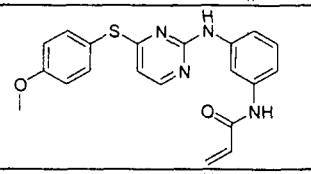
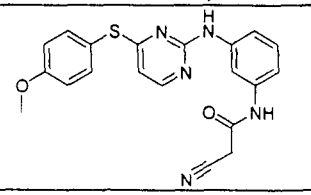
5		369 11	4-(phenylthio)-N-(3,4 5-trimethoxyphenyl)pyrimidin-2-ae	B	9 7	m/z 369 4 M+	^{1}H NMR ($CDCl_3$) δ 3 82 (s, 3H), 3 84 (s, 6H), 6 18 (d, *J*=5 39Hz, 1H) 6 88 (s, 2H), 7 01 (br s 1H) 7 42-7 50 (m, 3H), 7 59-7 63 (m, 2H) 8 04 (d, *J*=5 39Hz, 1H)
6		293 10	N-benzyl-4-(phenylthio)pyrimidin-2-ae	B	10 1	m/z 293 2 M+	^{1}H NMR ($CDCl_3$) δ 4 54 (d, *J*=5 97Hz, 2H), 5 41 (br s, 1H), 6 08 (d, *J*=5 37Hz, 1H), 7 24-7 31 (m 5H), 7 41-7 44 (m, 3H), 7 57-7 60 (m, 2H), 7 92 (d, *J*=5 37Hz, 1H)
7		286 09	N-(3-(4-(methylthio)pyrimidin-2-ylao)phenyl)acrylamide	H	NA	m/z 286 2 M$^+$	^{1}H NMR (300 MHz, $CDCl_3$) δ8 06 (d, *J*=5 4, 1H) 8 00 (brs, 1H), 7 38-7 42 (m, 1H), 7 13-7 30 (m 4H), 6 63 (d, *J*=5 4 , 1H), 6 43 (dd, *J*=16 8, 1 5, 1H), 6 24 (dd, *J*=16 9, 1 5 1H), 5 76 (dd, *J*=9 9 1 5 H, 1H), 2 55 (s, 3H)
8		298 09	N-(3-(4-(methylthio)pyrimidin-2-ylao)phenyl)but-2-ynamide	H	NA	m/z 298 3 M$^+$	^{1}H NMR (300 MHz, $CDCl_3$) δ8 06 (d, *J*=5 4, 1H) 7 96 (s, 1H), 7 37-7 40 (m, 1H), 7 26 (t, *J*=8 1, 1H), 7 08-7 15 (m, 2H), 6 63 (d, *J*=5 4 , 1H), 2 55 (s, 3H), 2 00 (s 3H)
9		299 08	2-cyano-N-(3-(4-(methylthio)pyrimidin-2-ylao)phenyl)acetamide	H	NA	m/z 299 3 M$^+$	
10		288 10	N-(3-(4-(methylthio)pyrimidin-2-ylao)phenyl)propionamide	H	NA	m/z 288 3 M$^+$	
11		232 08	N1-(4-(methylthio)pyrimidin-2-yl)benzene-1,3-diae	H	NA	m/z 232 3 M$^+$	^{1}H NMR (300 MHz, $CDCl_3$) δ8 04 (d, *J*=5 4, 1H), 7 15 (t *J*=2 1, 1H) 7 09 (t *J*=7 8 1H) 7 05 (brs 1H), 6 88-6 92 (m, 1H), 6 60 (d *J*=5 7 , 1H), 6 36-6 39 (m, 1H), 3 67 (brs 2H) 2 55 (s 3H)

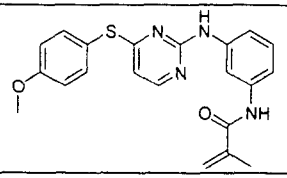
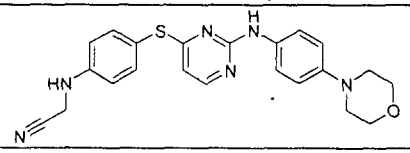
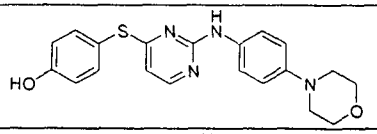
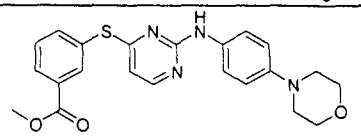
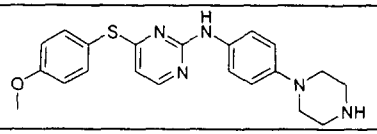
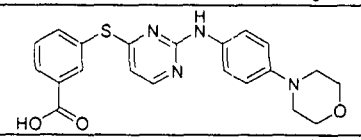
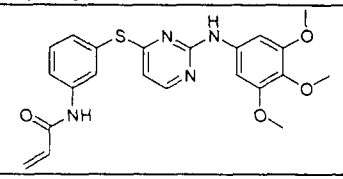
12		286 09	N-(2-(4-(methylthio)pyrimidin-2-ylao)phenyl)acrylamide	B	8 0	m/z 286 1 M+	^{1}H NMR (300 MHz, $CDCl_3$) δ8 43 (brs, 1H), 8 01 (d, *J*=5 4 1H), 7 86 (brs, 1H), 7 44 (br s, 1H), 7 18-7 20 (m 3H), 6 62 (d, *J*=5 4 , 1H), 6 14-6 39 (m, 2H), 5 69-5 74 (m, 1H), 2 46 (s, 3H)
13		286 09	N-(4-(4-(methylthio)pyrimidin-2-ylao)phenyl)acrylamide	B	7 8	m/z 286 1 M+	^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$) δ8 01 (d, *J*=5 4, 1H), 7 58 (brm, 4H), 6 61 (d *J*=5 4 1H) 6 26-6 39 (m, 2H), 5 73 (d, *J*=9 9, 1H), 2 54 (s, 3H)
14		298 09	N-(4-(4-(methylthio)pyrimidin-2-ylao)phenyl)but-2-ynamide	B	8 1	m/z 298 1 M+	
15		299 08	2-cyano-N-(4-(4-(methylthio)pyrimidin-2-ylao)phenyl)acetamide	B	7 6	m/z 299 1 M+	
16		348 10	N-(3-(4-(phenylthio)pyrimidin-2-ylao)phenyl)acrylamide	B	9 1	m/z 348 4 M+	^{1}H NMR ($CDCl_3$) δ 5 77 (dd, *J*=10 1, 1 13Hz 1H), 6 24 (m, 1H), 6 37 (d, *J*=5 41Hz, 1H), 6 42 (dd, *J*=16 8, 1 17Hz, 1H), 7 09 (br s, 1H), 7 14-7 16 (m, 3H), 7 31 (br s, 1H), 7 45-7 51 (m, 3H), 7 61-7 65 (m, 2H), 7 69 (br s, 1H), 8 07 (d, *J*=5 38Hz 1H)
17		361 10	2-cyano-N-(3-(4-(phenylthio)pyrimidin-2-ylao)phenyl)acetamide	B	8 9	m/z 361.4 M+	^{1}H NMR ($CDCl_3$) δ 3 54 (s, 2H), 6 33 (d, *J*=5 43Hz, 1H), 7 16-7 22 (m, 3H), 7 25 (br s, 1H), 7 47-7 52 (m, 3H), 7 61-7 64 (m, 2H), 7 69 (br s, 1H), 8 06 (d, *J*=5 37Hz, 1H)

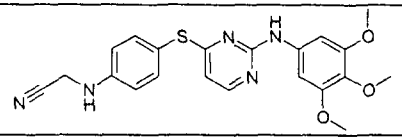
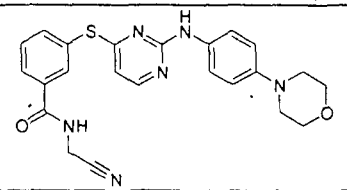
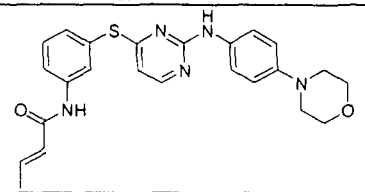
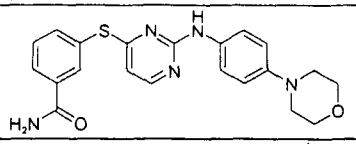
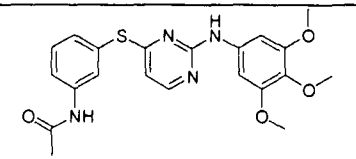
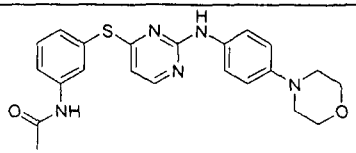
18		383 13	4-(phenylthio)-N-(3,4,5-trimethoxybenzyl)pyrimidin-2-ae	B	9 5	m/z 383 1 M+	^{1}H NMR ($CDCl_3$) δ 3 83 (s, 3H), 3 84 (s, 2H) 4 49 (d, *J*=5 92Hz 2H), 5 37-5 41 (m, 1H), 6 07 (d *J*=5 37Hz, 1H), 6 55 (s, 2H), 7 41-7 46 (m, 3H) 7 57-7 61 (m, 2H), 7 94 (d, *J*=5 37Hz, 1H)
19		379 15	4-(3-aophenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 6	m/z 380 [M+H]+	
20		307 11	(R)-N-(1-phenylethyl)-4-(phenylthio)pyrimidin-2-ae	B	10 4	m/z 307 5 M+	^{1}H NMR ($CDCl_3$) δ 1 48 (d, *J*=6 86Hz, 3H), 5 01-5 10 (m ,1H), 5 32 (d, *J*=7 61Hz, 1H), 6 05 (d *J*=5 33Hz, 1H), 7 19-7 32 (m, 5H), 7 38-7 47 (m, 3H), 7 54-7 57 (m, 2H), 7 89 (d, *J*=5 21Hz, 1H)
21		307 11	(S)-N-(1-phenylethyl)-4-(phenylthio)pyrimidin-2-ae	B	10 4	m/z 307 5 M+	^{1}H NMR ($CDCl_3$) δ 1 48 (d, *J*=6 86Hz, 3H), 5 01-5 10 (m, 1H), 5 30 (d, *J*=7 61Hz, 1H), 6 04 (d, *J*=5 33Hz, 1H), 7 19-7 32 (m, 5H), 7 37-7 46 (m, 3H), 7 54-7 57 (m, 2H), 7 89 (d, *J*=5 35Hz, 1H)
22		321 13	(S)-N-(1-phenylpropyl)-4-(phenylthio)pyrimidin-2-ae	B	10 7	m/z 321 5 M+	^{1}H NMR ($CDCl_3$) δ0 88 (t, *J*=7 36Hz, 3H), 1 73-1 88 (m, 2H), 4 75-4 88 (m, 1H), 5 30-5 39 (m, 1H), 6 03 (d, *J*=5 40Hz, 1H), 7 19-7 32 (m 5H) 7 39-7 47 (m, 3H), 7 54-7 57 (m, 2H), 7 88 (d, *J*=5 35Hz, 1H)
23		433 16	N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	B	8 5	m/z 433 5 M+	^{1}H NMR ($CDCl_3$) δ 3 06-3 09 (m, 4H), 3 83-3 86 (m, 4H), 5 79 (dd, J=10 18, 1 26Hz, 1H), 6 21 (dd, *J*=16 82, 10 18Hz, 1H), 6 36 (d, *J*=5 35Hz, 1H) 6 44 (dd, *J*=16 82, 1 26Hz, 1H) 6 77 (d, *J*=9 01Hz, 2H), 6 96 (br s, 1H), 7 24-7 47 (m, 5H) 7 68-7 73 (m, 1H), 7 95 (d, *J*=6 99Hz, 1H) 8 02 (d, *J*=5 35Hz, 1H)
24		446 15	2-cyano-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetamide	B	8 3	m/z 446 4 M+	^{1}H NMR ($CDCl_3$) δ 3 06-3 09 (m, 4H), 3 48 (s 2H) 3 83-3 85 (m, 4H), 6 32 (br s, 1H), 6 75 (br s, 2H), 7 19-7 25 (m, 3H), 7 37-7 40 (m 1H) 7 43 (t, *J*=7 71Hz, 1H), 7 78 (d, *J*=7 54Hz, 1H) 7 98 (d *J*=5 21Hz 1H), 8 19 (s, 1H)

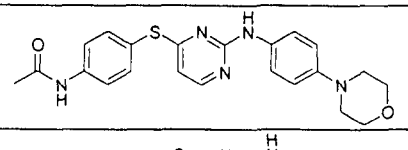
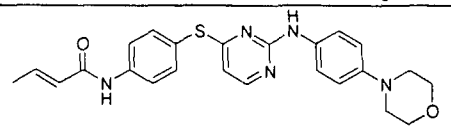
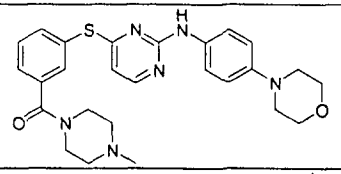
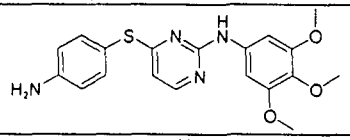
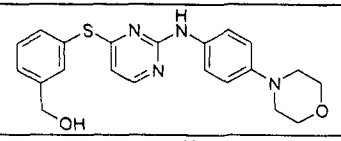
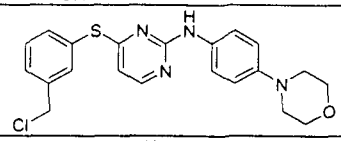
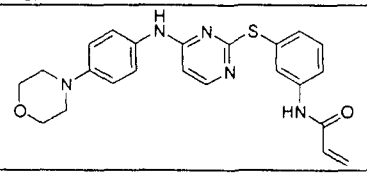
25		433 16	N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	8 5	m/z 433 6 M+	^{1}H NMR (d_6-DMSO) δ 2 91-2 94 (m, 4H), 3 66-3 69 (m, 4H), 8 53 (dd, J=9 90, 2 02Hz, 1H), 6 32 (dd, J=16 95 1 99Hz, 1H), 6 44-6 53 (m, 2H), 6 62 (d, J=9 06Hz, 2H), 7 19 (d, J=8 65Hz, 2H), 7 57 (d, J=8 58Hz 2H) 7 82 (d, J=8 58Hz, 2H) 8 10 (d, J=5 24Hz, 1H), 9 32 (s, 1H), 10 47 (s 1H)
26		446 15	2-cyano-N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	8 2	m/z 446 6 M+	^{1}H NMR (d_6-DMSO) δ 2 96 (m, 4H), 3 72-3 75 (m 4H), 3 96 (s, 2H), 6 38 (d, J=4 81Hz, 1H), 6 68 (d J=8 87Hz, 2H), 7 28 (d, J=8 53Hz, 2H), 7 73 (d J=8 59Hz, 2H), 8 10 (d, J=5 25Hz, 1H) 9 34 (s 1H), 10 59 (s, 1H)
27		379 15	4-(4-aophenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	B	8 4	m/z 379 1 M+	^{1}H NMR ($CDCl_3$) δ 3 08-3 12 (m, 4H), 3 84-3 87 (m, 4H), 3 93 (br s, 2H), 6 22 (d, J=5 38Hz, 1H) 6 74 (d, J=8 63Hz, 2H), 6 83 (d, J=9 03Hz, 2H), 6 89 (br s, 1H), 7 34 (d, J=9 08Hz, 2H), 7 36 (d, J=8 63Hz, 2H), 7 98 (d, J=5 38Hz, 1H)
28		394 15	4-(3-methoxyphenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	B	9 5	m/z 394 2 M+	^{1}H NMR ($CDCl_3$) δ3 09-3 12 (m, 4H), 3 81 (s, 3H) 3 86-3 89 (m, 4H), 6 29 (d, J=5 35Hz, 1H), 6 82 (d, J=9 02Hz, 2H), 6 89 (br s, 1H), 7 04 (ddd, J=8 30, 2 59, 0 98Hz, 1H), 7 16 (dd, J=2 51, 1 68Hz, 1H), 7 21 (ddd, J=7 59, 1 55, 1 02Hz, 1H), 7 32 (d, J=9 02Hz, 2H), 7 38 (t, J=7 86Hz, 1H), 8 03 (d, J=5 36Hz, 1H)
29		324 10	N1-(4-(3-methoxyphenylthio)pyrimidin-2-yl)benzene-1,3-diae	B	8 9	m/z 324 3 M+	^{1}H NMR ($CDCl_3$) δ 3 81 (s, 3H), 6 31-6 32 (m, 1H), 6 34 (d, J=5 40Hz, 1H), 6 34-6 35 (m, 1H), 6 69 (ddd, J=8 03, 2 07, 0 84Hz, 1H), 6 96-7 08 (m, 4H), 7 17 (dd, J=2 51, 1 63Hz, 1H), 7 22 (ddd, J=7 58, 1 57, 1 024Hz, 1H), 7 38 (t, J=7 83Hz 1H), 8 05 (d, J=5 40Hz, 1H)
30		324 10	N1-(4-(3-methoxyphenylthio)pyrimidin-2-yl)benzene-1,4-diae	B	8 6	m/z 324 3 M+	^{1}H NMR ($CDCl_3$) δ 3 54 (brs, 2H), 3 81 (s, 3H), 6 24 (d, J=5 35Hz, 1H), 6 59 (d, J=8 75Hz, 2H) 6 82 (brs, 1H), 7 03 (ddd, J=8 31 2 58, 0 99Hz 1H), 7 13-7 22 (m, 4H), 7 36 (t, J=7 85Hz, 1H), 7 99 (d, J=5 35Hz, 1H)

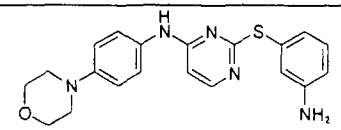
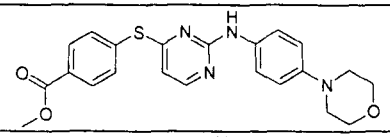
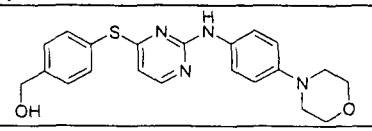
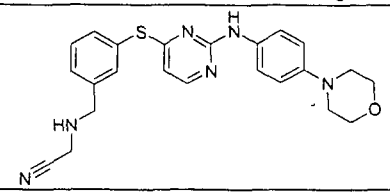
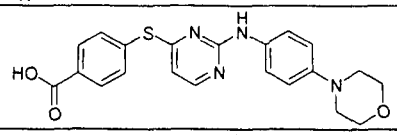
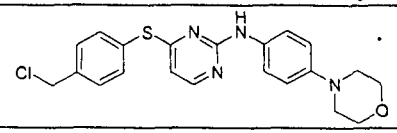
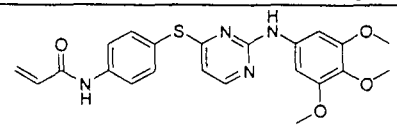
31		378 12	N-(3-(4-(3-methoxyphenylthio)pyrimidin-2-ylao)phenyl)acrylamide	B	9	m/z 378 3 M+	^{1}H NMR ($CDCl_3$) δ 3 80 (s, 3H), 5 77 (dd, *J*=10 09 1 43Hz, 1H), 6 25 (dd, *J*=16 87, 10 09Hz, 1H) 6 39 (d, *J*=5 44Hz, 1H), 6 44 (dd, *J*=16 84, 1 42Hz, 1H), 7 04 (ddd, *J*=8 30, 2 56, 0 91Hz, 1H), 7 11-7 18 (m, 3H), 7 19-7 23 (m, 1H), 7 28-7 41 (m, 3H), 7 69 (brs, 1H), 8 06 (d *J*=5 36Hz 1H)
32		391 11	2-cyano-N-(4-(4-(3-methoxyphenylthio)pyrimidin-2-ylao)phenyl)acetamide	B	8 6	m/z 391 2 M+	^{1}H NMR ($CDCl_3$) δ 3 54 (s, 2H), 3 83 (s, 3H), 6 33 (d, *J*=5 34Hz, 1H), 7 07 (ddd, *J*=8 33, 2 59 0 97Hz, 1H), 7 16 (dd, *J*=2 48, 1 73Hz, 1H), 7 20 (ddd, *J*=8 09, 1 58, 1 05Hz, 1H), 7 39-7 44 (m, 4H), 7 67 (s, 1H), 8 05 (d, *J*=5 53Hz, 1H), 9 55 (brs, 1H)
33		391 11	2-cyano-N-(3-(4-(3-methoxyphenylthio)pyrimidin-2-ylao)phenyl)acetamide	B	8 8	m/z 391 2 M+	^{1}H NMR ($CDCl_3$) δ 3 57 (s, 2H), 3 82 (s, 3H), 6 29 (d, *J*=5.36Hz, 1H), 7 04 (ddd, *J*=8 32, 2 59, 0 94Hz, 1H), 7 13-7 16 (m, 2H), 7 18-7 19 (m, 1H), 7 231 (dd, *J*=1 48, 0 95Hz, 1H), 7 34-7 39 (m, 3H), 7 76 (m, 1H), 7 91 (brs, 1H) 8 07 (d *J*=5 36Hz, 1H), 9 70 (brs, 1H)
34		378 12	N-(4-(4-(3-methoxyphenylthio)pyrimidin-2-ylao)phenyl)acrylamide	B	8 7	m/z 378 2 M+	^{1}H NMR ($CDCl_3$) δ 3 82 (s, 3H), 5 68 (dd, *J*=11 86 2 17Hz, 1H), 6 31 (d, *J*=5 35Hz, 1H), 6 37 (d, *J*=2.88Hz, 1H), 6 39 (s, 1H), 7 07 (ddd, *J*=8 35, 2 64, 0 96Hz, 1H), 7 15-7 16 (m, 1H), 7 20 (ddd, *J*=7 58, 1 55, 1 03Hz, 1H), 7 41 (d, *J*=8 93Hz, 2H), 7 53 (d, *J*=8 95Hz, 2H), 7 75 (brs, 1H), 8 05 (d, *J*=5 35Hz, 1H), 8 96 (brs, 1H)
35		324 10	N1-(4-(4-methoxyphenylthio)pyrimidin-2-yl)benzene-1,4-diae	B	8 6	m/z 324 1 M+	^{1}H NMR ($CDCl_3$) δ 3 61 (brs, 2H), 3 87 (s, 3H), 6 16 (d, *J*=5 35Hz, 1H), 6 58 (d, *J*=8 74Hz, 2H), 6 97 (d, *J*=8 88Hz, 2H), 7 19 (d, *J*=8 71Hz, 2H), 7 19 (d, *J*=8 71Hz, 1H), 7 51 (d, *J*=8 88Hz, 2H), 7 98 (d, *J*=5 35Hz, 1H)
36		324 10	N1-(4-(4-methoxyphenylthio)pyrimidin-2-yl)benzene-1,3-diae	B	8 9	m/z 324 4 M+	^{1}H NMR ($CDCl_3$) δ 3 68 (brs, 2H), 3 87 (s, 3H), 6 25 (d, *J*=5 36Hz, 1H), 6 30 (ddd, *J*=7 90, 2 18, 0 87Hz, 1H), 6 72-6 76 (m, 1H), 6 94-7 01 (m, 4H) 7 35 (brs, 1H) 7 53 (d, *J*=8 88Hz, 2H), 8 03 (d, *J*=5 36Hz, 1H)
37		394 15	4-(4-methoxyphenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	H	NA	m/z 394 4 M+	^{1}H NMR (d_6-DMSO) δ 2 98-3 01 (m, 4H), 3 72-3 75 (m, 4H), 3 85 (s, 3H), 6 27 (d, *J*=5 06Hz, 1H), 6 72 (d, *J*=9 04Hz, 2H), 7 10 (d, *J*=8 88Hz 2H) 7 32 (d *J*=8 90Hz, 2H), 7 54 (d, *J*=8 85Hz 2H) 8 09(d, *J*=5 29Hz, 1H), 9 35 (s 1H)

38		380 13	3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenol	B	8 3	m/z 380 2 M+	^{1}H NMR (d_6-DMSO) δ 2 99-3 02 (m, 4H), 3 72-3 75(m, 4H), 6 28 (d, *J*=5 29Hz, 1H), 6 78 (d, *J*=9 17Hz, 2H) 6 95-7 06 (m, 3H) 7 34 (t *J*=7 81Hz, 1H), 7 38 (d, *J*=9 07Hz 2H), 8 11 (d, *J*=5 29Hz, 1H), 9 38 (s, 1H)
39		378 12	N-(4-(4-(4-methoxyphenylthio)pyrimidin-2-ylao)phenyl)acrylamide	B	8 9	m/z 378 1 M+	^{1}H NMR (d_6-DMSO) δ 3 86 (s, 3H) 5 71 (dd, *J*=5 22, 7 42Hz, 1H), 6 23 (dd, *J*=2 18, 17 01Hz 1H), 6 29 (d, *J*=5 40Hz, 1H), 6 42 (dd, *J*=10 04 16 94Hz, 1H), 7 09 (d, *J*=8 88Hz, 2H), 7 44 (s 4H), 7 56(d, *J*=8 85Hz, 2H), 8 13(d, *J*=5 31Hz 1H), 9 56(s, 1H), 9 98 (s, 1H)
40		391 11	2-cyano-N-(4-(4-(4-methoxyphenylthio)pyrimidin-2-ylao)phenyl)acetamide	B	8 6	m/z 391 M+	^{1}H NMR (d_6-DMSO) δ 3 84 (s, 2H), 3 86 (s, 3H), 6 31 (d, *J*=5 38Hz, 1H), 7·10 (d, *J*=8 88Hz, 2H), 7 31 (d, *J*=9 02Hz, 2H), 7 44 (d, *J*=9 00Hz, 2H), 7 56 (d, *J*=8 84Hz, 2H), 8 13 (d, *J*=5 31Hz, 1H) 9 58 (s, 1H) 10 13 (s, 1H)
41		392 13	N-(4-(4-(4-methoxyphenylthio)pyrimidin-2-ylao)phenyl)methacrylamide	B	9 2	m/z 392 M+	^{1}H NMR (d_6-DMSO) δ 1 94 (s, 3H), 3 84 (s, 3H), 5 45-5 46 (m, 1H), 5 74-5 77 (m, 1H) 6 27 (d, *J*=5 26Hz, 1H), 7 09 (d, *J*=8 87Hz, 2H) 7 43 (s, 4H), 7 55 (d, *J*=8 84Hz, 2H), 8 13 (d, *J*=5 31Hz, 1H), 9 54 (s, 1H), 9 61 (s, 1H)
42		378 12	N-(3-(4-(4-methoxyphenylthio)pyrimidin-2-ylao)phenyl)acrylamide	B	9	m/z 378 1 M+	^{1}H NMR (d_6-DMSO) δ 3 84 (s, 3H), 5 73 (dd, *J*=2 14, 10 06Hz, 1H), 6 21 (d, *J*=5 29Hz, 1H), 6 25 (dd, *J*=2 10, 14 82Hz, 1H), 6 46 (dd, *J*=10 04, 16 92Hz, 1H), 7 04-7 12 (m, 3H), 7 28-7 33 (m, 2H), 7 57 (d, *J*=8 84Hz, 2H), 7 81-7 87 (m, 1H), 8 15 (d, *J*=5 35Hz, 1H), 9 65 (s, 1H), 10 04 (s, 1H)
43		391 11	2-cyano-N-(3-(4-(4-methoxyphenylthio)pyrimidin-2-ylao)phenyl)acetamide	B	8 8	m/z 391 M+	^{1}H NMR (d_6-DMSO) δ 3 84 (s, 3H), 3 87 (s, 2H), 6 21 (d, *J*=5 34Hz, 1H), 7 05-7 12 (m 3H), 7 17-7 22 (m, 1H), 7 28-7 35 (m, 1H), 7 57 (d, *J*=8 84Hz, 2H), 8 72-8 76 (m, 1H),8 16 (d *J*=5 35Hz, 1H), 9 69 (s, 1H), 10 19 (s, 1H)

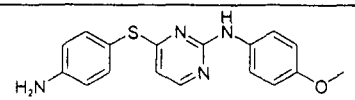
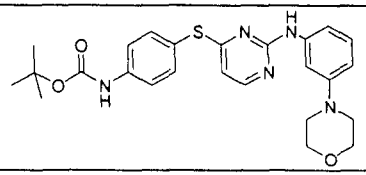
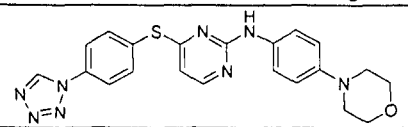
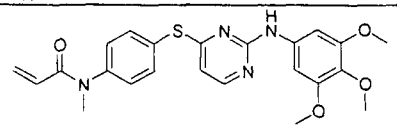
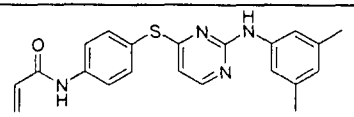
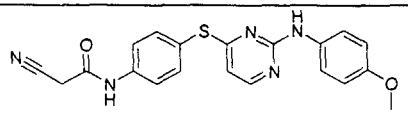
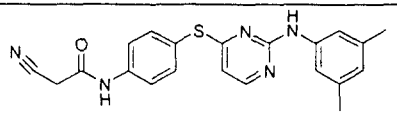
45		392 13	N-(3-(4-(4-methoxyphenylthio)pyrimidin-2-ylao)phenyl)methacrylamide	B	9 4	m/z 392 2 M+	^{1}H NMR (d_6-DMSO) δ 1 94 (s, 3H), 3 83 (s, 3H) 5 48-5 49 (m, 1H), 5 78 (s, 1H), 6 21 (d, *J*=5 33Hz, 1H), 7 05 (t, *J*=8 06Hz, 1H), 7 09 (d, *J*=8 92Hz, 2H), 7 16-7 22 (m, 1H), 7 27-7 33 (m, 1H), 7 57 (d, *J*=9 21Hz, 2H), 7 83-7 87 (m, 1H), 8 14 (d, *J*=5 33Hz, 1H), 9 60 (s, 1H), 9 69 (s, 1H)
46		418 16	2-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenylao)acetonitrile	B	8 5	m/z 418 4 M+	^{1}H NMR (d_6-DMSO) δ 2 98-3 01 (m, 4H), 3 71-3 74 (m, 4H), 4 36 (d, *J*=6 56Hz, 2H), 6 23 (d, *J*=5 23Hz, 1H), 6 75 (d, *J*=9 03Hz, 2H), 6 81 (d *J*=6 65Hz, 1H), 6 85 (d, *J*=8 69Hz, 2H), 7 36 (d *J*=9 07Hz, 2H), 7 41 (d, *J*=8 64Hz, 2H), 8 08 (d *J*=5 29Hz, 1H), 9 34 (s, 1H)
47		380 13	4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenol	B	8 3	m/z 380 M+	^{1}H NMR (d_6-DMSO) δ 2 99-3 02 (m, 4H), 3 71-3 74 (m, 4H), 6 24 (d, *J*=5 48Hz, 1H), 6 75 (d, *J*=9 09Hz, 2H), 6 92 (d, *J*=8 68Hz, 2H), 7 35 (d, *J*=8 94Hz, 2H), 7 41 (d, *J*=8 68Hz, 2H), 8 07 (d, *J*=5 29Hz, 1H), 9 34 (s, 1H), 10 06 (s, 1H)
48		422 14	methyl 3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzoate	B	9 4	m/z 422 2 M+	^{1}H NMR ($CDCl_3$) δ 3 06-3 09 (m, 4H), 3 85-3 88 (m, 4H), 3 92 (s, 3H), 6 33-6 35 (d, *J*=5 36Hz, 1H), 6 74 (d, *J*=9 01Hz, 2H), 7 04 (br s, 1H), 7 20 (d, *J*=8 97Hz, 2H), 7 54 (t, *J*=7 78Hz, 1H), 7 79 (ddd, *J*=1 23, 1 80, 7 72Hz, 1H), 8 02 (d, *J*=5 36Hz, 1H), 8 15-8 19 (m, 1H), 8 28-8 29 (m 1H)
49		393 16	4-(4-methoxyphenylthio)-N-(4-(piperazin-1-yl)phenyl)pyrimidin-2-ae	B	9	m/z 393 5 M+	^{1}H NMR ($CDCl_3$) δ 3 02-3 05 (m, 4H), 3 85 (s, 3H) 3 87-3 90 (m, 4H), 5 97 (d, *J*=5 31Hz, 1H), 6 65 (d, *J*=8 84Hz, 2H), 6 84 (d, *J*=8 83Hz, 2H), 6 95 (d, *J*=8 89Hz, 2H), 7 51 (d *J*=8 87Hz, 2H), 7 95 (d, *J*=5 32Hz, 1H)
50		408 13	3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzoic acid	B	8 2	m/z 408 2 M+	^{1}H NMR (d_6-DMSO) δ 2 97-3 01 (m, 4H) 3 71-3 75 (m, 4H), 6 47 (d, *J*=4 67Hz, 1H), 6 66 (d *J*=8 99Hz 2H) 7 22 (d *J*=8 14Hz 2H), 7 67 (t *J*=7 76Hz, 1H), 7 86 (ddd, *J*=1 22, 1 71, 7 70Hz, 1H), 8 11-8 17 (m, 2H) 8 14 (d, *J*=5 24Hz, 1H)
51		438 14	N-(3-(2-(3,4,5-trimethoxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	8 7	m/z 438 4 M+	^{1}H NMR ($CDCl_3$) δ3 81-3 85 (m 9H), 5 80 (dd *J*=1 34, 10 13Hz, 1H), 6 21-6 30 (m, 2H), 6 45 (dd, *J*=1 35 16 83Hz, 1H) 6 86-6 92 (m, 2H) 7 12 (br s 1H) 7 32-7 36 (m 1H), 7 41 (t 7 74Hz 1H) 7 52 (br s 1H) 7 69-7 72 (m, 1H) 7 90 (s 1H), 8 05 (d *J*=5 39Hz 1H)

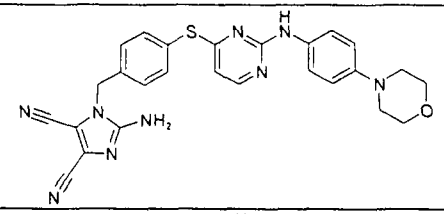
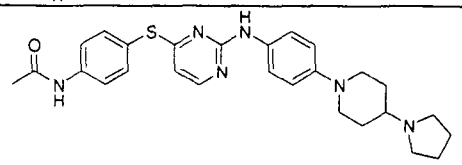
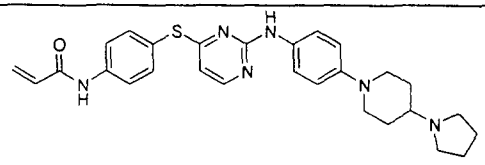
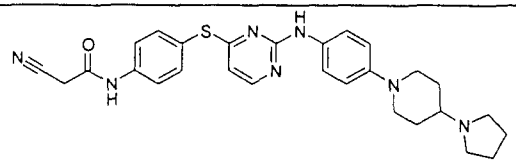
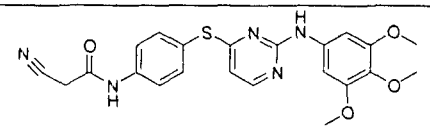
52		423 14	2-(4-(2-(3,4,5-trimethoxyphenylao)pyrimidin-4-ylthio)phenylao)acetonitrile	B	8 7	m/z 423 2 M+	^{1}H NMR ($CDCl_3$) δ 3 82 (s, 3H), 3 85 (s, 6H) 4 17 (d, *J*=6 97Hz, 2H), 6 16 (d, *J*=5 38Hz, 1H), 6 76 (d, *J*=8 75Hz, 2H), 6 89 (s, 2H), 6 94 (br s 1H), 7 49 (d, *J*=8 68Hz, 2H), 8 03 (d, *J*=5 39Hz 1H)
53		446 15	N-(cyanomethyl)-3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzamide	C	6 4	m/z 447 1 [M+H]+	^{1}H NMR ($CDCl_3$) δ 3 06-3 10 (m, 4H), 3 85-3 88 (m, 4H), 4 31 (d, *J*=5 77Hz, 2H), 6 25-6 32 (m, 1H), 6 41 (d, *J*=5 27Hz, 1H), 6 72 (d *J*=8 96Hz, 2H), 6 85 (br s, 1H), 7 15 (d, *J*=8 79Hz 2H), 7 58 (t, *J*=8 25Hz, 1H), 7 77-7 81 (m 1H) 7 93-7 97 (m, 2H), 8 08 (d, *J*=5 32Hz, 1H)
54		447 17	(E)-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-enamide	B	8 8	m/z 447 2 M+	^{1}H NMR ($CDCl_3$) δ 1 90 (dd, *J*=1 65, 6 90Hz, 3H), 3 06-3 09 (m, 4H), 3 85-3 88 (m, 4H), 5 95 (dd, *J*=1 67, 15 09Hz, 1H), 6 35 (d, *J*=5 43Hz, 1H), 6 78 (d, *J*=9 02Hz, 2H), 6 93-7 05 (m, 1H), 7 25 (d, *J*=9 20Hz, 2H), 7 30-7 34 (m, 1H), 7 42 (t, *J*=7 82Hz, 1H), 7 45 (br s, 1H), 7 57 (br s, 1H), 7 71 (br s, 1H) 7 71 (br s 1H), 7 94 (br s, 1H) 7 97 (d, *J*=5 40Hz, 1H)
55		407 14	3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzamide	B	7 6	m/z 407 1 M+	^{1}H NMR (d_6-DMSO) δ 2 97-3 00 (m, 4H), 3 71-3 74 (m, 4H), 6 41 (d, *J*=4 88Hz, 1H), 6 69 (d, *J*=8 97Hz, 2H), 7 24 (d, *J*=9 02Hz, 2H), 7 50 (br s 1H), 7 62 (t, *J*=7 72Hz, 1H), 7 76-7 79 (m, 1H), 8 09-8 16 (m, 4H), 9 37 (s, 1H)
56		426 14	N-(3-(2-(3,4,5-trimethoxyphenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	8 3	m/z 426 2 M+	^{1}H NMR ($CDCl_3$) δ 2 18 (s 3H), 3 81 (s, 3H), 3 83 (s, 6H), 6 26 (d, *J*=5 37Hz, 1H), 6 88 (s, 2H), 7 10 (s, 1H), 7 29-7 34 (m, 1H), 7 39 (t, *J*=7 88Hz, 1H), 7 44 (br s, 1H), 7 63-7 68 (m, 1H), 7 78(br s, 1H), 8 05(d, *J*=5 38Hz, 1H)
57		421 16	N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetamide	B	8 2	m/z 421 1 M+	^{1}H NMR ($CDCl_3$) δ 2 17 (s, 3H), 3 08-3 11 (m, 4H), 3 87-3 90 (m, 4H), 6 34 (d, *J*=5 40Hz, 1H), 6 82 (d, *J*=8 99Hz, 2H) 7 22 (br s, 1H), 7 26 (d, *J*=8 94Hz 2H), 7 29-7 36 (m, 1H), 7 42 (t *J*=7 80Hz, 1H), 7 53 (br s, 1H), 7 67 (br s, 1H) 7 85 (d, *J*=7 52Hz, 1H), 8 05 (d, *J*=5 38Hz, 1H)

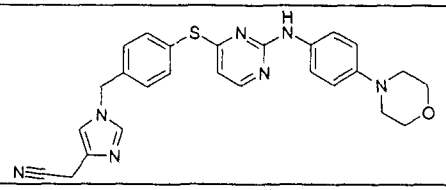
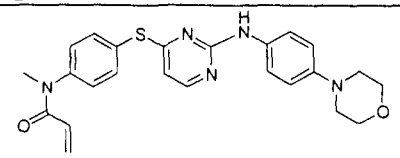
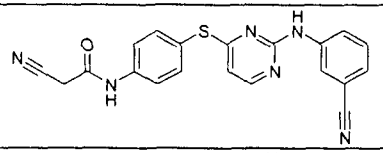
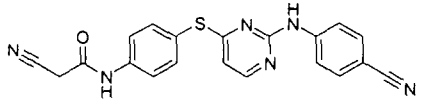
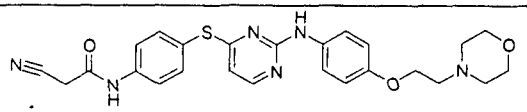
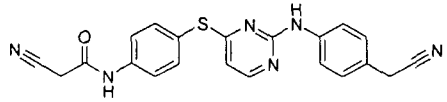
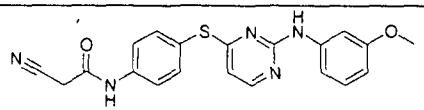
58		421 16	N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetamide	B	8 2	m/z 421 2 M+	^{1}H NMR (d_6-DMSO) δ 2 11 (s, 3H), 3 16-3 27 (m 4H), 3 83-3 92 (m, 4H), 6 49 (d *J*=5 10Hz, 1H) 7 03 (br s, 2H), 7 37 (d, *J*=8 68Hz, 2H), 7 53 (d, *J*=6 86Hz, 2H), 7 77 (d, *J*=8 71Hz, 2H), 8 14 (d *J*=5 41Hz, 1H), 9 69 (s, 1H), 10 34 (s, 1H)
59		447 17	(E)-N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-enamide	B	8 9	m/z 447 2 M+	^{1}H NMR (d_6-DMSO) δ 1 99 (dd, *J*=1 55, 6 90Hz, 3H), 3 04-3 14 (m, 4H), 3 72-3 78 (m, 4H), 6 19 (dd, *J*=1 68, 15 24Hz, 1H), 6 55 (d, *J*=5 34Hz, 1H), 6 83-6 91 (m, 3H), 7 27 (d, *J*=8 72Hz 2H), 7 55 (d, *J*=8 68, 2H), 7 84 (d, *J*=8 72Hz, 2H), 8 12 (d, *J*=5 37Hz, 1H), 9 58 (s, 1H), 10 33 (s, 1H)
60		490 22	(4-methylpiperazin-1-yl)(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)methanone	B	8	m/z 490 3 M+	^{1}H NMR ($CDCl_3$) δ 1 25 (m, 4H), 1 56 (s, 4H), 2 28 (s, 3H), 3 07-3 10 (m, 4H), 3 84-3 87 (m, 4H), 6 34 (d, *J*=5 31Hz, 1H), 6 78 (d, *J*=9 01Hz, 2H), 6 84 (s, 1H), 7 23 (d, *J*=9 02Hz, 2H), 7 49-7 63 (m, 3H), 7 66-7 69 (m, 1H), 8 04 (d, *J*=5 33Hz, 1H)
61		384 13	4-(4-aophenylthio)-N-(3,4,5-trimethoxyphenyl)pyrimidin-2-ae	B	8 6	m/z 384 4 M+	^{1}H NMR ($CDCl_3$) δ 3 82 (s, 3H), 3 86 (s, 6H), 3 93 (br s, 1H), 6 15 (d, *J*=5 39Hz, 1H), 6 73 (d, *J*=8 65Hz, 2H), 6 90 (s, 2H), 6 92 (br s, 1H), 7 36 (d, *J*=8 65Hz, 2H), 8 01 (d *J*=5 39Hz, 1H)
62		394 15	(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)methanol	B	8 2	m/z 394 4 M+	^{1}H NMR ($CDCl_3$) δ 3 07-3 10 (m, 4H), 3 84-3 88 (m, 4H), 4 65 (s, 1H), 4 70 (s, 2H), 6 30 (d, *J*=5 37Hz, 1H), 6 77 (d, *J*=9 02Hz, 2H), 7 24 (d *J*=8 70Hz 2H) 7 42-7 59 (m, 5H) 8 01 (d *J*=5 37Hz, 1H)
63		412 11	4-(3-(chloromethyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	B	9 9	m/z 411 9/41 3 8 M+	^{1}H NMR ($CDCl_3$) δ 3 07-3 10 (m, 4H), 3 84-3 87 (m, 4H), 4 59 (s, 2H), 6 30 (d, *J*=5 37Hz, 1H), 6 78 (d, *J*=9 06Hz, 2H), 7 01 (br s, 1H), 7 25 (d, *J*=8 98Hz, 2H), 7 42-7 59 (m, 3H), 7 61-7 65 (m 1H), 8 03 (d *J*=5 34Hz, 1H)
64		433 16	N-(3-(4-(4-morpholinophenylao) pyrimidin-2-ylthio)phenyl)acrylamide	B	8 0	m/z 432 9 M+	^{1}H NMR ($CDCl_3$) δ 3 10-3 14 (m, 4H), 3 84-3 87 (4H), 5 73 (dd, *J*=1 39, 10 16Hz, 1H), 6 16 (d, *J*=16 88Hz, 1H), 6 23 (d, *J*=5 86Hz, 1H), 6 41 (dd *J*=1 40, 16 82Hz, 1H) 6 78 (br s, 1H) 6 82 (d, *J*=8 90Hz, 2H), 7 10 (d, *J*=8 92Hz, 2H), 7 35-7 37 (m, 2H) 7 66 (br s, 1H), 7 71 (br s, 1H), 7 82 (br s 1H), 7 98 (d, *J*=5 88Hz, 1H)

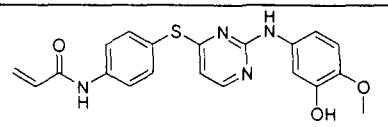
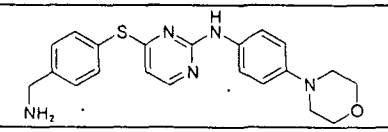
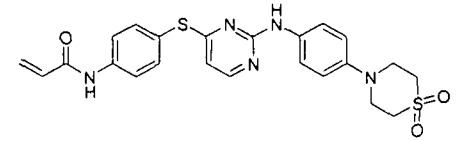
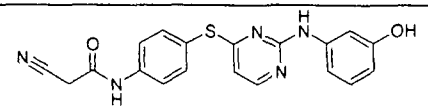
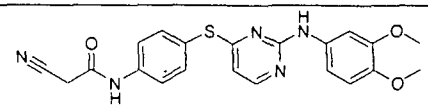
65		379 15	2-(3-aophenylthio)-N-(4-morpholinophenyl)pyrimidin-4-ae	B	7 8	m/z 379 4 M+	^{1}H NMR ($CDCl_3$) δ 3 10-3 14 (m 4H), 3 85-3 88 (m, 4H), 6 23 (d, *J*=5 93Hz, 1H) 6 75 (ddd, *J*=0 99, 2 36, 7 99Hz, 1H), 6 83 (d, *J*=9 05Hz, 2H), 6 99-7 01 (m, 1H), 7 04 (ddd, *J*=1 09, 1 62 7 58Hz, 1H), 7 13 (d, *J*=9 12Hz, 2H), 7 21 (t *J*=7 97Hz, 1H), 7 97 (d, *J*=5 93Hz, 1H)
66		422 14	methyl 4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzoate	B	9 6	m/z 422 5 M+	^{1}H NMR (d_6-DMSO) δ 2 93-2 96 (m, 4H), 3 71-3 74 (m, 4H), 3 91 (s, 3H), 6 56-6 61 (m, 3H), 7 18 (d, *J*=7 76Hz, 2H), 7 77 (d, *J*=8 61Hz, 2H), 8 07 (d, *J*=8 62Hz, 2H), 8 15 (d, *J*=5 25Hz, 1H), 9 39 (s, 1H)
67		394 15	(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)methanol	B	8 2	m/z 394 4 M+	^{1}H NMR (d_6-DMSO) δ 2 98-3 02 (m, 4H), 3 71-3 74 (m, 4H), 4 62 (s, 2H), 6 28 (d, *J*=5 44Hz, 1H) 6 73 (d, *J*=9 08Hz, 2H) 7 32 (d, *J*=8 91Hz, 2H), 7 48 (d, *J*=8 47Hz 2H), 7 59 (d, *J*=8 30Hz 2H), 8 10 (d, *J*=5 298Hz, 1H), 9 37 (s, 1H)
68		432 17	2-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzylao)acetonitrile	B	8 6	m/z 432 2 M+	^{1}H NMR (d_6-DMSO) δ 2 98-3 01 (m, 4H), 3 55 (d *J*=7 12Hz, 2H), 3 70-3 74 (m, 4H), 3 79 (d, *J*=5 83Hz, 2H), 6 28 (d, *J*=5 20Hz, 1H) 6 73 (d *J*=9 05Hz, 2H), 7 33(d, *J*=8 87Hz, 2H), 7 51-7 58 (m, 4H), 8 09 (d, *J*=5 29Hz, 1H), 9 37 (s 1H)
69		408 13	4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzoic acid	B	9 0 (broad)	m/z 408 2 M+	^{1}H NMR (d_6-DMSO) δ 2 95-3 04 (m,4H), 3 70-3 76 (m, 4H), 6 31 (d, *J*=5 31Hz, 1H), 6 73 (d, *J*=9 09Hz, 2H), 7 27 (d, *J*=8 76Hz, 2H), 7 53 (d, *J*=7 93Hz, 2H), 8 00 (d, *J*=8 38Hz, 2H), 8 09 (d, *J*=5 28Hz, 1H), 9 34 (s, 1H)
70		412 11	4-(4-(chloromethyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	B	9 9	m/z 412 2/414 2 M+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 3 08-3 12 (m, 4H), 3 85-3 88 (m, 4H), 4 68 (s, 2H), 6 35 (d, *J*=5 40Hz, 1H), 6 81 (d, *J*=9 13Hz, 2H), 7 29 (d, *J*=9 13Hz, 2H), 7 51 (d, *J*=8 47Hz, 2H), 7 62 (d *J*=8 40Hz, 2H), 8 00 (d, *J*=5 39Hz, 1H)
71		438 14	N-(4-(2-(3,4,5-trimethoxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 8	m/z 439 0 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ8 05 (d, *J* = 5 7, 1H) 7 69 (d, *J* = 8 7, 2H), 7 56 (d, *J* = 8 7, 2H), 7 52 (br s, 1H), 6 98 (br s, 1H), 6 86 (s, 2H), 6 50 (dd, *J* = 17 7, 1 5, 1H), 6 29 (dd, *J* = 17 1, 10 2, 1H), 6 21 (d *J* = 5 4, 1H) 5 34 (dd *J* = 10 2 1 5, 1H) 3 84 (s, 6H), 3 82 (s, 3H)

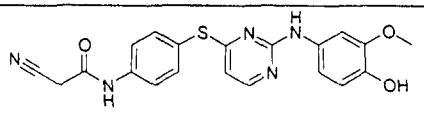
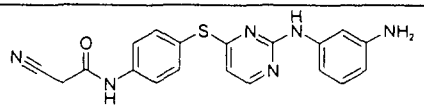
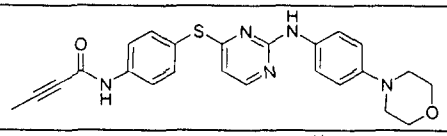
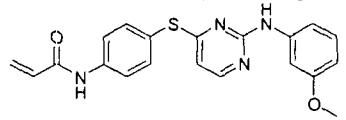
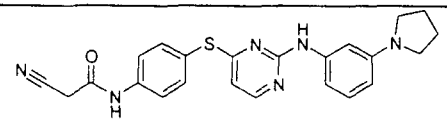
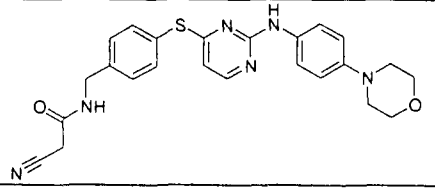
72		446 15	N-(cyanomethyl)-4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzamide	B	8 1	m/z 446 5 M+	^{1}H NMR (d_6-DMSO) δ 2 93-2 96 (m, 4H), 3 71-3 73 (m, 4H), 4 35 (d, *J*=5 48Hz, 1H), 6 51-6 61 (m 3H), 7 17 (d, *J*=8 68Hz, 2H), 7 77 (d, *J*=8 48Hz, 2H), 8 2 (d, *J*=8 42Hz, 2H), 8 14 (d *J*=5 25Hz, 1H), 9 46 (s, 1H), 9 43 (t, *J*=5 84Hz 1H)
73		432 17	2-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzylao)acetonitrile	B	8 6	m/z 432 3 M+	^{1}H NMR (d_6-DMSO) δ 2 98-3 01 (m, 4H), 3 64 (d *J*=5 78Hz, 2H), 3 71-3 74 (m, 4H), 3 85 (d, *J*=4 28Hz 2H) 6 27 (d, *J*=5 59Hz, 1H), 6 74 (d, *J*=9 08Hz, 2H), 7 35 (d, *J*=9 08Hz, 2H), 7 50 (d, *J*=7 94Hz, 2H), 7 60 (d, *J*=8 31Hz, 2H), 8 10 (d *J*=5 31Hz, 1H), 9 39 (s, 1H)
74		378 12	N-(4-(2-(4-methoxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	8 9	m/z 378 1 M+	^{1}H NMR (300 MHz, $CDCl_3$) δ7 98 (d, *J* = 5 4, 1H), 7 77 (d, *J* = 8 7, 2H), 7 56 (d, *J* = 8 7, 2H), 7 28 (s, 1H), 7 27 (d, *J* = 8 7, 2H), 6 76 (d, *J* = 8 7, 2H) 6 48 (dd, *J* = 16 8, 1 8, 1H), 6 35 (dd, *J* = 17 1, 10 2, 1H), 6 33 (d, *J* = 5 4, 1H), 5 80 (dd, *J* = 10 2 1 8, 1H), 3 76 (s, 3H)
75		393 16	4-(3-(aomethyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	A	6 8	m/z 393 2 M+	^{1}H NMR ($CDCl_3$) δ 3 07-3 10 (m, 4H), 3 84-3 88 (m, 4H) 3 91 (br s, 2H), 6 27 (d, *J*=5 35Hz, 1H), 6 78 (d, *J*=9 06Hz, 2H), 6 92 (br s, 1H), 7 27 (d *J*=9 09Hz, 2H), 7 43-7 54 (m, 3H), 7 58-7 59 (m 1H), 8 01 (d, *J*=5 36Hz, 1H)
76		446 15	2-cyano-N-(4-(2-(3-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	6 6	m/z 447 1 $[M+H]^+$	^{1}H NMR (300 MHz, $CDCl_3$) δ8 06 (d, *J* = 5 4, 1H) 7 82 (br s, 1H),7 62 (s, 4H), 7 18 (t, *J* = 2 1, 1H) 7 13 (t *J* = 8 1, 1H) 6 97 (br s, 1H), 6 95 (dd, *J* = 8 1 2 4 1H), 6 59 (dd, *J* = 8 1 2 4 1H), 6 26 (d *J* = 5 4, 1H), 3 86 (t, *J* = 4 5 4H), 3 60 (s 2H) 3 15 (t *J* = 4 5 4H)
77		433 16	N-(4-(2-(3-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	8 8	m/z 433 4 M+	^{1}H NMR (300 MHz, $CDCl_3$) δ8 05 (d, *J* = 5 6, 1H) 7 71 (d, *J* = 9 1, 2H), 7 58 (d, *J* = 8 7, 2H) 7 35 (br s, 1H) 7 21 (t, *J* = 2 2, 1H), 7 13 (t, *J* = 8 0 1H), 6 98 (br s, 1H), 6 95-6 94 (m, 1H), 6 58 (dd *J* = 8 2, 2 4, 1H), 6 52-6 47 (m, 1H), 6 30 (d, *J* = 10 1, 1H), 6 25-6 23 (m, 1H), 5 86-5 83 (m, 1H), 3 86 (t, *J* = 4 8, 4H), 3 16 (t, *J* = 4 8, 4H)

78		324 10	4-(4-aophenylthio)-N-(4-methoxyphenyl)pyrimidin-2-ae	B	8 8	m/z 324 1 M+	^{1}H NMR (300 MHz, $CDCl_3$) δ7 98 (d, *J* = 5 4 1H) 7 36 (d, *J* = 8 7, 2H), 7 33 (d, *J* = 9 0, 2H), 6 98 (br s 1H), 6 81 (d, *J* = 9 3, 2H), 6 74 (d, *J* = 8 7 2H), 6 25 (d, *J* = 5 7, 1H), 3 98 (br s, 2H), 3 79 (s 3H)
79		479 20	tert-butyl 4-(2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenylcarbamate	C	7 8	m/z 480 1 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ8 03 (d, *J* = 5 0, 1H), 7 54-7 46 (m, 4H), 7 23 (t, *J* = 2 3 1H), 7 14 (t *J* = 8 1, 1H), 7 04 (br s, 1H), 6 98-6 95 (m, 1H), 6 66 (br s 1H), 6 57 (dd, *J* = 8 3, 1 8, 1H), 6 20 (d *J* = 5 3, 1H), 3 86 (t, *J* = 4 8, 4H), 3 64 (s 2H) 3 16 (t *J* = 4 8, 4H), 1 55 (s, 9H)
80		432 15	4-(4-(1H-tetrazol-1-yl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 6	m/z 433 [M+H]+	^{1}H NMR (d_6-DMSO) δ 2 79-2 81 (m, 4H), 3 63-3 66 (m 4H), 6 54-6 59 (m, 3H), 7 19 (d, *J*=8 48Hz, 2H), 7 91 (d, *J*=8 81Hz, 2H), 8 12 (d, *J*=8 79Hz, 2H), 8 16 (d, *J*=5 24Hz, 1H), 9 39 (s, 1H), 10 25 (s, 1H)
81		452 15	N-methyl-N-(4-(2-(3,4,5-trimethoxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	8 8	m/z 452 3 M+	^{1}H NMR (300 MHz, $CDCl_3$) δ8 11 (d, *J* = 4 8, 1H) 7 65 (d *J* = 8 4, 2H) 7 27 (d, *J* = 8 4, 2H) 6 97 (br s 1H), 6 88 (s, 2H), 6 42 (dd, *J* = 16 8, 1 8, 1H), 6 27 (d, *J* = 5 4, 1H), 6 14 (dd, *J* = 17 1, 10 8, 1H), 5 61 (dd, *J* = 10 2, 1 8, 1H), 3 85 (s, 6H), 3 82 (s, 3H), 3 41 (s, 3H)
82		376 14	N-(4-(2-(3,5-dimethylphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	9 8	m/z 376 3 M+	
83		391 11	2-cyano-N-(4-(2-(4-methoxyphenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	8 3 (broad)	m/z 391 1 M+	^{1}H NMR (300 MHz, d_6-DMSO) δ8 11 (d, *J* = 5 7 1H), 7 75 (d, *J* = 8 7, 2H), 7 60 (d, *J* = 8 7, 2H), 7 36 (d, *J* = 9 3, 2H), 6 74 (d, *J* = 9 3, 2H), 6 37 (d *J* = 5 7, 1H), 3 69 (s, 3H), 3 43 (s, 1H)
84		389 13	2-cyano-N-(4-(2-(3,5-dimethylphenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	9 4	m/z 389 2 M+	^{1}H NMR (300 MHz, $CDCl_3$) δ8 01 (d, *J* = 5 1, 1H) 7 69 (d, *J* = 8 7, 2H), 7 58 (d, *J* = 8 7, 2H), 7 13 (s, 2H), 6 77 (br s, 1H), 6 25 (d, *J* = 5 4, 1H), 2 26 (s 6H)

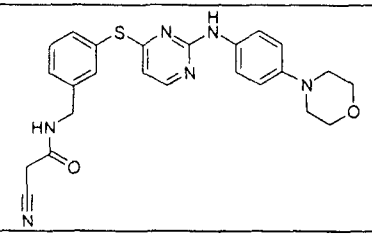
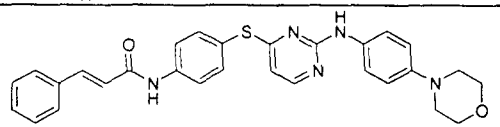
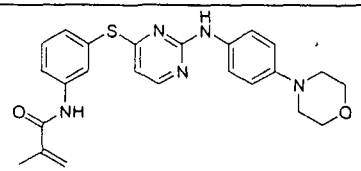
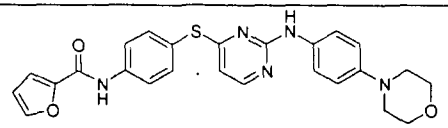
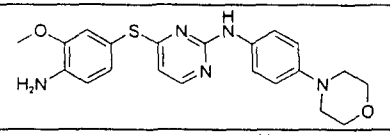
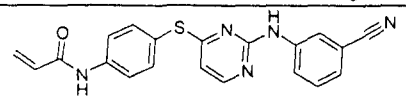
85		509 17	2-ao-1-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-imidazole-4,5-dicarbonitrile	A	9 3	m/z 509 1 M+	^{1}H NMR (d_6-DMSO) δ 3 00-3 03 (m, 4H), 3 71-3 74 (m, 4H), 5 27 (s, 2H) 6 19 (d, *J*=5 30Hz, 1H) 6 78 (d, *J*=9 12Hz, 2H), 7 23 (s, 2H), 7 37 (d, *J*=8 34Hz, 2H), 7 42 (d, *J*=9 05Hz, 2H) 7 69 (d *J*=8 34Hz, 2H) 8 11 (d, *J*=5 27Hz, 1H) 9 39 (s 1H)
86		488 24	N-(4-(2-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	6 3	m/z 488 3 M+	^{1}H NMR (DMSO-d_6, 300 MHz) δ 10 32 (s, 1H), 9 70 (br s , 1H), 8 15 (d, *J*=5 7Hz, 1H), 7 77 (d, *J*=9 3Hz, 2H), 7 56 (d, *J*=8 4Hz, 2H), 7 41-7 50 (m, 4H, TsOH), 7 20-7 05 (m, 4H, TsOH), 6 46 (d *J*=6 3Hz, 1H), 3 82 (m, 1H), 3 70 (m, 2H), 3 57 (m, 2H), 3 08 (m, 4H), 2 29 (s, 3H, TsOH) 2 13 (s, 3H), 2 01 (m, 4H), 1 89 (m, 4H)
87		500 24	N-(4-(2-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	6 5	m/z 500 2 M+	^{1}H NMR (DMSO-d_6, 300 MHz) δ10 60 (s, 1H), 10 33 (br s , 1H, TsOH), 9 78 (br s , 1H), 8 17 (d *J*=5 4Hz, 1H), 7 88 (d, *J*=8 7Hz, 2H), 7 60 (d, *J*=8 4Hz 2H), 7 49 (m, 4H, TsOH), 7 11 (m, 4H TsOH), 6 62-6 51 (m, 2H), 6 34 (dd, *J*=17 1, 2 1Hz, 1H) 5 86 (d, *J*=9 9, 1 5Hz 1H), 3 70-3 65 (m, 3H), 3 36 (m, 2H), 3 06 (m 4H), 2 28 (s, 3H, TsOH), 2 24-2 16 (m, 2H) 2 02 (m, 4H) 1 88 (m 2H)
88		513 23	2-cyano-N-(4-(2-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	6 4	m/z 513 1 M+	^{1}H NMR (DMSO-d_6, 300 MHz) δ10 74 (s, 1H), 10 19 (br s , 1H, TsOH), 9 78 (s, 1H), 8 18 (d *J*=5 1Hz, 1H), 7 73 (d, *J*=8 7Hz, 2H), 7 61 (d, *J*=8 1Hz 2H), 7 52-7 45 (m, 4H, TsOH), 7 42 (br d, *J*=8 1Hz, 1H), 7 20-7 08 (m, 4H, TsOH) 6 55 (br d, *J*=4 8Hz, 1H), 4 06 (s, 2H), 3 70-3 64 (m, 4H), 3 36 (m, 1H), 3 10 (m, 4H), 2 28 (s, 3H, tsOH), 2 50-2 20 (m, 2H), 2 04-1 98 (m 4H), 1 95-1 80 (m, 2H)
89		451 13	2-cyano-N-(4-(2-(3,4,5-trimethoxyphenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	7 9	m/z 451 3 M+	^{1}H NMR (300 MHz d_6-DMSO) δ10 57 (s, 1H), 9 50 (s 1H), 8 16 (d, *J* = 5 4, 1H), 7 71 (d, *J* = 9 1 2H), 7 62 (d, *J* = 9 1, 2H), 7 13 (s, 2H), 6 12 (d, *J* = 4 8 1H) 3 95 (s, 2H), 3 71 (s 6H), 3 61 (s, 3H)

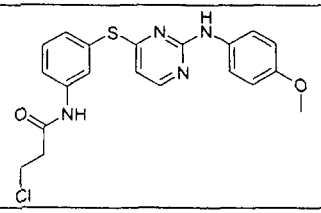
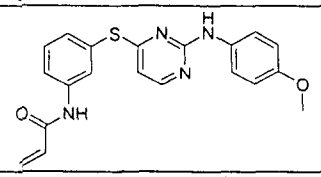
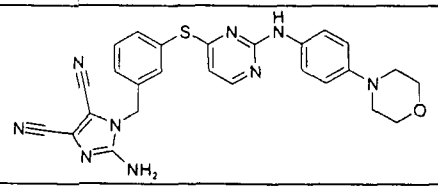
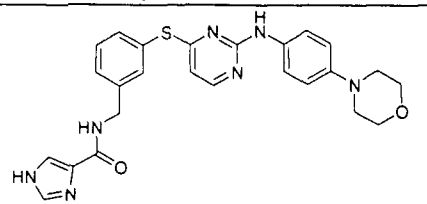
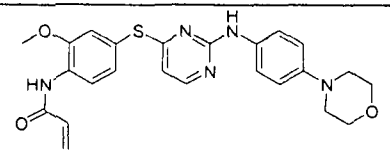
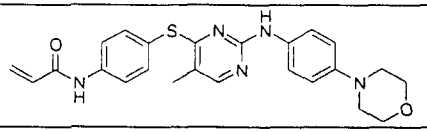
90		483 18	2-(1-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-imidazol-4-yl)acetonitrile	A	8 3	m/z 483 2 M+	^{1}H NMR (d_6-DMSO) δ 3 01-3 08 (m, 4H), 3 70 (d *J*=0 99Hz, 2H), 3 84-3 88 (m, 4H), 5 15 (s, 2H), 6 21 (d, *J*=5 33Hz, 1H), 6 82-6 85 (m, 3H), 6 94-6 98 (m, 1H), 7 23 (d, *J*=10 10Hz, 2H) 7 37 (d *J*=9 08Hz, 2H), 7 51-7 53 (m, 1H), 7 62 (d, *J*=8 36hz, 2H) 8 04 (d, J=5 33Hz, 1H)
91		447 17	N-methyl-N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	B	8 3	m/z 447 5 M+	(300MHz $CDCl_3$) δ 8 06 (d, *J*=5 7 Hz, 1H), 7 66 (d, *J*=8 7 Hz, 2H), 7 36 (d, *J*=9 3 Hz, 2H), 7 27 (d, *J*=8 7 Hz 2H), 7 13, (s, 1H), 6 82 (d, *J*=9 0 Hz, 2H), 6 43 (dd *J*=15 0, 2 0 Hz, 1H), 6 33 (d, *J*=5 4 Hz, 1H), 6 15 (dd *J*=16 5, 10 3 Hz, 1H), 5 59 (dd *J*=10 0, 1 7 Hz, 1H) 3 85 (m 4H) 3 42 (s 3H) 3 08 (m 4H)
92		386 09	2-cyano-N-(4-(2-(3-cyanophenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	8 1	m/z 386 1 M+	^{1}H NMR (300 MHz, d_6-DMSO) δ10 58 (s, 1H), 9 99 (s, 1H), 8 23 (d, *J* = 5 1, 1H), 7 99 (br s, 1H), 7 84-7 80 (m,1H), 7 72 (d, *J* = 9 0, 2H), 7 62 (d, *J* = 8 7, 2H), 7 63-7 60 (m, 2H), 6 43 (d, *J* = 5 4, 1H), 3 96 (s, 2H)
93		386 09	2-cyano-N-(4-(2-(4-cyanophenylao)pyrimidin-4-ylthio)phenyl)acetamide	B	8 1	m/z 386 1 M+	^{1}H NMR (300 MHz, d_6-DMSO) δ10 62 (s, 1H), 10 17 (s, 1H), 8 25 (d, *J* = 5 3, 1H), 7 73 (d, *J* = 8 7, 2H), 7 67 (d, *J* = 9 1, 2H), 7 62 (d, *J* = 8 7, 2H), 7 54 (d, *J* = 9 1, 2H), 6 54 (d, *J* = 5 5, 1H), 3 96 (s, 3H)
94		490 18	2-cyano-N-(4-(2-(4-(2-morpholinoethoxy)phenylao)pyrimidin-4-ylthio)phenyl)acetamide	A	7 6	m/z 490 3 M+	^{1}H NMR (300 MHz, $CDCl_3$) δ8 03 (d, *J* = 5 5, 2H), 7 61 (m, 4H) 7 25 (d, *J* = 9 3, 2H), 6 89 (br s, 1H) 6 76 (d, *J* = 9 2, 2H), 6 32 (d, *J* = 5 2, 1H), 4 08 (t, *J* = 5 7, 2H), 3 75 (t, *J* = 4 7, 4H), 3 64 (s, 2H), 2 80 (t, *J* = 5 7, 2H), 2 59 (t, *J* = 4 8, 4H)
95		400 11	2-cyano-N-(4-(2-(4-(cyanomethyl)phenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	6 6	m/z 401 0 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 74 (s, 1H), 9 73 (s, 1H), 8 17 (d, *J* = 5 4, 1H), 7 74 (d, *J* = 8 7, 2H), 7 60 (d, *J* = 8 7, 2H), 7 43 (d, *J* = 8 6, 2H), 7 06 (d, *J* = 8 6, 2H), 6 48 (d, *J* = 5 3, 1H), 3 98 (s 2H), 3 89 (s 2H)
96		391 11	2-cyano-N-(4-(2-(3-methoxyphenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	6 8	m/z 392 0 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 68 (s, 1H), 9 63 (s 1H), 8 16 (d, *J* = 5 4, 1H), 7 79 – 7 67 (m, 2H) 7 66 – 7 55 (m, 2H), 7 24 (t *J* = 2 1 1H) 7 13 (d

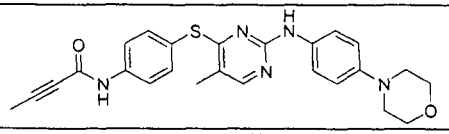
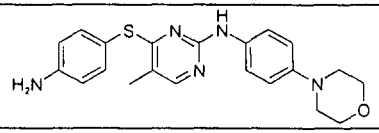
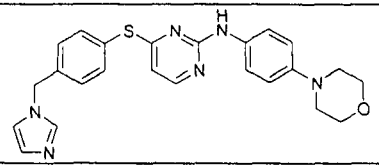
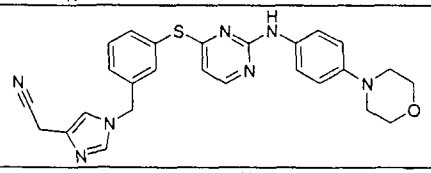
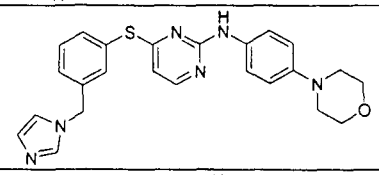
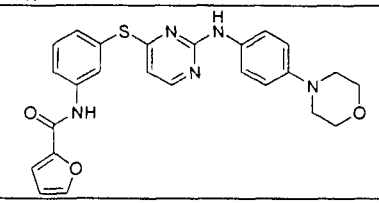
							J = 8 2 1H), 7 03 (t, J = 8 1, 1H), 6 54 – 6 44 (m 1H) 6 31 (d J = 5 4, 1H), 3 98 (s, 2H), 3 69 (s· 3H)
97		394 11	N-(4-(2-(3-hydroxy-4-methoxyphenylao)pyrımıdın-4-ylthıo)phenyl)acrylamıde	B	7 7	m/z 394 3 M+	^{1}H NMR (300 MHz, d_6-DMSO) δ10 43 (s, 1H), 9 30 (s, 1H), 8 78 (br s, 1H), 8 09 (d, J = 5 3, 1H), 7 85 (d, J = 8 7, 2H), 7 58 (d, J = 8 7, 2H), 6 97-6 96 (m, 1H), 6 88 (dd, J = 8 7, 2 9, 1H), 6 58 (d, J = 9 1, 1H), 6 48 (dd, J = 17 0, 10 0, 1H), 6 33-6 27 (m, 1H), 5 80 (dd, J = 10 1, 2.5, 1H), 5 74 (s, 1H), 3 56 (s, 3H)
98		393 16	4-(4-(aomethyl)phenylthıo)-N-(4-morpholınophenyl)pyrımıdın-2-ae	A	7 1	m/z not observed	^{1}H NMR (d_6-DMSO) δ 3 32-3 43 (m, 4H), 3 91-4 01 (m, 4H), 4 15-4 25 (m, 2H), 6 46 (d, J=5 39Hz, 1H), 7 35 (d, J=8 82Hz, 2H), 7 52 (d, J=8 99Hz 2H), 7 63-7 73 (m, 4H), 8 19 (d, J=5 37Hz, 1H), 8 54 (br s, 1H), 9 83 (s, 1H)
99		481 12	N-{4-[(2-{[4-(1,1-dıoxo-1λ^6,4-thıomorpholın-4-yl)phenyl]ao}pyrımıdın-4-yl)sulfanyl]phenyl}prop-2-enamıde	C	6 6	m/z 482 0 [M+H]+	^{1}H NMR (300 MHz, d_6-DMSO) δ10 55 (s, 1H) 9 58 (s, 1H), 8 12 (d, J = 5 5, 1H), 7 87 (d, J = 8 7 2H), 7 58 (d, J = 8 7 2H), 7 25 (d, J = 8 2, 2H), 6 74 (d, J = 9 3, 2H), 6 57-6 48 (m, 2H), 6 37-6 30 (m 1H) 5 84 (dd, J = 10 0, 2 2, 1H), 3 56-3 55 (m, 4H) 3 06-3 05 (m 4H)
100		377 09	2-cyano-N-(4-(2-(3-hydroxyphenylao)pyrımıdın-4-ylthıo)phenyl)acetamıde	C	6 3	m/z 378 0 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 57 (s 1H), 9 49 (s, 1H), 9 17 (s, 1H) 8 14 (d, J = 5 3, 1H), 7 71 (d J = 8 7 2H), 7 61 (d J = 8 8, 2H) 7 08 (t, J = 2 0 1H), 7 04 – 6 95 (m 1H), 6 89 (t, J = 8 0, 1H), 6 37 – 6 27 (m, 1H), 6 23 (d, J = 5 3, 1H), 3 96 (s, 2H)
101		421 12	2-cyano-N-(4-(2-(3,4-dımethoxyphenylao)pyrımıdın-4-ylthıo)phenyl)acetamıde	C	6 5	m/z 422 0 [M+H]+	^{1}H-NMR (300 MHz, CD_3OD) δ 8 02 (d, J = 5 4 1H), 7 72 (d J = 8 8, 2H), 7 58 (d J = 8 8, 2H), 7 09 (d J = 2 5, 1H) 6 97 (dd J = 2 5 8 7 1H) 6 71 (d, J = 8 8 1H), 6 38 (d, J = 5 4 1H) 3 79 (s 3H), 3 77 (s, 3H)

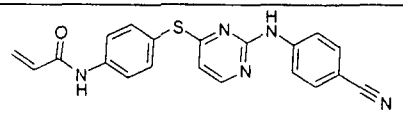
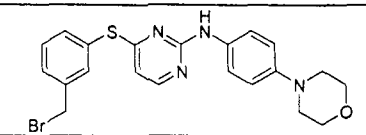
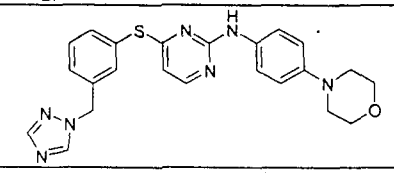
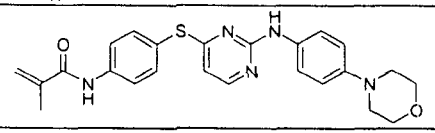
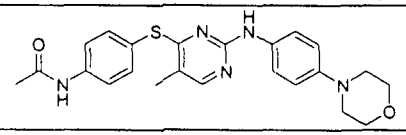
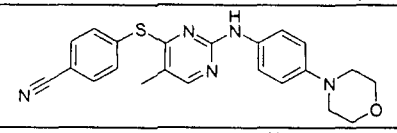
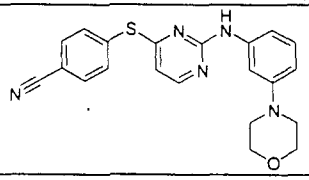
102		407 11	2-cyano-N-(4-(2-(4-hydroxy-3-methoxyphenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	6 2	m/z 408 0 [M+H]+	^{1}H-NMR (300 MHz, CD_3OD) δ 7 99 (d, *J* = 5 4 1H) 7 72 (d, *J* = 8 8, 2H) 7 58 (d, *J* = 8 8 2H) 6 91 (d *J* = 2 5 1H), 6 85 (dd *J* = 2 6, 8 7 1H) 6 68 (d *J* = 8 8 1H), 6 35 (d, *J* = 5 4 1H), 3 81 (s 3H)
103		376 11	N-(4-(2-(3-aophenylao)pyrimidin-4-ylthio)phenyl)-2-cyanoacetamide	C	6 2	m/z 377 1 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 56 (s, 1H), 9 30 (s, 1H) 8 11 (d *J* = 5 3 1H), 7 71 (d, *J* = 8 7, 2H), 7 60 (d *J* = 8 7, 2H), 6 85 – 6 68 (m, 3H), 6 25 – 6 08 (m, 2H), 4 84 (s, 2H), 3 95 (s, 2H)
104		445 16	N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)but-2-ynamide	C	6 8	m/z 446 1 [M+H]+	(300MHz, $CDCl_3$) δ 10 96 (s, 1H), 9 34 (s, 1H), 8 10 (d, *J*=5 7Hz, 1H) 7 78 (d *J*=8 7Hz, 2H), 7 56 (d, *J*=8 7Hz, 2H), 7 18 (d, *J*=8 7Hz, 2H), 6 61 (d *J*=8 7Hz, 2H), 6 47 (d, *J*=4 8Hz, 1H) 3 73 (m, 4H), 2 97 (m, 4H), 2 08 (s 3H)
105		378 12	N-(4-(2-(3-methoxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	8 5	m/z 378 4 M+	^{1}H NMR (300 MHz, $CDCl_3$) δ8 05 (d, *J* = 4 9, 1H), 7 71 (d, *J* = 8 7 2H), 7 58 (d, *J* = 8 7, 2H) 7 43 (br s, 1H) 7 14 (br s, 1H), 7 13 (t, *J* = 8 1, 1H), 7 01-6 98 (m, 1H), 6 57-6 52 (m, 1H), 6 46 (m, 1H), 6 31 (d, *J* = 10 5, 1H), 6 25 (d, *J* = 11 0 1H) 5 85-5 82 (m, 1H), 3 78 (s, 3H)
106		430 16	2-cyano-N-(4-(2-(3-(pyrrolidin-1-yl)phenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	7 4	m/z 431 1 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 57 (s, 1H), 9 35 (s, 1H), 8 13 (d, *J* = 5 3, 1H), 7 71 (d, *J* = 8 8, 2H), 7 60 (d, *J* = 8 7, 2H), 6 99 – 6 78 (m 3H), 6 21 (d *J* = 5 3, 1H), 6 17 – 6 09 (m, 1H), 3 96 (s, 2H), 3 16 (t, *J* = 6 4, 4H), 1 92 (dd, *J* = 5 0, 8 0, 5H)
107		460 17	2-cyano-N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)acetamide	B	7 6	m/z 460 1 M+	^{1}H NMR (d_6-DMSO) δ 2 99-3 02 (m, 4H), 3 71-3 73 (m 4H) 3 74 (s, 2H), 4 39-4 41 (m, 2H), 6 22 (d, *J*=4 93Hz, 1H), 6 75 (d, *J*=9 04Hz, 2H), 7 37 (d, *J*=8 62Hz, 2H), 7 43 (d, *J*=8 41Hz, 2H), 7 60 (d, *J*=8 23Hz, 2H), 8 10 (d *J*=5 28Hz, 1H), 8 67-8 82 (m, 1H), 9 38 (s, 1H)

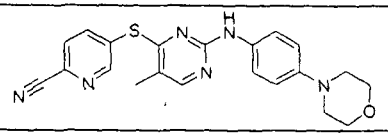
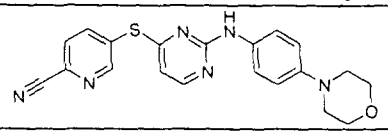
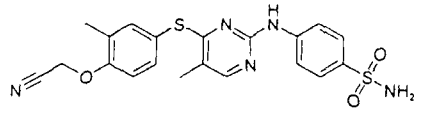
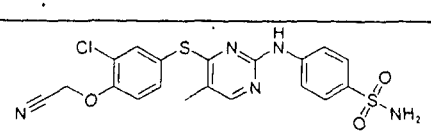
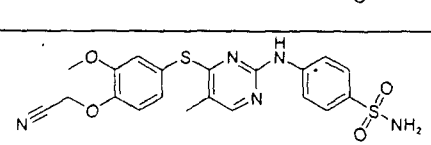
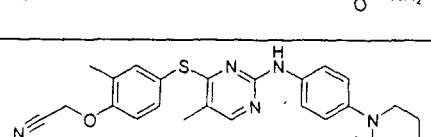
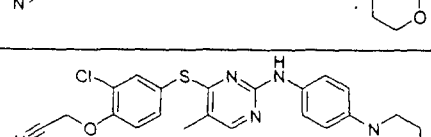
108		487 18	N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-4-carboxamide	B	7 2	m/z 486 9 M+	^{1}H NMR (d_6-DMSO) δ 2 99-3 03 (m, 4H), 3 70-3 73 (m, 4H), 4 51 (d, *J*=6 74Hz, 2H), 6 21 (d, *J*=5 34Hz, 1H), 6 76 (d, *J*=8 95Hz, 2H) 7 38 (d *J*=8 74Hz, 2H), 7 44 (d, *J*=8 21Hz, 2H) 7 57 (d, *J*=8 28Hz, 2H), 7 63 (s, 1H), 7 72 (s, 1H), 8 09 (d *J*=5 28Hz, 1H), 8 51-8 59 (m, 1H), 12 47 (br s 1H)
109		446 16	4-(4-((1H-tetrazol-1-yl)methyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	B	7 8	m/z 446 1 M+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 3 09-3 12 (m, 4H) 3 85-3 89 (m, 4H), 5 67 (s, 2H), 6 27 (d, *J*=5 36Hz, 1H), 6 82 (d, *J*=9 10Hz, 2H), 7 31-7 36 (m, 5H), 7 66 (d, *J*=8 36Hz, 2H), 8 08 (d *J*=5 35Hz, 1H), 8 65 (s, 1H)
110		433 16	N-(3-(2-(3-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	B	8 3	m/z 433 M+	^{1}H NMR (d_6-DMSO) δ 3 01-3 04 (m, 4H), 3 70-3 74 (m 4H), 5 78 (dd, *J*=2 11, 9 24Hz, 1H), 6 26 (dd, *J*=2 15, 16 96Hz, 1H), 6 34 (d, *J*=5 28Hz, 1H), 6 45 (dd, *J*=9 90, 16 92Hz, 1H), 6 48-6 58 (m 1H), 6 97 (t, *J*=8 10Hz, 1H), 7 06-7 11 (m, 1H), 7 19-7 22 (m, 1H), 7 34 (ddd, *J*=1 08 7 71,7 70Hz, 1H), 7 50 (t, *J*=7 87Hz, 1H), 7 83 (ddd, *J*=1 02, 2 09, 8 22Hz, 1H), 7 98-8 01 (m 1H), 8 17 (d, *J*=5 31Hz, 1H), 9 47 (s, 1H), 10 34 (s, 1H)
111		447 17	N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)acrylamide	B	7 7	m/z 447 4 M+	^{1}H NMR (d_6-DMSO) δ 3 00-3 03 (m, 4H), 3 71-3 74 (m, 4H), 4 46 (d, *J*=5 95Hz, 2H), 5 64 (dd, *J*=2 31, 9 99Hz, 1H), 6 15 (dd, *J*=2 30, 17 09Hz, 1H), 6 23 (d, *J*=4 99Hz, 1H), 6 31 (d, *J*=9 99Hz, 17 10Hz, 1H), 6 75 (d, *J*=9 14Hz, 2H), 7 37 (d, *J*=9 02Hz, 2H), 7 43 (d *J*=8 42Hz, 2H), 7 60 (d *J*=8 33Hz, 2H) 8 10 (d, *J*=5 27Hz, 1H) 8 68 (t *J*=6 25Hz, 1H), 9 38 (s, 1H)
112		447 17	N-(3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)acrylamide	B	7 8	m/z 447 4 M+	^{1}H NMR (d_6-DMSO) δ 2 99-3 02 (m, 4H), 3 71-3 74 (m, 4H), 4 41 (d, *J*=6 05Hz, 2H), 5 62 (dd, *J*=2 34, 9 96Hz, 1H), 6 12 (dd, *J*=2 34, 17 10Hz 1H), 6 27 (dd, *J*=9 95, 17 07Hz, 1H), 6 28 (d, *J*=5 27Hz 1H) 6 74 (d, *J*=9 07Hz 2H) 7 35 (d *J*=9 05Hz, 2H), 7 43-7 53 (m, 4H), 8 12 (d, *J*=5 29Hz, 1H), 8 76 (t, *J*=5 96Hz, 1H), 9 37 (s 1H)

113		460 17	2-cyano-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)acetamide	B	7 7	m/z 460 5 M+	^{1}H NMR (d_6-DMSO) δ 2 99-3 02 (m, 4H), 3 70 (s 2H), 3 71-3 75 (m, 4H), 4 35 (d, *J*=5 93Hz, 2H), 6 27 (d, *J*=5 52Hz, 1H), 6 75 (d, *J*=9 10Hz, 2H), 7 35 (d, *J*=8 68Hz, 2H), 7 48-7 55 (m, 4H), 8 11(d *J*=5 29Hz, 1H), 8 76 (t, *J*=5 25Hz, 1H) 9 38 (s 1H)
114		509 19	N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)cinnamamide	C	7 5	m/z 510 1 [M+H]+	^{1}H NMR (300 MHz, DMSO-d_6) δ 10 6 (br s, 1H) 9 34 (br s 1H) 8 11 (d, *J* = 5 1 1H), 7 91 (d *J* = 8 7, 2H) 7 69-7 64 (m, 3H), 7 59 (d, *J* = 8 1 2H) 7 51-7 44 (m, 3H), 7 18 (d, *J* = 8 7, 2H), 6 89 (d, *J* = 16 2, 1H), 6 62-6 53 (m, 3H), 3 59 (m, 4H), 2 91 (m, 4H)
115		447 17	N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)methacrylamide	C	6 9	m/z 448 1 [M+H]+	^{1}H-NMR (300 MHz, CD_3OD) δ 8 01 (d, *J* = 5 4 1H), 7 98 (ddd, *J* = 1 1, 2 1 8 2 1H), 7 88 (t *J* = 1 8, 1H), 7 47 (t, *J* = 7 9, 1H), 7 39 – 7 32 (m, 1H), 7 25 (d, *J* = 9 1, 2H), 6 77 (d, *J* = 9 0 2H) 6 46 (d, *J* = 5 4, 1H), 5 78 (s, 1H), 5 51 (d, *J* = 0 9, 1H), 3 89 – 3 76 (m 4H), 3 16 – 2 95 (m, 4H), 2 02 (s, 3H)
116		473 15	N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)furan-2-carboxamide	C	6 9	m/z 474 [M+H]+	^{1}H NMR (300 MHz, DMSO-d_6) δ 10 5 (br s 1H) 9 34 (br s, 1H), 8 12 (d, *J* = 5 1, 1H), 8 02-7 98 (m, 3H), 7 59 (d, *J* = 8 7, 2H), 7 43 (dd, *J* = 3 6, 0 9, 1H), 7 17 (d, *J* = 9 0, 2H), 6 76 (dd, *J* = 3 6, 1 5, 1H), 6 60 (d, *J* = 9 0, 2H), 6 54 (d, *J* = 5 1, 1H), 3 52 (m, 4H), 2 87 (m, 4H)
117		409 16	4-(4-ao-3-methoxyphenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 8	m/z 410 [M+H]+	(300MHz, $CDCl_3$) δ 7 98 (d, *J*=4 8, 1H), 7 33 (d *J*=8 4, 2H), 7 05 (dd, *J*=1 8, 7 8, 1H), 6 97 (d, *J*=1 8, 1H), 6 89 (br s, 1H), 6 83 (d, *J*=9 3, 2H), 6 75 (d, *J*=7 8, 1H), 6 24 (d, *J*=5 4, 1H), 3 82-3 88 (m, 4H), 3 82 (s, 3H), 3 08-3 13 (m, 4H)
118		373 10	N-(4-(2-(3-cyanophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 374 1 [M+H]+	1H NMR (300 MHz, DMSO) δ 10 42 (s, 1H), 10 00 (s, 1H), 8 24 (d, J = 5 5, 1H), 8 01 (s, 1H), 7 85 (d, J = 8 7, 3H), 7 61 (d, J = 8 2, 2H) 7 33 (d, J = 5 0, 2H) 6 52-6 28 (m 3H), 5 82 (dd, J = 10 0 1 8 1H)

119		414 09	3-chloro-N-(3-(2-(4-methoxyphenylao)pyrimidin-4-ylthio)phenyl)propanamide	C	7 1	m/z 415 0/41 7 0 [M+H]+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 2 80 (t, *J*=6 47Hz, 2H), 3 78 (s, 3H), 3 86 (t, *J*=6 50Hz, 2H), 6 35 (d *J*=5 38Hz, 1H), 6 76 (d, *J*=9 10Hz, 2H), 7 26 (d, *J*=9 30Hz, 2H), 7 32-7 36 (m, 1H) 7 42 (t, *J*=7 76Hz, 1H), 7 72-7 74 (m, 1H) 7 81 (m, 1H) 8 00 (d, *J*=5 39Hz, 1H)
120		378 12	N-(3-(2-(4-methoxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 379 [M+H]+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 3 79 (s, 3H), 5 77 (dd, *J*=1 45, 10 14Hz, 1H), 6 25 (dd, *J*=10 14 16 87Hz, 1H), 6 36 (d, *J*=5 37Hz, 1H), 6 44 (dd *J*=1 45, 16 87Hz, 1H), 6 75 (d, *J*=9 14Hz, 2H), 7 26 (d, *J*=9 00Hz, 2H), 7 33-7 37 (m, 1H), 7 43 (t, *J*=7 67Hz, 1H), 7 77-7 78 (m, 1H), 7 91 (d, *J*=7 04Hz, 1H), 8 01 (d, *J*=5 36Hz, 1H)
121		509 17	2-ao-1-(3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-4,5-dicarbonitrile	C	6 7	m/z 510 1 [M+H]+	^{1}H NMR (d_6-DMSO) δ2 98-3 10 (m, 4H), 3 71-3 74 (m, 4H), 5 22 (s, 2H), 6 29 (d, *J*=5 17Hz 1H) 6 71 (d, *J*=8 71Hz, 2H), 7 21 (s, 2H), 7 30-7 39 (m, 3H), 7 54-7 64 (m, 3H), 8 11 (d, *J*=5 27Hz 1H), 9 38 (s, 1H)
122		487 18	N-(3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-4-carboxamide	C	6 1	m/z 488 1 [M+H]+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 3 07-3 10 (m 4H) 3 84-3 87 (m, 4H), 4 64 (s, 2H), 6 28 (d *J*=5 40Hz, 1H), 6 80 (d, *J*=9 02Hz, 2H), 7 33 (d, *J*=9 16Hz, 2H), 7 40-7 51 (m, 4H), 7 63 (m, 2H), 7 98 (d, *J*=5 39Hz, 1H)
123		463 17	N-(2-methoxy-4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 464 1 [M+H]+	(300MHz $CDCl_3$) δ 8 64 (d, *J*=8 4Hz, 1H) 8 02 (d *J*=5 1Hz, 1H), 7 99 (br s , 1H), 7 03 (d *J*=1 8Hz 1H), 7 22 (s, 1H), 7 09 (d, *J*=1 8Hz, 1H), 6 92 (br s , 1H), 6 75 (d, *J*=9 0Hz, 2H), 6 48 (dd, *J*=16 8 1 2Hz, 1H), 6 37-6 27 (m, 2H), 5 83 (dd, *J*=9 9 1 5Hz, 1H) 3 86 (s, 3H), 3 83 (m 4H) 3 06 (m 4H)
124		447 17	N-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 8	m/z 448 2 [M+H]+	^{1}H NMR (300 MHz DMSO-d_6) δ 10 5 (br s 1H) 9 11 (br s, 1H), 8 01 (s 1H), 7 89 (d *J* = 8 4, 2H) 7 55 (d, *J* = 9 0, 2H), 6 98 (d *J* = 9 3 2H), 6 52 (dd, *J* = 16 8, 10 2, 1H), 6 46 (d *J* = 9 3, 2H) 6 34 (dd *J* = 16 8, 2 1, 1H) 5 86 (dd, *J* = 9 9 2 1, 1H)

							3 64 (m, 4H), 2 85 (m, 4H), 2 13 (s, 3H)
125		459 17	N-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-ynamide	C	6 9	m/z 460 2 [M+H]+	^{1}H NMR (300 MHz DMSO-d_6) δ 11 0 (br s 1H), 9 11 (br s, 1H), 8 00 (s, 1H), 7 80 (d, *J* = 8 7, 2H) 7 53 (d, *J* = 8 7, 2H), 6 96 (d, *J* = 9 3, 2H), 6 46 (d *J* = 9 0, 2H), 3 73 (m, 4H), 2 93 (m, 4H), 2 12 (s 3H), 2 09 (s, 3H)
126		393 16	4-(4-aophenylthio)-5-methyl-N-(4-morpholinophenyl)pyr imidin-2-ae	C	6 8	m/z 394 2 [M+H]+	^{1}H NMR (300 MHz DMSO-d_6) δ 9 02 (br s, 1H) 7 94 (s, 1H), 7 17 (d, *J* = 8 4, 2H), 7 12 (d, *J* = 9 3, 2H), 6 69 (d, *J* = 8 7, 2H), 6 64 (d, *J* = 9 0, 2H) 5 68 (br s, 2H), 3 72 (m 4H) 2 99 (m 4H) 2 09 (s, 3H)
127		444 17	4-(4-((1H-imidazol-1-yl)methyl)phenylthio)-N-(4-morpholinophenyl)pyr imidin-2-ae	C	6 3	m/z 445 2 [M+H]+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 3 09-3 12 (m, 4H) 3 86-3 89 (m, 4H), 5 22 (s, 2H), 6 21 (d, *J*=5 39Hz, 1H), 6 84 (d, *J*=9 02Hz, 2H), 6 97-6 98 (m, 1H), 7 07-7 09 (m, 1H), 7 25 (d, *J*=8 14Hz, 2H), 7 37 (d, *J*=8 87Hz, 2H), 7 60-7 63 (m 3H), 7 99 (d, *J*=5 39Hz, 1H)
128		483 18	2-(1-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-imidazol-4-yl)acetonitrile	C	6 4	m/z 484 2 [M+H]+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 3 07-3 10 (m, 4H), 3 65-3 66 (m, 2H), 3 86-3 89 (m, 4H), 5 11 9s 2H), 6 31-6 33 (d, *J*=5 40Hz, 1H), 6 77 (d, *J*=9 00Hz, 2H), 6 87 (br s, 1H), 7 27 (d, *J*=8 96Hz, 2H), 7 29-7 36 (m, 1H), 7 40-7 42 (m, 1H), 7 49-7 54 (m, 2H), 7 60-7 64 (m, 1H), 8 01 (d, *J*=5 35Hz, 1H),
129		444 17	4-(3-((1H-imidazol-1-yl)methyl)phenylthio)-N-(4-morpholinophenyl)pyr imidin-2-ae	C	6 4	m/z 445 2 [M+H]+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 3 06-3 09 (m, 4H) 3 86-3 89 (m, 4H), 5 14 (s, 2H), 6 30 (s, *J*=5 37Hz, 1H), 6 77 (d, *J*=9 05Hz, 2H), 6 87-6 91 (m, 1H), 7 03-7 06 (m, 1H), 7 22-7 29 (m, 1H), 7 29 (d, *J*=9 09Hz, 2H), 7 39-7 42 (m, 1H), 7 48 (t, *J*=7 68Hz, 1H), 7 56-7 57 (m, 1H), 7 57-7 61 (m, 1H), 8 01(d, *J*=5 36Hz, 1H)
130		473 15	N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)furan-2-carboxamide	C	6 8	m/z 474 2 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 38 (s, 1H), 9 37 (s, 1H), 8 13 (d, *J* = 5 3, 1H), 8 10 – 8 04 (m, 2H) 7 94 (m, 1H), 7 56 – 7 44 (m, 1H), 7 39 – 7 23 (m 4H), 6 77 – 6 63 (m, 3H), 6 42 (d, *J* = 5 0, 1H), 3 69 (t, *J* = 4 8, 4H), 2 93 (t, *J* = 4 8, 4H)

131		373 10	N-(4-(2-(4-cyanophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 374 2 [M+H]+	1H NMR (300 MHz, Acetone) d 9 68 (s 1H), 9 06 (s, 1H), 8 22 (d J = 5 5, 1H), 7 95 (d, J = 8 2 2H) 7 75 (d, J = 8 7, 2H), 7 61 (d, J = 8 7, 2H) 7 51 (d, J = 8 7, 2H), 6 63 (d, J = 5 0, 1H) 6 58-6 38 (m 2H), 5 78 (dd, J = 9 1, 2 7, 1H)
132		456 06	4-(3-(bromomethyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 5	m/z 457 1/459 1 [M+H]+	^{1}H NMR ($CDCl_3$) δ3 07-3 10 (m, 4H), 3 84-3 88 (m, 4H), 4 49 (s, 2H), 6 30 (d, *J*=5 37Hz, 1H), 6 79 (d, *J*=9 02Hz, 2H), 6 91 (s, 1H), 7 27(d *J*=8 90Hz 2H), 7 41-7 46 (m, 1H), 7 52-7 57 (m, 2H), 7 63-7 66 (m, 1H), 8 03 (d, *J*=5 34Hz, 1H)
133		445 17	4-(3-((1H-1,2,4-triazol-1-yl)methyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 3	m/z 446 2 [M+H]+	^{1}H NMR ($CDCl_3$ + d_4-MeOH) δ 3 07-3 10 (m, 4H), 3 86-3 89 (m, 4H), 5 37 (s, 2H), 6 31 (d, *J*=5 33Hz, 1H), 6 78 (d, *J*=9 11Hz, 2H), 7 27 (d, *J*=9 14Hz, 2H), 7 35-7 39 (m, 1H), 7 46-7 52 (m 2H), 7 58-7 62 (m, 1H), 7 97 (s 1H), 8 01 (d, *J*=5 37Hz 1H), 8 11 (s, 1H)
134		447 17	N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)methacrylamide	C	6 9	m/z 448 3 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$/MeOD) δ 7 97 (d *J* = 5 7 1H), 7 79 (d, *J* = 8 7, 2H), 7 57 (d *J* = 8 7, 2H), 7 28 (d, *J* = 9 0, 2H), 6 80 (d, *J* = 9 0, 2H), 6 35 (d, *J* = 5 4, 1H), 5 86 (s, 1H), 5 55 (s, 1H), 3 85 (m, 4H), 3 08 (m, 4H), 2 08 (s, 3H)
135		435 17	N-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	6 5	m/z 436 4 [M+H]+	^{1}H NMR (300 MHz, DMSO-d_6) δ 10 3 (br s, 1H), 9 10 (br s 1H) 8 00 (s, 1H), 7 78 (d, *J* = 8 7, 2H) 7 51 (d, *J* = 8 7 2H), 7 00 (d, *J* = 8 7, 2H) 6 49 (d, *J* = 9 0, 2H), 3 72 (m, 4H) 2 92 (m, 4H) 2 13 (s 3H), 2 10 (s, 3H)
136		403 15	4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzonitrile	C	7 3	m/z 404 3 [M+H]+	^{1}H NMR (500 MHz, $CDCl_3$) δ 7 94 (d, *J* = 1 0 1H) 7 71 (AB, *J* = 8 5, 2H), 7 69 (AB, *J* = 8 5, 2H), 6 93 (d, *J* = 9 0, 2H), 6 75 (br s, 1H), 6 64 (d, *J* = 9 0, 2H), 3 87 (m, 4H), 3 11 (m, 4H), 2 20 (d, *J* = 1 0, 3H)
137		389 13	4-(2-(3-morpholinophenylao)pyrimidin-4-ylthio)benzonitrile	C	7 1	m/z 390 3 [M+H]+	^{1}H NMR (500 MHz, $CDCl_3$) δ 8 13 (d, *J* = 5 5, 1H) 7 71 (AB, *J* = 8 5, 2H), 7 69 (AB, *J* = 8 5, 2H), 7 08 (t *J* = 8 0, 1H), 7 01 (br s, 1H), 6 99 (m, 1H) 6 86 (dd, *J* = 8 0 2 0, 1H), 6 60 (dd, *J* = 8 0, 2 0, 1H), 6 46 (d, *J* = 5 5 1H), 3 84 (m, 4H), 3 12 (m, 4H)

138		404 14	5-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)picolinonitrile	C	6 9	m/z 405 3 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ 8 83 (m, 1H) 8 01-7 97 (m 2H) 7 68 (dd, *J* = 8 1, 0 9, 1H), 6 95 (d J = 9 0, 2H), 6 73 (br s, 1H), 6 70 (d *J* = 9 0 2H) 3 88 (m 4H), 3 14 (m, 4H) 2 21 (s, 3H)
139		390 13	5-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)picolinonitrile	C	6 6	m/z 391 3 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ 8 85 (dd, *J* = 2 4 0 9 1H) 8 13 (d, *J* = 5 4, 1H), 8 02 (dd, *J* = 7 5 2 4, 1H), 7 69 (dd, *J* = 7 8, 0 9, 1H), 7 07 (d *J* = 8 4, 2H) 6 92 (br s 1H), 6 75 (d, *J* = 8 7 2H), 6 58 (d *J* = 5 1 1H), 3 88 (m 4H) 3 14 (m 4H)
140		441 09	4-(4-(4-(cyanomethoxy)-3-methylphenylthio)-5-methylpyrimidin-2-ylao)benzenesulfonamide	C	7 0	m/z 442 3 [M+H]+	^{1}H NMR (500 MHz, DMSO-d_6) δ 9 75 (br s, 1H) 8 14 (s, 1H), 7 51 (m, 2H), 7 34 (d, *J* = 9 0, 2H) 7 29-7 23 (m, 3H), 7 04 (br s, 2H), 5 27 (s, 2H), 2 23 (s 3H) 2 18 (s 3H)
141		461 04	4-(4-(3-chloro-4-(cyanomethoxy)phenylthio)-5-methylpyrimidin-2-ylao)benzenesulfonamide	C	7 0	m/z 462 3 [M+H]+	^{1}H NMR (500 MHz, DMSO-d_6) δ 9 78 (br s, 1H), 8 17 (s, 1H), 7 82 (d *J* = 2 5, 1H), 7 66 (dd, *J* = 8 5, 2 0, 1H), 7 46 (d, *J* = 9 0, 1H), 7 40 (d *J* = 9 5, 2H) 7 31 (d, *J* = 9 0, 2H), 7 06 (br s, 2H), 5 36 (s, 2H), 2 18 (s, 3H)
142		457 09	4-(4-(4-(cyanomethoxy)-3-methoxyphenylthio)-5-methylpyrimidin-2-ylao)benzenesulfonamide	C	6 6	m/z 458 3 [M+H]+	^{1}H NMR (500 MHz, DMSO-d_6) δ 9 76 (br s, 1H) 8 15 (s, 1H), 7 40-7 20 (m, 7H), 7 05 (br s, 2H), 5 21 (s, 2H), 3 77 (s, 3H), 2 18 (s, 3H)
143		447 17	2-(2-methyl-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenoxy)acetonitrile	C	7 5	m/z 448 4 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ 7 88 (s 1H) 7 44 (m, 2H), 7 00-6 95 (m, 3H), 6 74 (br S_1 1H), 6 59 (d, *J* = 9 3, 2H), 4 87 (s, 2H), 3 88 (m, 4H), 3 06 (m, 4H), 2 27 (s, 3H), 2 18 (s, 3H)
144		467 12	2-(2-chloro-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenoxy)acetonitrile	C	7 5	m/z 468 3 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ 7 91 (s, 1H), 7 69 (d *J* = 1 8 1H), 7 49 (dd, *J* = 8 7, 1 8 1H), 7 10 (d *J* = 8 7, 1H), 7 00 (d, *J* = 9 0, 2H), 6 73 (br s, 1H) 6 66 (d, *J* = 9 0, 2H), 4 90 (s, 2H) 3 88 (m 4H) 3 08 (m, 4H), 2 18 (s, 3H)

145		463 17	2-(2-methoxy-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenoxy)aceto nitrile	C	7 0	m/z 464 4 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ 7 90 (s, 1H), 7 21-7 09 (m, 3H), 7 00 (d, J = 9 3, 2H), 6 78 (br s, 1H) 6 64 (d, J = 9 0, 2H), 4 89 (s, 2H), 3 87 (m, 4H), 3 77 (s 3H), 3 08 (m, 4H), 2 19 (s 3H)
146		404 14	5-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)nicotinonitrile	C	6 56	m/z 405 3 [M+H]+	^{1}H NMR (300 MHz, DMSO-d_6) δ 9 26 (d, J = 1 8, 1H), 9 17 (br s, 1H), 8 99 (d, J = 2 7, 1H), 8 65 (t, J = 1 8, 1H), 8 10 (s, 1H), 6 95 (d, J = 8 4, 2H) 6 59 (d, J = 9 3, 2H), 3 74 (m, 4H), 3 00 (m, 4H) 2 17 (s, 3H)
147		490 03	4-(4-iodophenylthio)-N-(4-morpholinophenyl)pyr imidin-2-ae	C	7 8	m/z 491 2 [M+H]+	^{1}H NMR (300 MHz, DMSO-d_6) δ 9 40 (br s 1H) 8 13 (d, J = 4 8, 1H), 7 91 (d, J = 8 4, 2H), 7 41 (d J = 8 4, 2H), 7 21 (d J = 9 0, 2H), 6 69 (d J = 9 3, 2H), 6 51 (m, 1H), 3 74 (m, 4H), 3 04 (m, 4H)
148		516 19	ethyl 1-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-imidazole-2-carboxylate	E	9 4	m/z 517 4 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ 8 02 (d, J = 5 4, 1H) 7 59 (d, J = 8 4 2H), 7 35 (d, J = 9 3, 2H), 7 26 (d J = 8 1 2H), 7 23 (d J = 0 9, 1H), 7 12 (d J = 0 9 1H), 6 95 (br s, 1H) 6 84 (d, J = 9 0, 2H), 6 21 (d J = 5 7, 1H), 5 72 (s, 2H) 4 38 (q, J = 7 2 2H) 3 87 (m 4H) 3 11 (m, 4H), 1 41 (t J = 7 2, 3H)
149		487 18	1-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-imidazole-2-carboxamide	C	6 2	m/z 488 3 [M+H]+	^{1}H NMR (300 MHz, DMSO-d_6) δ 9 41 (br s 1H) 8 11 (d, J = 5 4 1H), 7 83 (br s, 1H), 7 62 (d J = 8 1 2H) 7 48 (s, 1H) 7 37 (m, 4H), 7 05 (s, 1H), 6 77 (d, J = 9 3, 2H), 6 22 (d, J = 5 1, 1H), 5 79 (s, 2H) 5 30 (br s 1H), 3 74 (m, 4H) 3 02 (m 4H)
150		469 17	1-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-imidazole-2-carbonitrile	C	6 7	m/z 470 3 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ 8 04 (d, J = 5 7, 1H), 7 65 (d J = 8 4, 2H) 7 36 (d, J = 8 7, 2H), 7 30 (d J = 8 4 2H), 7 26 (d, J = 1 2, 1H), 7 12 (d, J = 1 2 1H), 6 90 (br s, 1H), 6 83 (d, J = 8 7 2H) 6 25 (d J = 5 4 1H) 5 36 (s, 2H), 3 87 (m 4H) 3 10 (m 4H)
151		405 14	5-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)pyrimidine-2-carbonitrile	C	6 8	m/z 406 2 [M+H]+	^{1}H NMR (300 MHz, DMSO-d_6) δ 9 22 (s, 2H) 9 20 (br s, 1H) 8 14 (s, 1H), 6 98 (d, J = 8 4 2H), 6 65 (d, J = 9 0 2H) 3 74 (m, 4H), 3 03 (m 4H) 2 18 (s, 3H)

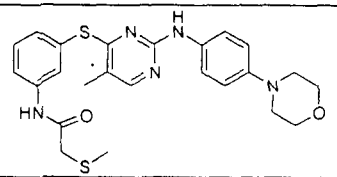
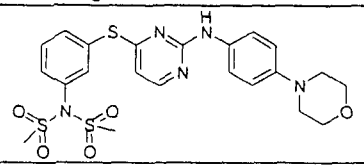
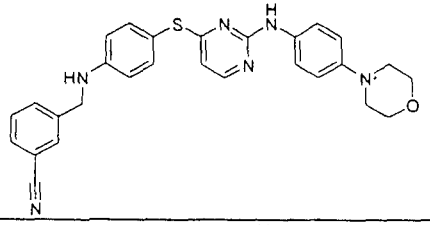
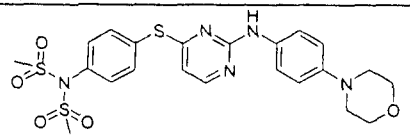
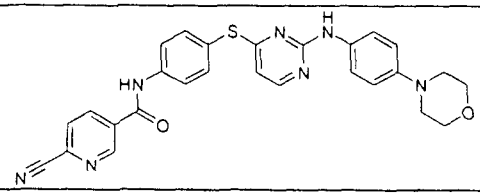
152		508 09	4-(4-(2 chloropyrimidin-4 ylthio)phenylthio) N-(4-morpholinophenyl)pyrimidin 2-ae	C	7 4	m/z 509 2 [M+H]+	^{1}H NMR (300 MHz $CDCl_3$) δ 8 20 (d J = 5 4 1H) 8 09 (d J = 5 4 1H) 7 74 (AB J = 8 4 2H) 7 67 (AB J = 8 4 2H) 7 24 (d J = 8 7 2H) 6 94 (br s 1H) 6 75 (d J = 8 4 2H) 6 75 (d J = 5 4 1H) 6 44 (d J = 5 4 1H) 3 84 (m 4H) 3 05 (m 4H)
153		467 15	5-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)pyrimidine-2-carbonitrile	C	7 1	m/z 468 3 [M+H]+	^{1}H NMR (300 MHz DMSO-d_6) δ 9 54 (s 2H) 9 40 (br s 1H) 8 16 (d J = 5 4 1H) 8 13 (d J = 8 7 2H) 7 84 (d J = 8 7 2H) 7 24 (d J = 8 7 2H) 6 57 (d J = 9 0 2H) 6 53 (d J = 5 1 1H) 3 64 (m 4H) 2 79 (m 4H)
154		499 12	4-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylthio)pyrimidine-2-carbonitrile	C	7 4	m/z 500 3 [M+H]+	^{1}H NMR (300 MHz $CDCl_3$) δ 8 40 (d J = 5 7 1H) 8 10 (d J = 5 4 1H) 7 75 (AB J = 8 4 2H) 7 66 (AB J = 8 4 2H) 7 26 (d J = 9 0 2H) 7 03 (d J = 5 7 1H) 6 89 (br s 1H) 6 76 (d J = 9 0 2H) 6 43 (d J = 5 4 1H) 3 86 (m 4H) 3 06 (m 4H)
155		471 16	1-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-tetrazole-5-carbonitrile	C	7 0	m/z 472 3 [M+H]+	^{1}H NMR (300 MHz, $CDCl_3$) δ 8 06 (d J = 5 1 1H) 7 69 (d J = 8 4 2H) 7 46 (d J = 8 4 2H) 7 35 (d J = 9 0 2H) 6 86 (br s 1H) 6 83 (d J = 9 3 2H) 6 29 (d J = 5 7 1H) 5 79 (s 2H) 3 87 (m 4H) 3 11 (m 4H)
156		471 16	2-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-2H-tetrazole-5-carbonitrile	C	7 1	m/z 472 3 [M+H]+	^{1}H NMR (300 MHz $CDCl_3$) δ 8 05 (d J = 5 4 1H) 7 67 (d J = 8 4 2H) 7 46 (d J = 8 4 2H) 7 33 (d J = 9 0 2H) 6 86 (br s 1H) 6 82 (d J = 9 0 2H) 6 27 (d J = 5 1 1H) 5 91 (s 2H) 3 87 (m 4H) 3 11 (m 4H)

157		469 17	1-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-4-carbonitrile	C	6 4	m/z 470 3 [M+H]+	^{1}H NMR (300 MHz CDCl$_3$) δ 8 05 (d, J = 5 1 1H) 7 65 (d, J = 8 4, 2H), 7 60 (d, J = 1 2, 1H), 7 47 (d J = 1 5, 1H), 7 36 (d, J = 9 0, 2H), 7 24 (d, J = 8 4 2H), 6 88 (br s, 1H), 6 83 (d, J = 9 0, 2H), 6 24 (d J = 5 4, 1H), 5 21 (s, 2H), 3 86 (m, 4H), 3 10 (m 4H)
158		469 17	1-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-5-carbonitrile	C	6 4	m/z 470 3 [M+H]+	^{1}H NMR (300 MHz, CDCl$_3$) δ 8 04 (d, J = 5 4 1H) 7 72 (s, 1H), 7 71 (s, 1H), 7 65 (d, J = 8 1, 2H) 7 37 (d, J = 9 0, 2H), 7 30 (d, J = 8 1, 2H), 6 92 (br s, 1H), 6 84 (d, J = 9 0, 2H), 6 24 (d, J = 5 7 1H), 5 31 (s, 2H), 3 86 (m, 4H), 3 10 (m, 4H)
159		586 00	4-(4-(5-bromo-2-chloropyrimidin-4-ylthio)phenylthio)-N-(4- morpholinophenyl)pyrimidin-2-ae	C	7 9	m/z 587 0 [M+H]+	^{1}H NMR (300 MHz, CDCl$_3$) δ 8 41 (s, 1H) 8 06 (d J =5 4, 1H), 7 71 (AB J = 8 7, 2H), 7 62 (AB J = 8 7, 2H), 7 24 (d, J = 8 4, 2H), 6 91 (br s, 1H), 6 77 (d, J = 9 0, 2H) 6 39 (d, J = 5 4 1H) 3 85 (m, 4H), 3 09 (m, 4H)
160		427 12	4-(4-ao-2-chloro-3-methylphenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 0	m/z 428 1/43 0 1 [M+H]$^+$	(300MHz, d$_6$-DMSO) δ 8 86 (s 1H) 7 61 (d J=5 1, 1H), 6 86 (d, J=9 6, 2H), 6 82 (d, J=8 4 1H), 6 27 (d, J=9 6, 2H), 6 23 (d, J=6 0, 1H) 5 82 (d J=5 1, 1H) 5 35 (br s, 2H) 3 25-3 29 (m 4H) 2 53-2 56 (m, 4H), 1 73 (s, 3H)
161		481 13	N-(3-chloro-2-methyl-4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 8	m/z 482 3/48 4 3 [M+H]$^+$	(300MHz, CDCl$_3$) δ 9 87 (s, 1H), 9 37 (s. 1H), 8 14 (d J=5 7 Hz 1H), 7 78 (d J=8 1 Hz, 1H) 7 66 (d, J=8 4 Hz, 1H), 7 16 (d, J=8 1 Hz, 2H), 6 62 (m, 3H), 6 53 (br s, 1H), 6 32 (dd J=16 8, 1 8 Hz, 1H), 5 85 (dd J=10 2, 1 8 Hz, 1H), 3 67 (m 4H), 2 93 (m 4H), 2 32 (s. 3H)
162		407 18	4-(4-ao-2-methylphenylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 0	m/z 408 3 [M+H]$^+$	(300MHz, CDCl$_3$) δ 7 85 (s 1H), 7 33 (d, J = 8 0 1H), 7 03 (d, J = 9 5, 2H), 6 74-6 70 (m 3H), 6 60 (dd, J = 8 0, 1H), 3 86 (m, 4H), 3 08 (m 4H) 2 26 (s, 3H), 2 20 (s, 3H)

163		461 19	N-[3-methyl-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl]acrylamide	C	7 0	m/z 462 3 [M+H]+	(300MHz CDCl3) δ 7 88 (s 1H) 7 81 (d, J=1 8Hz 1H) 7 55 (d, J=8 4Hz 1H) 7 48 (dd J=8 4, 2 1Hz, 1H), 7 36 (br s , 1H), 6 94 (d, J=8 7Hz 2H), 6 81 (br s , 1H), 6 60 (d, J=8 7Hz 2H) 6 52 (dd J=16 5, 1 5Hz, 1H) 6 28 (dd, J=16 8 10 5Hz 1H), 5 85 (dd J=10 2, 1 2Hz 1H) 3 78 (m 4H) 2 99 (m 4H) 2 37 (s 3H) 2 21 (s, 3H)
164		475 20	N-(3,5-dimethyl-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	7 2	m/z 476 3 [M+H]+	(300MHz CDCl3) δ 7 87 (s, 1H), 7 55 (s. 1H) 7 31 (s, 1H), 6 93 (d, J=9 3Hz, 2H), 6 79, (br s 1H), 6 60 (d, J=9 0Hz, 2H), 6 50 (dd, J=16 8 1 2Hz, 1H) 6 27 (dd J=16 8, 10 2Hz, 1H), 5 84 (dd, J=10 2, 1 5Hz, 1H), 3 79 (m 4H) 2 98 (m 4H), 2 39 (s, 6H), 2 42 (s, 3H)
165		421 19	4-(4-ao-2,6-dimethylphenylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 2	m/z 422 4 [M+H]+	(300 MHz, d6-DMSO) δ 9 00 (br s, 1H), 7 94 (s. 1H), 7 10 (d, J = 9 0, 2H), 6 64 (d, J = 9 0, 2H) 6 49 (s, 2H) 5 46 (s 2H), 3 73-3 70 (m 4H) 3 00-2 97 (m 4H) 2 15 (s, 9H)
166		433 19	5-methyl-N-(4-morpholinophenyl)-4-(1,2,3,4-tetrahydroquinolin-6-ylthio)pyrimidin-2-ae	C	7 6	m/z 434 4 [M+H]+	(300MHz, CDCl3) δ 7 82 (s. 1H), 7 14 (m, 2H) 7 08 (d, J=5 4 Hz, 2H), 6 88 (s, 1H), 6 73 (d, J=5 7 Hz, 2H), 6 55 (d, J=5 4 Hz, 1H), 3 86 (m 4H), 3 40 (m, 2H), 3 07 (m 4H), 2 76 (m, 2H) 2 16 (s, 3H), 1 97 (m, 3H)
167		419 18	4-(indolin-5-ylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 3	m/z 420 4 4 [M+H]+	
168		487 20	1-(6-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)-3,4-dihydroquinolin-1(2H)-yl)prop-2-en-1-one	C	7 4	m/z 488 4 [M+H]+	
169		441 14	4-(4-ao-2-chloro-3-methylphenylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 3	m/z 442 3 [M+H]+	

170		473 19	1-(5-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)indolin-1-yl)prop-2-en-1-one	C	7 2	m/z 474 3 $[M+H]^+$	
171		495 15	N-(3-chloro-2-methyl-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	7 1	m/z 496 3 $[M+H]^+$	
172		461 15	4-(4-ao-3-(trifluoromethyl)phenylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 5	m/z 462 3 $[M+H]^+$	
173		461 19	N-methyl-N-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	7 0	m/z 462 3 $[M+H]^+$	
174		458 19	6-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)-3 4-dihydroquinoline-1(2H)-carbonitrile	C	7 3	m/z 459 4 $[M+H]^+$	
175		472 20	2-(6-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)-3,4-dihydroquinolin-1(2H)-yl)acetonitrile	C	7 3	m/z 473 4 $[M+H]^+$	
176		316 14	5-methyl-4-(methylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 9	m/z 317 3 $[M+H]^+$	(300MHz $CDCl_3$) δ 2 08 (s 3 H) 2 54 (s 3 H) 3 12 (m 4 H) 3 77 - 3 94 (m 4 H) 6 90 (m 3 H) 7 49 (d J=9 0 Hz 2 H) 7 84 (s 1 H)

177		460 17	N-(cyanomethyl)-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzamide	C	6 4	m/z 461 3 [M+H]+	(300MHz CDCl3) δ 2 20 (s 3 H) 3 06 (m 4 H) 3 87 (m 4 H) 4 42 (d J=5 94 Hz 2 H) 6 61 (d J=9 0 Hz 2 H) 6 71 (s 1 H) 6 97 (d J=9 0 Hz 2 H) 7 71 (d J=8 22 Hz 2 H) 7 86 (d J=8 22 Hz 2 H) 7 93 (s 1 H)
178		420 16	1-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)ethanone	C	7 1	m/z 421 4 [M+H]+	(300 MHz DMSO-d6) δ 2 15 (s 3 H) 2 67 (s 3 H) 2 90 (m 4 H) 3 70 (m 4 H) 6 43 (d J=9 0 Hz 2 H) 6 99 (d J=9 0 Hz 2 H) 7 75 (d J=9 0 Hz 2 H) 8 07 (m 3 H) 9 14 (s 1 H)
179		464 16	(E)-2-(hydroxyio)-N-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetamide	C	6 5	m/z 465 4 [M+H]+	(300 MHz DMSO-d6) δ 2 13 (s 3 H) 2 84-2 87 (m 4 H) 3 64-3 67 (m 4 H) 6 46 (d J=9 0 Hz 2 H) 6 98 (d J=9 0 Hz 2 H) 7 56 (d J=9 0 Hz 2 H) 7 74 (s 1H) 7 93 (d J=9 0 Hz 2 H) 8 01 (s 1H) 9 11 (s 1H) 10 57 (s 1H)
180		393 16	4-(3-aophenylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 6	m/z 394 3 [M+H]+	(300 MHz DMSO-d6) δ 2 11 (d J=0 6 Hz 3 H) 2 94-2 98 (m 4 H) 3 71-3 75 (m 4 H) 5 33 (bs 2H) 6 62 (d J=9 0 Hz 2 H) 6 67-6 70 (m 1H) 6 76-6 80 (m 2H) 7 12-7 19 (m 3H) 7 99 (s 1H) 9 06 (s 1H)
181		527 20	N-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-2-phenoxyacetamide	C	7 5	m/z 528 3 [M+H]+	(300 MHz DMSO-d6) δ 2 14 (s 3 H) 2 87 2 93 (m 4 H) 3 61-3 64 (m 4 H) 4 73 (s 1H) 6 52 (d J=9 0 Hz 2 H) 6 98 -7 07 (m 5 H) 7 56 (d J=9 0 Hz 2 H) 7 74 (s, 1H) 7 93 (d J=9 0 Hz 2 H) 8 01 (s 1H) 9 11 (s 1H) 10 57 (s 1H)
182		513 18	N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-2-phenoxyacetamide	C	7 2	m/z 514 3 [M+H]+	(300 MHz DMSO-d6) δ 2 96-2 99 (m 4H) 3 66 3 69 (m 4H) 4 74 (s 1H) 6 38 (d J=5 3 Hz 1 H) 6 70 (d J=9 0 Hz 2H) 6 97-7 05 (m 3H) 7 28 7 36 (m 4 H) 7 59 (d J=9 0 Hz 2H) 7 86 (d J=9 0 Hz 2H) 8 10 (d J=5 3 Hz 1 H) 9 35 (s 1H) 10 44 (s 1H)

183		481 16	N-(3-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-2-(methylthio)acetamide	E	9 7	m/z 482 3 $[M+H]^+$	(300 MHz, DMSO-d_6) δ 2 10 (s, 3 H) 2 14 (s, 3 H), 2 93-2 96 (m, 4 H) 3 25 (s, 2H) 3 71-3 74 (m, 4 H) 6 53 (d, *J*=9 3 Hz, 2 H) 7 01 -7 04 (d, *J*=9 3 Hz, 2H) 7 25-7 29 (m, 1H) 7 48 (t, *J*=9 3 Hz, 1H), 7 84-7 85 (m, 4H), 7 91-7 94 (m, 4H) 8 04 (s 1H) 9 10 (s, 1H) 10 25 (s, 1H)
184		535 10	N-(methylsulfonyl)-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)methanesulfonamide	B	8 7	m/z 535 1 M+	^{1}H NMR (300MHz, $CDCl_3$) δ 3 07-3 10 (m 4H) 3 42 (s, 6H), 3 84-3 87 (m, 4H), 6 41 (d, *J*=5 34Hz, 1H), 6 83 (d, *J*=9 02Hz, 2H), 7 13 (br s 1H), 7 36 (d, *J*=8 98Hz, 2H), 7 43-7 47 (m, 1H), 7 54 (t, *J*=8 04Hz, 1H), 7 68-7 72 (m, 2H) 8 08 (d, *J*=5 35Hz, 1H)
185		494 19	3-((4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)methyl)benzonitrile	B	9 7	m/z 494 3 M+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 99-3 02 (m, 4H) 3 69-3 72 (m,, 4H), 4 41 (d, *J*=6 14Hz, 2H), 6 19 (d, *J*=5 34Hz, 1H), 6 72 (d, *J*=8 75Hz 2H), 6 77 (d, *J*=9 12Hz, 2H), 6 93 (t, *J*=6 15Hz, 1H), 7 28 (d *J*=8 64Hz, 2H), 7 38 (d, *J*=9 05Hz, 2H), 7 56 (d *J*=7 86Hz, 1H), 7 70-7 75 (m, 2H), 7 81-7 84 (m 1H) 8 05 (d *J*=5 30Hz, 1H), 9 32 (s 1H)
186		535 10	N-(methylsulfonyl)-N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)methanesulfonamide	B	8 6	m/z 535 6 M+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 99-3 03 (m 4H) 3 57 (s, 6H), 3 70-3 73 (m, 4H) 6 35 (d *J*=5 31Hz, 1H), 6 83 (d *J*=9 14Hz, 2H) 7 45 (d *J*=9 03Hz, 2H) 7 67 (d, *J*=8 64Hz, 2H) 7 77 (d *J*=8 64Hz, 2H), 8 19 (d, *J*=5 26Hz, 1H), 9 47 (s 1H)
187		509 16	6-cyano-N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)nicotinamide	B	9 0	m/z 509 5 M+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 88-2 92 (m, 4H) 3 54-3 56 (m, 4H), 6 45 (d, *J*=5 08Hz, 1H), 6 67 (d, *J*=9 04Hz, 2H), 7 26 (d, *J*=8 63Hz, 2H), 7 65 (d, *J*=8 66Hz, 2H), 7 98 (d, *J*=8 70Hz, 2H), 8 12 (d *J*=5 28Hz, 1H), 8 29 (d, *J*=8 10Hz, 1H) 8 58 (dd, *J*=2 20, 8 10Hz, 1H) 9 25-9 32 (m 1H) 9 36 (s, 1H), 10 93 (s, 1H)

188		509 17	2-(2-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)-2-oxoethoxy)acetic acid	G	6 0	m/z 510 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 13 (d, J=0 66Hz 3H), 2 88-2 92 (m, 4H) 3 69-3 72 (m 4H) 4 23 (s, 2H), 4 26 (s, 2H), 6 49 (d, J=9 11Hz 2H), 7 02 (d, J=9 06Hz, 2H), 7 54 (d J=8 71Hz, 2H) 7 86 (d, J=8 74Hz, 2H), 8 00 (d, J=0 68Hz 1H) 9 09 (s, 1H), 10 25 (s, 1H)
189		523 19	methyl 2-(2-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)-2-oxoethoxy)acetate	C	6 6	m/z 524 3 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$) δ 2 18 (s, 3H), 3 00-3 03 (m, 4H), 3 78-3 82 (m, 4H), 3 81 (s 4H), 4 23 (s 2H), 4 30 (s, 2H), 6 63 (d, J=9 02Hz 2H) 6 75 (br s, 1H), 7 02 (d, J=9 03Hz, 2H), 7 57 (d, J=8 64Hz, 2H), 7 78 (d, J=8 66Hz 2H) 7 87 (s 1H), 9 24 (br s, 1H)
190		491 16	4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)morpholine-3,5-dione	C	6 6	m/z 492 3 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$) δ 2 19 (s, 3H) 3 04-3 07 (m, 4H), 3 82-3 85 (m, 4H), 4 54 (s, 4H), 6 77(d, J=9 04Hz, 2H), 6 86 (brs, 1H), 7 18 (d J=8 97Hz, 2H), 7 26 (d, J=8 54Hz. 2H), 7 72 (d J=8 54Hz, 2H), 7 79 (s, 1H)
191		324 10	4-(4-(4-aophenylthio)-5-methylpyrimidin-2-ylao)phenol	C	6 2	m/z 325 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 09 (d, J=0 61Hz, 3H), 6 46 (d, J=8 65Hz, 2H), 6 68 (d, J=8 63Hz, 2H), 7 08 (d, J=8 97Hz, 2H) 7 17 (d, J=8 56Hz, 2H), 7 93 (d, J=0 68Hz, 1H) 8 71 9s 1H), 8 92 (s, 1H)
192		580 23	4-benzyl-1-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)piperazine-2,6-dione	C	7 3	m/z 581 3 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$) δ 2 18 (d, J=0 47Hz, 3H), 3 03-3 06 (m, 4H), 3 57 (s, 4H), 3 73 (s, 2H) 3 77-3 80 (m, 4H), 6 78 (d, J=9 07Hz, 2H), 6 89 (brs, 1H), 7 18 (d, J=8 88Hz, 2H), 7 22 (d, J=8 61Hz 2H), 7 31-7 45 (m, 5H), 7 68 (d, J=8 64Hz, 2H), 7 91 (brs, 1H
193		400 08	2-chloro-N-(4-(2-(4-hydroxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acetamide	C	6 5	m/z 401 2/40 3 2 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 12 (d, J=0 49Hz, 3H), 4 34 (s, 2H), 6 36 (d, J=8 97Hz, 2H), 6 99 (d, J=9 16Hz, 2H), 7 54 (d, J=8 68Hz, 2H) 7 76 (d J=8 74Hz, 2H), 8 00 (d, J=0 68Hz 1H), 8 75 (s, 1H), 8 97 (s, 1H), 10 58 (s 1H)
194		400 08	2-chloro-N-(4-(2-(3-hydroxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acetamide	C	6 5	m/z 401 2/40 3 2 [M+H]+	^{1}H NMR (300MHz d_6-DMSO) δ2 15 (d J=0 67Hz 3H), 4 33 (s, 2H), 6 24 (ddd, J=1 17, 2 42, 7 93Hz 1H), 6 58-6 65 (m, 2H), 6 67-6 74 (m, 1H) 7 55 (d, J=8 71Hz, 2H), 7 77 (d, J=8 83Hz, 2H), 8 07 (d J=0 74Hz, 1H) 9 45 (s, 1H) 10 67 (s 1H)

195		416 05	2-chloro-N-(4-(2-(3-mercaptophenylao)-5-methylpyrimidin-4-ylthio)phenyl)acetamide	C	7 2	m/z 417 2/419 2 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ2 16 (d J=0 65Hz 3H), 4 32 (s, 2H), 5 02 (s, 1H), 6 66-6 72 (m, 2H) 6 69-7 05 (m, 1H), 7 07-7 13 (m, 1H), 7 55 (d, J=8 77Hz, 2H), 7 76 (d, J=8 77Hz, 2H), 8 09 (d J=0 73Hz, 1H), 9 40 (s 1H) 10 66 (s 1H)
196		324 10	3-(4-(4-aophenylthio)-5-methylpyrimidin-2-ylao)phenol	C	6 4	m/z 325 3 [M+H]+	^{1}H NMR (300MHz $CDCl_3$) δ 2 19 (d J=0 65Hz 3H), 4 10 (br s, 2H), 6 37-6 48 (m, 2H), 6 81 (d J=8 65Hz, 2H), 6 95 (br s, 1H), 6 96-7 03 (m, 2H) 7 43 (d J=8 65Hz, 2H) 7 88 (d J=0 66Hz 1H)
197		493 16	4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)thiomorpholin-3-one	C	7 1	m/z 494 2 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ2 14 (d J=0 56Hz, 3H), 2 92-2 95 (m, 4H) 3 07-3 11 (m 2H) 3 47 (s, 2H) 3 69-3 72 (m 4H) 4 06-4 10 (m 2H) 6 59 (d, J=9 14Hz, 2H) 7 12 (d, J=9 05Hz, 2H), 7 51 (d, J=8 76Hz, 2H), 7 60 (d J=8 76Hz, 2H), 8 04 (d J=0 69Hz 1H) 9 12 (s 1H)
198		484 18	5-ao-1-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-imidazole-4-carbonitrile	C	6 2	m/z 485 2 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 98-3 01 (m 4H) 3 72-3 75 (m, 4H), 5 13 (s, 2H), 6 27-6 29 (m 3H), 6 73 (d, J=9 02Hz, 2H), 7 30 (s, 1H) 7 34 (d J=8 83Hz 2H), 7 36-7 42 (m, 1H), 7 50-7 59 (m 3H), 8 11 (d J=5 29Hz, 1H), 9 39 (s 1H)
199		484 18	4-ao-1-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzyl)-1H-imidazole-5-carbonitrile	C	6 2	m/z 485 2 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 99-3 02 (m 4H) 3 71-3 75 (m, 4H), 5 16 (s, 2H), 5 89 (s, 2H), 6 26 (d, J=5 20Hz, 1H), 6 75 (d, J=9 00Hz 2H), 7 35 (d, J=9 26Hz, 2H), 7 39-7 45 (m, 1H), 7 49-7 62 (m 3H) 7 67 (s, 1H), 8 10 (d, J=5 29Hz 1H) 9 38 (s, 1H)
200		444 17	4-(4-((1H-pyrazol-1-yl)methyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 8	m/z 445 2 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 3 01-3 04 (m, 4H) 3 72-3 75 (m, 4H), 5 46 (s, 2H), 6 26 (d, J=5 08Hz, 1H), 6 31 (dd, J=1 92, 2 33Hz, 1H), 6 77 (d, J=9 13Hz, 2H), 7 30 (d, J=8 47Hz, 2H), 7 37 (d, J=8 95Hz, 2H), 7 51 (dd, J=0 68, 1 86Hz 1H), 7 61 (d, J=8 33Hz, 2H), 7 88 (dd, J=0 68, 2 25Hz, 1H), 8 10 (d, J=5 31Hz, 1H) 9 38 (s 1H)

201		494 16	1-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-4,5-dicarbonitrile	C	7 0	m/z 495 2 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 3 01-3 03 (m 4H) 3 72-3 75 (m, 4H), 5 58 (s, 2H), 6 24 (d *J*=5 36Hz, 1H), 6 77 (d, *J*=9 08Hz, 2H), 7 39 (d, *J*=9 01Hz, 2H), 7 50 (d, *J*=8 47Hz 2H), 7 70 (d *J*=8 34Hz, 2H), 8 11 (d *J*=5 28Hz, 1H), 8 51 (s, 1H) 9 39 (s 1H)
202		484 18	5-ao-1-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-4-carbonitrile	C	6 2	m/z 485 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 3 00-3 04 (m 4H) 3 72-3 76 (m, 4H), 5 18 (s, 2H), 6 18 (d *J*=5 23Hz, 1H) 6 31 (br s 2H), 6 78 (d *J*=9 07Hz 2H), 7 34 (s, 1H), 7 36 (d, *J*=8 37Hz, 2H), 7 42 (d *J*=8 87Hz, 2H), 7 65 (d, *J*=8 30Hz, 2H), 8 11 (d *J*=5 29Hz, 1H), 9 40 (s 1H)
203		484 18	4-ao-1-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-5-carbonitrile	C	6 2	m/z 485 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 3 00-3 03 (m 4H) 3 72-3 75 (m, 4H), 5 21 (s, 2H), 5 91 (s 2H), 6 21 (d, *J*=5 23Hz, 1H), 6 78 (d, *J*=9 10Hz, 2H), 7 38 (d, *J*=8 33Hz, 2H), 7 41 (d, *J*=8 84Hz, 2H), 7 67 (d, *J*=8 35Hz, 2H), 7 70 (s, 1H) 8 11 (d *J*=5 30Hz, 1H), 9 39 (s 1H)
204		445 17	4-(4-((1H-1,2,4-triazol-1-yl)methyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 2	m/z 446 2 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 3 01-3 04 (m 4H) 3 72-3 75 (m, 4H), 5 54 (s, 2H), 6 26 (d, *J*=5 17Hz, 1H), 6 77 (d, *J*=9 10Hz, 2H) 7 36 (d *J*=8 54Hz, 2H), 7 40 (d, *J*=8 43Hz, 2H), 7 64 (d *J*=8 35Hz, 2H), 8 03 (s, 1H) 8 11 (d *J*=5 28Hz 1H), 8 70 (s, 1H), 9 39 (s 1H)
205		445 17	4-(4-((2H-1,2,3-triazol-2-yl)methyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 9	m/z 446 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 3 01-3 05 (m 4H) 3 72-3 75 (m, 4H), 5 79 (s 2H), 6 29 (d *J*=4 93Hz, 1H), 6 76 (d, *J*=9 07Hz 2H), 7 33 (d *J*=8 44Hz, 2H) 7 34 (d, *J*=9 01Hz, 2H), 7 62 (d, *J*=8 33Hz, 2H) 7 87 (s 2H) 8 11 (d *J*=5 10Hz 1H), 9 38 (s 1H)

206		445 17	4-(4-((1H-1,2,3-triazol-1-yl)methyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 4	m/z 446 3 [M+H]+	^{1}H NMR (300MHz, d$_6$-DMSO) δ 3 01-3 04 (m, 4H) 3 72-3 75 (m, 4H), 5 74 (s, 2H), 6 26 (d, *J*=5 16Hz, 1H), 6 76 (d, *J*=9 11Hz, 2H), 7 37 (d *J*=9 00Hz, 2H), 7 40(d, *J*=8 02Hz, 2H), 7 65 (d *J*=8 39Hz, 2H), 7 78 (d, *J*=1 02Hz, 1H), 8 11 (d *J*=5 28Hz 1H), 8 24 (d, *J*=1 02Hz, 1H), 9 39 (s, 1H)
207		407 14	4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzamide	C	5 8	m/z 408 3 [M+H]+	^{1}H NMR (300MHz, d$_6$-DMSO) δ 2 96-2 99 (m, 4H)T 3 70-3 74 (m, 4H) 6 52 (d, *J*=4 71Hz, 1H) 6 62 (d, *J*=8 91Hz, 2H), 7 16 (d, *J*=8 28Hz, 2H), 7 57 (br s, 1H), 7 71 (d, *J*=8 51Hz, 2H), 8 02 (d, *J*=8 53Hz, 2H), 8 13 (d, *J*=5 24Hz, 1H), 9 37 (s 1H)
208		389 13	3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzonitrile	C	6 9	m/z 390 2 [M-H]+	^{1}H NMR (300MHz, CDCl$_3$) δ 3 08-3 12 (m, 4H) 3 85-3 88 (m, 4H), 6 40 (d *J*=5 31Hz, 1H), 6 77 (d, *J*=9 02Hz 2H), 6 97 (br s, 1H), 7 19 (d *J*=8 82Hz, 2H), 7 55 (dt, *J*=0 57, 7 85Hz 1H), 7 73-7 77 (m, 1H), 7 82 (ddd, *J*=1 19, 1 81, 7 85Hz 1H), 7 91-92 (m 1H), 8 08 (d J=5 31Hz 1H)
209		389 13	4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzonitrile	C	7 0	m/z 390 2 [M+H]+	^{1}H NMR (300MHz, CDCl$_3$) δ 3 10-3 13 (m, 4H) 3 85-3 87 (m, 4H), 6 47 (d, *J*=5 28Hz 1H), 6 74 (d, *J*=8 94Hz, 2H), 6 91 (br s, 1H), 7 13 (d, *J*=8 80Hz 2H), 7 71 (s 4H), 8 09 (d, *J*=5 31Hz 1H)
210		403 15	2-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetonitrile	C	6 9	m/z 404 3 [M+H]+	^{1}H NMR (300MHz, d$_6$-DMSO) δ 2 99-3 02 (m, 4H). 3 70-3 74 (m. 4H), 4 18 (s, 2H), 6 34 (d, *J*=5 10Hz, 1H), 6 72 (d, *J*=9 07Hz 2H) 7 32 (d *J*=9 08Hz, 2H), 7 52 (d, *J*=8 50Hz, 2H) 7 67 (d, *J*=8 36 Hz, 2H), 8 12 (d, *J*=5 27Hz, 1H), 9 38 (s, 1H)
211		436 16	methyl 3-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzoate	C	7 5	m/z 437 3 [M+H]+	^{1}H NMR (300MHz, CDCl$_3$) δ 2 03 (d, J=O 68Hz, 3H), 3 02-3 05 (m, 4H), 3 85-3 88 (m, 4H), 3 89 (s, 3H) 6 57 (d, *J*=9 03Hz, 2H), 6 70 (br S, 1H) 6 92 (d, *J*=8 98Hz, 2H), 7 53 (dt *J*=O 51 7 76Hz 1H), 7 77 (ddd, *J*=1 26, 1 82, 7 73Hz, 1H), 7 91 (d, *J*=0 71Hz, 1H), 8 19 (ddd, *J*=1 20 1 69, 7 79Hz, 1H) 8 26-8 27 (m 1H)

212		408 16	(3-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)methanol	C	6 6	m/z 409 4 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 13 (d J=0 59Hz 3H), 2 93-2 96 (m 4H) 3 71-3 75 (m 4H), 4 55 (d, J=5 55Hz, 2H), 5 31 (t, J=5 59Hz, 1H), 6 52 (d, J=9 13Hz, 2H), 7 01 (d J=9 05Hz 2H), 7 40-7 61 (m, 4H), 8 02 (s, 1H), 9 07 (s, 1H)
213		403 15	2-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetonitrile	C	6 8	m/z 404 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 99-3 01 (m 4H) 3 71-3 73 (m, 4H), 4 14 (s, 2H), 6 32-6 38 (br s 1H) 6 72 (d, J=8 84Hz, 2H) 7 30 (d, J=7 76Hz, 2H) 7 58-7 63 (m, 4H), 8 13 (d, J=5 24Hz 1H) 9 38 (s, 1H)
214		417 16	2-(3-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetonitrile	C	7 1	m/z 418 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 15 (d, J=0 62Hz, 3H), 2 96-2 98 (m, 4H) 3 72-3 74 (m 4H), 4 10 (s, 2H), 6 52 (d, J=8 97Hz, 2H), 7 01 (d J=8 94Hz, 2H), 7 55-7 65 (m, 4H), 8 05 (d, J=0 73 1H), 9 10 (s, 1H)
215		422 14	3-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzoic acid	C	6 5	m/z 423 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 14 (d, J=0 61Hz, 3H), 2 93-2 95 (m, 4H), 3 71-3 72 (m 4H), 6 52 (d, J=9 08Hz, 2H), 6 97 (d, J=8 87Hz, 2H), 7 42 (t, J=7 35Hz, 1H), 7 49-7 51 (m, 1H), 8 01 (d, J=0 73Hz, 1H), 8 04-8 06 (m, 1H), 8 07-8 09 (m, 1H), 9 02 (s, 1H)
216		436 16	methyl 4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzoate	C	7 6	m/z 437 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 15 (s 3H), 2 87-2 90 (m 4H), 3 71-3 74 (m, 4H), 3 91 (s, 3H) 6 43 (d, J=9 22Hz, 2H), 6 95 (d, J=8 84Hz, 2H), 7 76 (d, J=8 28Hz, 2H), 8 06-8 09 (m 3H) 9 15 (s, 1H)
217		422 14	4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzoic acid	C	0 9	m/z 423 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 15 (s, 3H), 2 89-2 92 (m, 4H), 3 70-3 73 (m, 4H), 6 44 (d, J=9 10Hz, 2H), 7 73 (d, J=8 57Hz, 2H), 8 06 (d J=8 55Hz 1H), 8 06 (d, J=0 68Hz 1H), 9 16 (s 1H)
218		465 18	N-methoxy-N-methyl-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)benzamide	C	7 0	m/z 466 4 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 15 (s, 3H), 2 93-2 96 (m, 4H), 3 29 (s, 3H), 3 58 (s, 3H), 3 69-3 72 (m 4H) 6 56 (d, J=9 00Hz, 2H), 6 97 (d, J=8 96Hz 2H) 7 68 (d, J=8 58Hz, 2H) 7 75 (d J=8 57Hz 2H) 8 05 (d J=0 65Hz 1H) 9 15 (s 1H)

219		406 15	4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzaldehyde	C	7 2	m/z 407 4 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 15 (d J=0 57Hz, 3H), 2 87-2 90 (m, 4H), 3 69-3 72 (m 4H), 6 43 (d, J=9 01Hz, 2H), 6 97 (d, J=8 78Hz, 2H), 7 83 (d, J=8 07Hz, 2H), 8 04 (d, J=8 47Hz 2H), 8 08 (d, J=0 65Hz, 1H), 9 16 (s 1H), 10 18 (s, 1H)
220		408 16	(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)methanol	C	6 6	m/z 409 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 13 (d. J=0 59Hz, 3H), 2 94-2 97 (m, 4H), 3 69-3 73 (m 4H), 4 66 (d, J=5 19Hz, 2H), 5 45 (t J=5 34Hz, 1H), 6 52 (d, J=9 14Hz, 2H), 6 99 (d, J=9 07Hz 2H), 7 49 (d, J=8 51Hz, 2H), 7 55 (d, J=8 37Hz 2H), 8 01 (d, J=0 68Hz, 1H), 9 09 (s, 1H)
221		508 18	1-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)benzyl)-1H-imidazole-4,5-dicarbonitrile	C	7 3	m/z 509 4 [M+H]+	^{1}H NMR (300MHz d_6-DMSO) δ 2 13 (d J=0 60Hz, 3H), 2 96-2 99 (m, 4H), 3 72-3 75 (m 4H), 5 60 (s, 2H), 6 52 (d, J=9 08Hz 2H) 7 09 (d J=9 10Hz, 2H), 7 53 (d, J=8 46Hz, 2H) 7 65 (d J=8 39Hz, 2H), 8 04 (d, J=0 68Hz 1H) 8 50 (s, 1H), 9 09 (s 1H)
222		417 16	2-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acetonitrile	C	7 1	m/z 418 4 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 13 (s, 3H), 2 94-2 98 (m 4H), 3 69-3 72 (m, 4H), 4 21 (s, 2H) 6 50 (d, J=9 10Hz, 2H), 7 04 (d, J=8 87Hz, 2H) 7 52 (d, J=8 39Hz, 2H) 7 63 (d, J=8 26Hz 2H), 8 03 (s, 1H) 9 13 9s 1H)
223		502 22	2-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)-2-morpholinoacetonitrile	C	7 4	m/z 503 4 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 13 (s, 3H), 2 35-2 44 (m, 2H), 2 53-2 64 (m, 2H), 2 96-2 99 (m 4H), 3 57-3 60 (m, 4H), 3 69-3 72 (m, 4H), 5 55 (s 1H), 6 54 (d, J=9 04Hz, 2H), 7 07 (d J=8 93Hz, 2H), 7 60 (d, J=8 24Hz, 2H), 7 70 (d, J=8 33Hz 2H) 8 05 (s, 1H) 9 12 (s, 1H)
224		475 20	(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)(pyrrolidin-1-yl)methanone	C	6 8	m/z 476 4 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$) δ 1 88-2 01 (m, 4H) 2 20 (d, J=0 68Hz, 3H), 3 08-3 11 (m, 4H), 3 44-3 48 (m 2H), 3 64-3 69 (m, 2H), 3 84-3 88 (m 4H), 6 71 (d, J=9 07Hz, 2H), 6 79 (br s, 1H), 7 01 (d, J=9 08Hz, 2H) 7 64 (s, 4H), 7 91 (d J=0 70Hz 1H)

225		515 25	2-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)-2-(4-methylpiperazin-1-yl)acetonitrile	D	5 6	m/z 489 0 [M-CN]+	^{1}H NMR (300MHz, $CDCl_3$) δ 2 20 (d, J=0 66Hz 3H), 2 30 (s, 3H), 2 43-2 52 (m, 4H), 2 62-2 69 (m 4H) 3 06-3 10 (m, 4H), 3 85-3 88 (m 4H) 4 92 (s 1H) 6 67 (d, J=9 05Hz, 2H) 6 69 (s, 1H) 7 07 (d, J=9 01Hz, 2H), 7 64 (s, 4H), 7 92 (d, J=0 71Hz 1H)
226		416 10	N-(3-(4-(4-(hydroxymethyl)phenylthio)-5-methylpyrimidin-2-ylao)phenyl)methanesulfonamide	E	9 4	m/z 417 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 14 (d, J=0 58, 3H), 2 85 (s, 3H), 4 70 (d, J=5 41Hz, 2H), 5 29 (t J=5 73Hz, 1H), 6 76 (d, J=8 99Hz, 2H), 7 10 (d J=9 02Hz, 2H), 7 46 (d, J=8 48Hz, 2H), 7 55 (d, J=8 29Hz, 2H), 8 05 (d, J=0 68Hz, 1H), 9 24 (s 1H), 9 31 (s, 1H)
227		425 10	N-(4-(4-(4-(cyanomethyl)phenylthio)-5-methylpyrimidin-2-ylao)phenyl)methanesulfonamide	C	6 7	m/z 426 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 17 (s, 3H), 2 87 (s, 3H), 4 24 (s, 2H), 6 76 (d, J=8 84Hz, 2H), 7 09 (d, J=8 74Hz, 2H), 7 52 (d, J=8 25Hz, 2H), 7 65 (d, J=8 13Hz, 2H), 8 08 (s, 1H), 9 31 (s, 1H), 9 38 (s, 1H)
228		477 18	3-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenylao)dihydrofuran-2(3H)-one	C	6 8	m/z 478 4 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 12 (d, J=0 60Hz, 3H), 2 57-2 75 (m, 1H), 2 88-2 97 (m, 4H), 3 68-3 71 (m, 4H), 4 23-4 32 (m, 1H), 4 38-4 45 (m, 1H), 4 58-4 69 (m, 1H), 6 56-6 59 (m, 1H), 6 57 (d, J=9 16Hz, 2H), 6 84 (d J= 8 77Hz 2H), 7 09 (d, J=9 11Hz, 2H), 7 28 (d, J=8 67Hz 2H), 7 95 (d J=0 67Hz, 1H), 9 07 (s 1H)\
229		451 17	2-hydroxy-N-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	6 1	m/z 452 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 12 (d, J=0 44Hz, 3H), 2 84-2 87 (m, 4H), 3 64-3 68 (m 4H), 4 04 (s, 2H), 6 48 (d, J=9 08Hz, 2H) 7 01 (d J=8 88Hz, 2H), 7 52 (d, J=8 61Hz, 2H) 7 93 (d J=8 66Hz, 2H), 8 00 (d, J=0 69Hz, 2H) 9 08 (s 1H), 10 13 (s, 1H)
230		525 15	2-(2-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenylao)-2-oxoethylthio)acetic acid	D	4 70	m/z 526 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 13 (d, J=0 47Hz, 3H) 2 90-2 93 (m 4H) 3 48 (s 2H) 3 50 (s, 2H), 3 71-3 74 (m, 4H), 6 50 (d J=9 06Hz 2H), 7 03 (d, J=9 01Hz. 2H) 7 54 (d, J=8 68Hz, 2H) 7 76 (d J=8 75Hz, 2H) 8 00 (d J=0 64Hz 1H), 9 08 (s 1H) 10 47 (s 1H)

231		507 14	4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)thiomorpholine-3,5-dione	I	10 3	m/z 508 3 [M+H]+	^{1}H NMR (300MHz, d_6-DMSO) δ 2 16 (d, J=0 49Hz, 3H), 2 94-2 97 (m, 4H), 3 70-3 74 (m 4H), 3 87 (s, 4H), 6 65 (d, J=9 21Hz, 2H), 7 24 (d J=9 06Hz, 2H), 7 27 (d, J=8 54Hz, 2H) 7 69 (d J=8 56Hz, 2H), 8 07 (d, J=0 65Hz, 1H), 9 14 (s, 1H)
232		445 16	N-(3-(2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-ynamide	C	6 90	m/z 446 2 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$) δ ppm 8 48 (d, 1H, J = 5 7 Hz), 7 83 (br s, 1H), 7 76 (d, 1H, J = 7 5 Hz), 7 69 (m 1H), 7 41 (dd, 1H, J = 7 8, 7 8 Hz), 7 36 (d, 1H, J = 7 2 Hz), 7 29 (s, 1H) 7 13 (m, 1H), 7 09 (d, 1H, J = 8 4 Hz), 6 94 (dd, 1H, J = 7 5 1 2 Hz), 6 56 (dd, 1H, J = 8 1, 1 8 Hz), 6 31 (d, 1H, J = 5 4 Hz), 3 84 (dd, 4H, J = 5 0 4 8 Hz), 3 13 (dd 4H, J = 5 1, 4 8 Hz), 1 98 (s, 3H)
233		445 16	N-(4-(2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-ynamide	C	6 91	m/z 446 3 [M+H]+	^{1}H NMR (300MHz, d-Acetone) δ ppm 9 71 (br s, 1H), 8 29 (br s, 1H), 7 99 (d, J = 3 0 Hz, 1H) 7 71 (d, J = 5 4 Hz, 2H), 7 46 (d, J = 4 8 Hz, 2H), 7 21 (m, 1H), 7 06 (dd, J = 4 8, 0 9 Hz 1H), 6 92 (dd J = 5 0, 4 8 Hz, 1H), 6 43 (dd, J = 4 8, 1 5 Hz, 1H) 6 19 (d, J = 3 0 Hz, 1H), 3 63 (dd, J = 2 9, 2 7 Hz 4H), 2 97 (dd, J = 3 0, 2 9 Hz, 4H), 1 88 (s, 3H)
234		501 18	3-(3-methoxyphenylao)-N-(4-(2-(3-methoxyphenylao)pyrimidin-4-ylthio)phenyl)propanamide	C	7 45	m/z 502 3 [M+H]+	^{1}H NMR (300MHz, d-Acetone) δ ppm 9 51 (br s, 1H) 8 53 (br s, 1H), 8 12 (d, J = 5 4 Hz, 1H), 7 83 (d, J = 5 1 Hz, 2H), 7 56 (d, J = 8 7 Hz, 2H), 7 41 (m, 1H), 7 24 (m, 1H), 7 09 (t, J = 8 4 Hz 1H), 7 00 (t, J = 7 5 Hz, 1H), 6 50 (m, 1H), 6 32 (d, J = 5 4 Hz, 1H), 6 22 (m, 3H), 5 04 (m, 1H), 3 75 (s 3H), 3 72 (s, 3H), 3 52 (q, J = 6 4 Hz, 2H), 2 73 (t, J = 6 4 Hz, 2H)
235		392 13	N-(4-(2-(3-methoxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	7 07	m/z 393 3 [M+H]+	^{1}H NMR (300MHz, d-Acetone) δ ppm 9 62 (br s 1H), 8 27 (br s, 1H), 8 01 (s, 1H), 7 89 (dd, J = 6 3, 1 5 Hz, 2H), 7 54 (dd, J = 6 9, 1 8 Hz, 2H), 7 02 (m, 1H), 6 95 (dd, J = 2 4, 2 1 Hz, 1H), 6 89 (dd, J = 8 0, 7 8 Hz, 1H), 6 49 (d, J = 10 2 Hz, 1H), 6 43 (d, J = 2 4 Hz, 1H), 6 37 (m, 1H), 5 77 (dd J = 10 2 2 7 Hz, 1H), 3 67 (s 3H) 2 19 (s, 3H)
236		515.20	3-(3-methoxyphenylao)-N-(4-(2-(3-methoxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)propanamide	C	7 53	m/z 516 3 [M+H]+	^{1}H NMR (300MHz, d-Acetone) δ ppm 9 52 (br s 1H), 8 26 (br s, 1H), 7 99 (s, 1H), 7 82 (d, J = 8 7 Hz, 2H), 7 51 (d, J = 8 7 Hz, 2H) 7 01 (dd J = 7 8, 7 8 Hz, 2H), 6 90 (m, 2H), 6 28 (m, 4H), 5 05 (bt 1H) 3 72 (s, 3H) 3 66 (s 3H) 3 54 (m 2H) 2 76 (m 2H) 2 18 (s, 3H)

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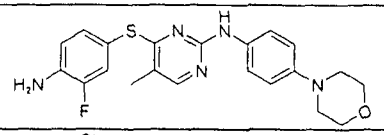
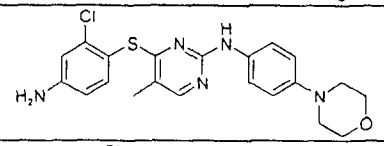
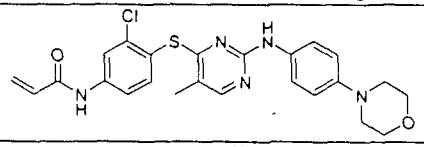
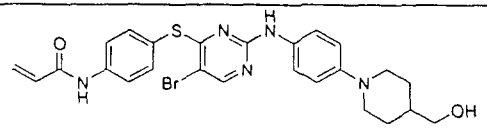
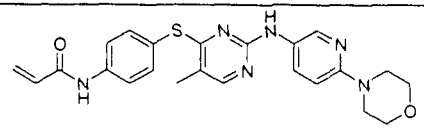
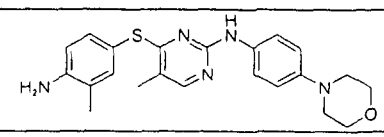
237		447 17	N-(4-(5-methyl-2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	6 98	m/z 448 3 [M+H]+	^{1}H NMR (300MHz, d-Acetone) δ ppm 9 62 (br s 1H) 8 13 (br s, 1H), 7 99 (d, J = 0 9 Hz 1H) 7 89 (d, J = 8 7 Hz, 2H), 7 54 (d, J = 8 7 Hz, 2H), 6 99 (m, 1H), 6 85 (m, 2H), 6 47 (m, 3H), 5 78 (dd, J = 9 6, 2 7 Hz 1H), 3 72 (m 4H) 3 02 (m, 4H) 2 18 (s 3H)
238		446 19	N-(4-(2-(4-(4-methylpiperazin-1-yl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	5 89	m/z 447 4 [M+H]+	^{1}H NMR (300MHz, d-Acetone) δ ppm 9 53 (br s 1H), 8 33 (br s 1H) 8 05 (m, 3H) 7 50 (m, 1H) 7 41 (d J = 8 7 Hz, 2H), 7 34 (m 1H) 6 78 (d J = 9 3 Hz, 2H), 6 41 (m, 2H), 5 74 (dd, J = 9 0, 2 7 Hz, 1H), 3 07 (m, 4H), 2 47 (m, 4H), 2 25 (s, 3H)
239		460 20	N-(4-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	5 28	m/z 461 4 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$) δ ppm 7 87 (s, 1H), 7 75 (d, J = 8 4 Hz, 2H), 7 56 (m, 3H), 6 96 (d J = 9 3 Hz, 2H), 6 69 (br s, 1H), 6 63 (d, J = 9 3 Hz, 2H), 6 53 (dd, J = 17 1, 1 4 Hz, 1H), 6 32 (m 1H), 5 86 (dd, J = 10 2, 1 4 Hz, 1H), 3 05 (m 4H) 2 53 (m, 4H) 2 33 (s, 3H), 2 19 (s, 3H)
240		368 13	4-(4-aophenylthio)-N-(3,4-dimethoxyphenyl)-5-methylpyrimidin-2-ae	C	10 13	m/z 369 3 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$) δ ppm 7 86 (s, 1H) 7 33 (d, J = 8 4 Hz, 2H), 6 88 (dd, J = 8 7 2 7 Hz, 1H), 6 80 (br s, 1H), 6 75 (d, J = 8 7 Hz, 2H), 6 67 (d, J = 8 7 Hz, 1H), 6 62 (m, 1H), 3 85 (s, 3H), 3 78 (s, 3H), 2 18 (s, 3H)
241		422 14	N-(4-(2-(3,4-dimethoxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 92	m/z 423 3 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$ + CD_3OD) δ ppm 7 70 (d, J = 0 9 Hz, 1H), 7 65 (d, J = 8 7 Hz 2H), 7 39 (d, J = 8 7 Hz, 2H), 6 64 (dd, J = 8 7 2 7 Hz, 1H) 6 49 (d, J = 2 1 Hz, 1H), 6 35 (d, J = 9 0 Hz, 1H) 6 29 (m, 2H), 5 65 (dd, J = 7 8, 4 1 Hz, 1H), 3 60 (s, 3H), 3 59 (s, 3H), 2 06 (s, 3H)
242		454 05	N-(4-(2-(3-bromo-4-methylphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	7 78	m/z 455 3/45 7 3 [M+H]+	^{1}H NMR (300MHz, d-MeOH + DMSO) δ ppm 8 02 (s, 1H), 7 87 (d, J = 8 4 Hz, 2H), 7 57 (d, J = 8 4 Hz, 2H), 7 38 (d, J = 2 4 Hz, 1H), 7 17 (dd, J = 8 4, 2 7 Hz, 1H), 6 82 (d, J = 8 7 Hz, 1H) 6 53 (d J = 9 6 Hz, 1H), 6 48 (d, J = 2 1 Hz, 1H), 5 87 (dd J = 9 6 2 4 Hz, 1H), 2 23 (s, 3H) 2 21 (s, 3H)

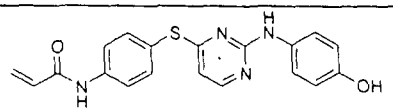
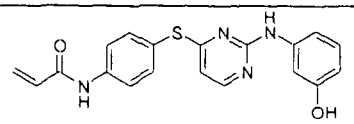
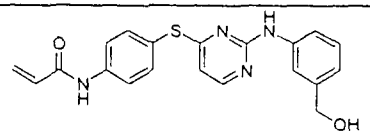
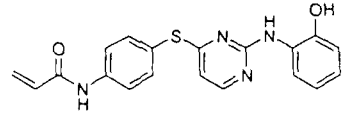
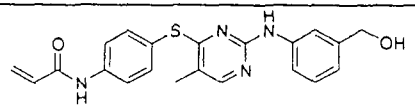
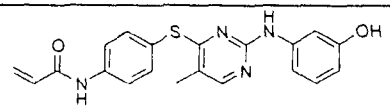
243		460 20	N-(4-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	5 35	m/z 461 4 [M+H]+	^{1}H NMR (300MHz $CDCl_3$) δ ppm 7 92 (s 1H) 7 68 (m 2H), 7 54 (m, 3H), 6 88 (m, 2H), 6 77 (br s, 1H), 6 63 (br s, 1H), 6 50 (m, 2H), 6 30 (m 1H) 5 84 (dd, J = 9 9, 1 4 Hz, 1H) 3 10 (m 4H) 2 53 (m, 4H), 2 33 (s, 3H), 2 19 (s 3H)
244		406 19	4-(4-aophenylthio)-5-methyl-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-ae	D	4 46	m/z 407 4 [M+H]+	^{1}H NMR (300MHz d-MeOH + DMSO) δ ppm 7 86 (s, 1H), 7 25 (d J = 8 4 Hz, 2H), 7 12 (d, J = 9 0 Hz, 2H), 6 78 (m, 4H), 3 13 (m, 4H), 2 62 (m 4H) 2 36 (s, 3H) 2 16 (s, 3H)
245		406 19	4-(4-aophenylthio)-5-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-ae	D	5 31	m/z 407 4 [M+H]+	^{1}H NMR (300MHz, d-DMSO) δ ppm 8 95 (s 1H) 7 98 (s 1H), 7 16 (d, J = 8 7 Hz 2H) 6 98 (d J = 9 6 Hz, 1H), 6 83 (dd, J = 8 4, 8 3 Hz, 1H) 6 72 (m 1H), 6 67 (d, J =9 0 Hz, 2H) 6 38 (dd J = 8 1, 1 8 Hz, 1H) 5 59 (br s 2H), 3 01 (m 4H) 2 41 (m, 4H) 2 20 (s 3H), 2 11 (s 3H)
246		459 21	N-(4-(5-methyl-2-(4-(1-methylpiperidin-4-yl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	D	4 54	m/z 460 3 [M+H]+	^{1}H NMR (300MHz, $CDCl_3$ + CD_3OD) δ ppm 7 86 (m, 3H), 7 54 (d J = 8 1 Hz 2H), 6 97 (d, J = 8 1 Hz, 2H), 6 85 (d J = 8 7 Hz, 2H), 6 53 (m 2H) 5 77 (dd J = 9 3 2 7 Hz 1H) 2 96 (d, J = 10 5 Hz, 2H) 2 38 (s 3H), 2 20 (s, 3H), 1 7 (m, 6H)
247		348 12	N-(4-(4-aophenylthio)-5-methylpyrimidin-2-yl)-1H-indazol-5-ae	C	6 30	m/z 349 3 [M+H]+	^{1}H NMR (300MHz *d*-DMSO) δ ppm 7 96 (s 1H) 7 89 (s 1H), 7 72 (dd, J = 1 8 0 9 Hz 1H), 7 31 (d, J = 8 7 Hz, 2H), 7 23 (m, 2H) 6 81 (d, J = 8 7 Hz, 2H), 2 19 (s, 3H)
248		477 18	N-(4-(2-(3-methoxy-4-morpholinophenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 68	m/z 478 4 [M+H]+	^{1}H NMR (300MHz, *d*-DMSO) δ ppm 10 49 (br s 1H), 9 07 (br s, 1H), 8 02 (s, 1H), 7 88 (d, J = 8 7 Hz, 2H), 7 54 (d, J = 8 7 Hz, 2H), 6 70 (m, 2H) 6 51 (dd, J = 16 9, 10 1 Hz, 1H), 6 33 (dd, J = 17 1 1 8 Hz, 1H), 6 20 (d J = 8 7 Hz 1H) 5 85 (dd, J = 9 9, 2 1 Hz, 1H), 3 63 (m, 3H), 3 62 (m 4H), 2 73 (m, 4H), 2 14 (s, 3H)
249		490 22	N-(4-(2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylam	D	4 53	m/z 491 4 [M+H]+	^{1}H NMR (300MHz, *d*-DMSO) δ ppm 10 47 (br s 1H), 9 04 (br s, 1H), 8 02 (s, 1H), 7 88 (d, J = 8 7 Hz, 2H), 7 53 (d, J = 8 7 Hz, 2H) 6 69 (m 2H) 6 50 (dd J = 17 1 10 2 Hz, 1H) 6 32 (dd J = 17 1, 2 7 Hz 1H) 6 21 (d, J = 8 4 Hz 1H) 5 84

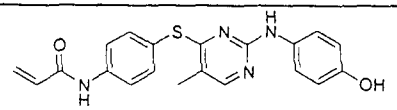
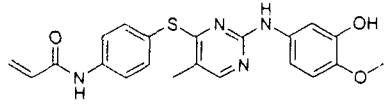
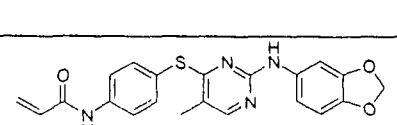
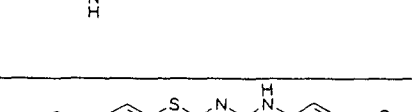
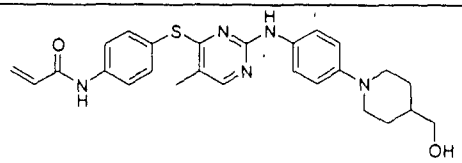
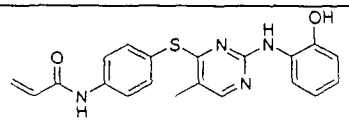
			ide				(dd J = 10 2, 2 1 Hz, 1H), 4 01 (d, J = 0 9 Hz 3H), 3 63 (s, 3H) 2 73 (br s 4H) 2 37 (br s 4H) 2 19 (s, 3H)
250		411 15	4-(4-ao-3-fluorophenylthio)-5-methyl-N-(4-morpholinophenyl)pyr imidin-2-ae	C	6 93	m/z 412 3 [M+H]+	^{1}H NMR (300MHz, d-DMSO) δ ppm 9 11 (s 1 H) 7 97 (s, 1 H) 7 18 (dd, J = 11 4, 2 1 Hz, 1 H) 7 07 (m, 3 H) 6 88 (dd, J = 9 9, 9 0 Hz, 1 H) 6 62 (d, J = 9 3 Hz 2 H) 5 80 (br s, 2H) 3 73 (m, 4H), 2 99 (m, 4 H) 2 10 (s, 3 H)
251		427 12	4-(4-ao-2-chlorophenylthio)-5-methyl-N-(4-morpholinophenyl)pyr imidin-2-ae	C	6 93	m/z 428 3/43 0 3 [M+H]+	^{1}H NMR (300 MHz DMSO-d) δ ppm 9 11 (s, 1H) 7 98 (s, 1H) 7 30 (d, J = 8 7 Hz, 1H) 7 12 (d, J = 9 0 Hz, 2H) 6 87 (d, J = 2 4 Hz, 1H) 6 63 (m, 3H) 6 02 (s, 2H) 3 72 (m 4H), 2 99 (m, 4H) 2 12 (s 3H)
252		481 13	N-(3-chloro-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylam ide	C	7 00	m/z 482 3/48 4 3 [M+H]+	^{1}H NMR (300 MHz, DMSO-d) δ ppm 10 69 (s 1H) 9 19 (s, 1H) 8 24 (d, J = 1 8 Hz, 1H) 8 04 (s, 1H) 7 71 (m, 2H) 6 98 (d, J = 9 0 Hz, 2H) 6 38 (m, 2H) 5 90 (dd, J = 9 0, 2 1 Hz 1H) 3 64 (m 4H) 2 84 (m, 4H) 2 16 (s, 3H)
253		539 10	N-(4-(5-bromo-2-(4-(4-(hydroxymethyl)piperi din-1-yl)phenylao)pyrimidin -4-ylthio)phenyl)acrylam ide	C	6 78	m/z 540 2/54 2 2 [M+H]+	^{1}H NMR (300 MHz, d6-acetone) δ ppm 9 76 (br s 1H) 8 42 (br s 1H), 8 15 (s, 1H), 7 98 (d J = 8 7 Hz, 2H), 7 58 (d, J = 8 7 Hz, 2H), 7 05 (d, J = 9 3 Hz, 2H) 6 62 (m 2H), 6 59 (m 1H), 6 45 (dd J = 17 1, 2 7 Hz, 1H), 5 82 (dd, J = 9 6, 2 4 Hz, 1H), 3 51 (m, 2-3H), 3 42 (m 2H), 1 78 (m 2H) 0 87 (m, 2H)
254		448 17	N-(4-(5-methyl-2-(6-morpholinopyridin-3-ylao)pyrimidin-4-ylthio)phenyl)acrylam ide	C	6 51	m/z 449 3 [M+H]+	^{1}H NMR (300MHz, d-DMSO) δ ppm 10 50 (br s, 1H), 9 23 (br s 1H), 8 03 (br s 1H), 7 93 (d J = 2 4 Hz, 1H), 7 86 (d, J = 9 0 Hz, 2H), 7 54 (d J = 8 7 Hz, 2H), 7 30 (dd, J = 9 6 2 7 Hz 1H), 6 49 (dd, J = 17 1 10 2 Hz, 2H), 6 33 (dd, J = 17 1, 2 4 Hz, 1H), 6 19 (d, J = 9 0 Hz, 1H) 5 86 (dd J = 10 2, 2 1 Hz, 1H), 3 62 (m, 4H) 3 15 (m 4H) 2 14 (s 3H)
255		407 18	4-(4-ao-3-methylphenylthio)-5-methyl-N-(4-morpholinophenyl)pyr imidin-2-ae	C	6 84	m/z 408 3 [M+H]+	^{1}H NMR (300 MHz, d-acetone) δ ppm 8 01 (br s 1H) 7 88 (s 1H), 7 16 (m, 4H), 6 84 (d J = 8 4 Hz 1H) 6 69 (d J = 9 0 Hz 2H) 5 05 (br s 2H) 3 74 (m 4H) 3 05 (m 4H) 2 18 (s 3H) 2 14 (s 3H)

256		421 19	4-(4-ao-3-ethylphenylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 10	m/z 422 4 [M+H]+	^{1}H NMR (300 MHz, d-acetone) δ ppm 8 01 (br s 1H), 7 88 (s, 1H), 7 16 (m, 4H), 6 85 (d, J = 8 4Hz 1H), 6 70 (d J = 9 0 Hz, 2H) 5 07 (br s 2H), 3 74 (m 4H), 3 05 (m, 4H), 2 54 (q J = 7 6 Hz 2H) 2 14 (s 3H), 1 17 (t, J = 7 5 Hz, 3H)
257		427 12	4-(4-ao-3-chlorophenylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 17	m/z 428 2/43 0 2 [M+H]+	^{1}H NMR (300 MHz d-DMSO) δ ppm 9 08 (s 1H) 7 97 (d J = 0 9 Hz 1H) 7 37 (d J = 2 1 Hz 1H) 7 19 (dd, J = 8 4, 2 1 Hz, 1H), 7 10 (d, J = 9 0 Hz 2H), 6 91 (d, J = 8 4 Hz, 1H), 6 61 (d, J = 9 3 Hz 2H), 5 97 (br s, 2H), 3 73 (m 4H) 2 99 (m 4H) 2 10 (d, J = 0 3 Hz 3H)
258		394 16	4-(4-aophenylthio)-5-methyl-N-(6-morpholinopyridin-3-yl)pyrimidin-2-ae	C	6 45	m/z 395 3 [M+H]+	^{1}H NMR (300 MHz d-MeOH) δ ppm 7 88 (d J = 3 0 Hz 1H) 7 84 (d, J = 0 9 Hz, 1H) 7 60 (dd J = 9 0 3 0 Hz 1H), 7 22 (d J = 8 7 Hz 2H) 6 76 (d J = 8 7 Hz, 2H) 6 58 (d J = 9 3 Hz 1H), 3 80 (m 4H), 3 36 (m, 4H), 2 16 (d, J = 0 6 Hz, 3H)
259		461 19	N-(2-methyl-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	6 72	m/z 462 3 [M+H]+	^{1}H NMR (300 MHz, d-DMSO) δ ppm 9 56 (s, 1H) 9 11 (s, 1H), 8 01 (m 2H) 7 44 (m, 2H) 7 01 (d, J = 5 4 Hz 2H), 6 71 (dd, J = 9 9 6 3 Hz 1H) 6 50 (d J = 5 1 Hz 2H), 6 32 (d J = 9 9 Hz 1H) 5 85 (d, J = 6 3 Hz 1H) 3 66 (m 4H) 2 88 (m 4H) 2 27 (s, 3H), 2 13 (s, 3H)
260		475 20	N-(2-ethyl-4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	7 02	m/z 476 3 [M+H]+	^{1}H NMR (300 MHz, d-DMSO) δ ppm 9 55 (s 1H) 9 10 (s, 1H), 8 03 (s, 1H), 7 97 (d, J = 5 1 Hz, 1H) 7 44 (m, 2H), 7 01 (d, J = 5 4 Hz, 2H), 6 72 (dd J = 10 2 5 7 Hz, 1H), 6 51 (d, J = 5 4 Hz 2H), 6 33 (d, J = 10 2 Hz, 1H), 5 84 (d, J = 5 7 Hz, 1H) 3 66 (m 4H), 2 89 (m 4H), 2 69 (q J = 4 5 Hz 2H) 2 15 (s, 3H), 1 05 (t J = 4 5 Hz, 3H)
261		525 08	N-(4-(5-bromo-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-N-methylacrylamide	C	7 26	m/z 526 2/52 8 2 [M+H]+	^{1}H NMR (300MHz, d-DMSO) δ ppm 7 35 (s 1H) 6 86 (d J = 8 7 Hz 2H), 6 57 (d, J = 8 7 Hz 2H) 6 32 (d, J = 9 3 Hz 2H) 6 15 (s, 1H), 5 89 (d, J = 9 0 Hz 2H), 5 48 (d, J = 17 1 Hz, 2H), 4 98 (dd J = 6 9, 10 8 Hz, 1H), 2 99 (m, 4H), 2 61 (s 3H) 2 19 (m, 4H)
262		394 16	4-(6-aopyridin-3-ylthio)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	5 89	m/z 395 3 [M+H]+	^{1}H NMR (300MHz d-DMSO) δ ppm 9 08 (br s 1H), 7 99 (m 2H), 7 46 (dd J = 8 7 2 4 Hz 1H) 7 15 (d J = 9 3 Hz, 2H), 6 67 (d J = 9 0 Hz, 2H) 6 59 (dd, J = 8 7, 0 6 Hz 2H) 6 55 (br s 1H) 3 73 (m 4H), 3 00 (m 4H) 2 12 (s 3H)

263		397 14	4-(4-aophenylthio)-5-fluoro-N-(4-morpholinophenyl)pyrimidin-2-ae	E	10 1	m/z 398 3 [M+H]+	^{1}H NMR (DMSO-d_6, 300 MHz) δ 9 31 (s, 1H), 8 19 (d, J=2 3 1H) 7 21 (d, J=8 2Hz, 2H), 7 10 (d, J=8 7Hz, 2H), 6 75-6 62 (m, 4H), 5 78 (s, 2H), 3 73 (m, 4H), 3 00 (m, 4H)
264		505 04	4-(4-aophenylthio)-5-iodo-N-(3-morpholinophenyl)pyrimidin-2-ae	E	10 9	m/z 506 2 [M+H]+	^{1}H NMR ($CDCl_3$, 300 MHz) δ8 26 (s, 1H), 7 34 (d, J=8 7Hz 2H) 7 00 (t, J=8 5Hz, 1H), 6 95-6 82 (m 2H), 6 75 (d, J=8 7Hz, 2H), 6 52 (d, J=6 9Hz, 2H), 3 97 (s, 2H), 3 84 (t, J=4 6Hz, 4H), 3 09 (t, J=5 0Hz, 4H)
265		397 14	4-(4-aophenylthio)-5-fluoro-N-(3-morpholinophenyl)pyrimidin-2-ae	C	6 9	m/z 398 3 [M+H]+	^{1}H NMR (DMSO-d_6, 300 MHz) δ9 27 (s, 1H), 8 23 (d, J=1 8Hz, 1H), 7 21 (d, J=8 2Hz, 2H), 7 00-6 93 (m, 1H), 6 88 (t, J=8 0Hz, 1H), 6 77 (s, 1H), 6 68 (d, J=8 7Hz, 2H), 6 44 (d, J=7 8Hz, 1H), 5 67 (s, 2H), 3 71 (m, 4H), 2 98 (m, 4H)
266		629 26	N-(4-(5-fluoro-2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-3-(3-morpholinophenylao) propanamide	C	7 1	m/z 630 4 [M+H]+	^{1}H NMR ($CDCl_3$, 300 MHz) δ7 98 (d, J=1 8Hz 1H), 7 89 (s, 1H), 7 63-7 55 (m, 2H), 7 55-7 49 (m, 2H), 7 12 (t, J=8 0Hz, 1H), 6 95 (t, J=8 2Hz 1H) 6 89 (s, 1H), 6 83 (d, J=8 7Hz, 1H), 6 70 (s, 1H), 6 47 (dd, J=8 2, 1 8Hz, 1H), 6 37 (dd, J=8 2, 1 8Hz, 1H), 6 30-6 20 (m, 2H), 3 88-3 75 (m, 8H), 3 60 (t, J=5 7Hz, 2H), 3 11 (m, 4H), 3 05 (m, 4H) 2 71 (t, J=5 7Hz, 2H)
267		451 15	N-(4-(5-fluoro-2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 452 3 [M+H]+	^{1}H NMR (DMSO-d_6, 300 MHz) δ10 44 (s, 1H), 9 32 (s, 1H), 8 31 (d, J=1 8Hz, 1H), 7 85 (d, J=8 7Hz, 2H), 7 59 (d, J=8 7Hz, 2H), 6 83-6 74 (m, 2H) 6 70 (t, J=8 45Hz, 1H), 6 50 (dd, J=16 9 10 0Hz, 1H), 6 41 (d, J=8 7Hz, 1H), 6 33 (dd, J=16 9, 1 8), 5 83 (dd, J=10 0, 1 8Hz, 1H), 3 69 (m, 4H), 2 96 (m, 4H)
268		451 15	N-(4-(5-fluoro-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 452 3 [M+H]+	^{1}H NMR (DMSO-d_6, 300 MHz) δ10 54 (s, 1H), 9 37 (s, 1H), 8 26 (d, J=1 8Hz, 1H), 7 91 (d, J=8 7Hz, 2H), 7 60 (d, J=8 2Hz, 2H), 6 98 (d, J=9 1Hz 2H), 6 59-6 42 (m, 3H), 6 34 (dd, J=16 9 1 8Hz, 1H), 5 87 (dd, J=10 0 1 8 1H) 3 65 (m 4H), 2 86 (m, 4H)

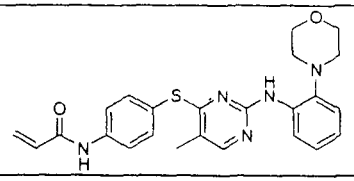
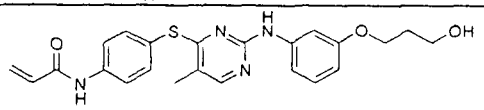
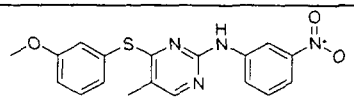
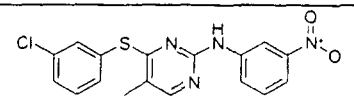
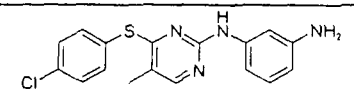
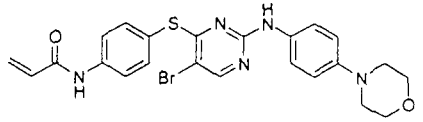
269		559 05	N-(4-(5-iodo-2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	E	10 9	m/z 560 2 [M+H]+	^{1}H NMR (DMSO-d_6, 300 MHz) δ10 44 (s, 1H) 9 35 (s, 1H), 8 39 (s, 1H), 7 83 (d, J=8 7Hz 2H) 7 55 (d, J=8 7Hz, 2H), 6 76-6 58 (m, 3H), 6 51 (dd, J=16 9, 10 0Hz, 1H) 6 40 (m, 1H), 6 33 (dd J=16 9, 1 8Hz, 1H), 5 83 (dd, J=10 0, 1 8Hz, 1H) 3 68 (m, 4H), 2 95 (m, 4H)
270		404 14	4-(4-aophenylthio)-2-(4-morpholinophenylao) pyrimidine-5-carbonitrile	C	6 6	m/z 405 3 [M+H]+	^{1}H NMR (DMSO-d_6, 300 MHz) δ10 12 (s, 1H) 8 52 (s 1H), 7 21 (d, J=8 2Hz, 2H), 7 12 (d J=8 7Hz, 2H), 6 70 (m, 4H), 5 83 (br s , 2H) 3 73 (m 4H), 3 04 (m, 4H)
271		403 15	4-(4-aophenylthio)-5-ethynyl-N-(3-morpholinophenyl)pyrimidin-2-ae	C	6 8	m/z 404 3 [M+H]+	^{1}H NMR (CD_3OD, 300 MHz) δ9 24 (s, 1H) 8 51 (d J=8 6Hz 2H) 8 10 (m, 5H), 7 78 (m 1H) 5 09 (s 1H), 4 91 (m, 4H), 4 26 (m, 4H)
272		403 15	4-(4-aophenylthio)-5-ethynyl-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 7	m/z 404 3 [M+H]+	^{1}H NMR (DMSO-d_6, 300 MHz) δ9 56 (s, 1H) 8 21 (s, 1H), 7 17 (d, J=8 6Hz, 2H), 7 13 (m, 2H), 6 68 (m, 4H) 5 72 (br s 2H), 4 65 (s, 1H) 3 73 (m 4H) 3 01 (m, 4H)
273		405 16	4-(4-aophenylthio)-N-(4-morpholinophenyl)-5-vinylpyrimidin-2-ae	E	10 0	m/z 406 3 [M+H]+	^{1}H NMR ($CDCl_3$, 300 MHz) δ 8 19 (s, 1H), 7 35 (d J=8 7Hz 2H), 7 05 (d, J=8 9Hz, 2H) 6 92 (br s 1H), 6 75 (m, 5H), 5 64 (dd, J=17 3, 0 9Hz, 1H) 5 30 (dd J=11 1, 0 9Hz, 1H) 3 95 (br s 2H) 3 86 (m, 4H), 3 09 (m, 4H)
274		434 19	N4-allyl-6-(4-aophenylthio)-N2-(4-morpholinophenyl)pyrimidine-2,4-diae	C	4 3	m/z 435 3 [M+H]+	^{1}H NMR ($CDCl_3$, 300 MHz) δ7 33 (d, J=6 7Hz, 2H), 7 26 (s, 1H), 7 12 (d, J=8 8Hz, 2H), 6 80 (d, J=7 6Hz, 2H), 6 67 (d, J=8 8Hz, 2H), 6 20 (br s 1H), 5 92 (m, 1H), 5 25 (d, J=17 2Hz, 1H), 5 10 (d, J=10 0Hz, 1H), 4 00 (m, 2H), 3 85 (m 6H) 3 10 (m, 4H)
275		488 20	N-(4-(6-(allylao)-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	6 7	m/z 489 3 [M+H]+	^{1}H NMR ($CDCl_3$, 300 MHz) δ 7 61 (d, J=8 7Hz 2H), 7 52 (d, J=8 6Hz, 2H), 7 47 (br s , 1H), 7 09 (d J=8 8Hz, 2H), 6 79 (d, J=8 9Hz, 2H), 6 46 (dd J=16 7, 1 2Hz, 1H), 6 26 (dd, J=16 7, 10 2Hz 1H), 5 90 -5 74 (m, 2H), 5 39 (s, 1H), 5 21 (m, 1H), 5 10 (m, 1H), 4 99 (m, 1H), 4 92 (m, 1H) 3 99 (m, 2H), 3 82 (m, 4H), 3 07 (m, 4H)

276		364 10	N-(4-(2-(4-hydroxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 3	m/z 365 3 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 62 (br s 1H) 8 29 (br s 1H) 8 06 (d, *J* = 5 5, 1H), 7 93 (br s, 1H), 7 91 (dd, *J* = 7 0, 2 0, 2H), 7 58 (2H, dd *J* = 7 0, 2 0) 7 43 (dd, *J* = 7 0, 2 0, 2H), 7 70 (dd, *J* = 7 0, 2 0 2H), 6 50 (dd, *J* = 17 0, 9 5, 1H), 6 39 (dd, *J* = 17 0, 2 5 1H) 6 29 (d, *J* = 5 5, 1H), 5 77 (dd, *J* = 9 5, 2 5, 1H)
277		364 10	N-(4-(2-(3-hydroxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 3	m/z 365 2 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 64 (br s, 1H), 8 46 (br s, 1H), 8 19 (br s, 1H), 8 11 (d, *J* = 5 5, 1H), 7 92 (d, *J* = 9 0, 2H), 7 59 (d, *J* = 9 0, 2H), 7 32 (ap t *J* = 2 5, 1H), 7 16 (ddd, *J* = 8 5, 2 0, 1 0 1H) 7 01 (ap t, *J* = 8 0 1H), 6 50 (dd, *J* = 17 0, 9 5 1H) 6 44 (ddd *J* = 8 0, 2 5, 1 0, 1H), 6 39 (dd, *J* = 17 0, 2 5, 1H), 6 30 (d, *J* = 5 0, 1H) 5 77 (dd *J* = 9 5, 2 5, 1H)
278		378 12	N-(4-(2-(3-(hydroxymethyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 2	m/z 379 3 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 66 (br s, 1H), 8 52 (br s, 1H), 8 12 (d, *J* = 5 0, 1H), 7 91 (d, *J* = 8 5, 2H) 7 59 (d, *J* = 8 5, 2H), 7 59 (m, 2H), 7 14 (dd, *J* = 8 5, 8 0, 1H), 6 94 (m, 1H), 6 50 (dd, *J* = 17 0, 9 5 1H), 6 39 (dd, *J* = 17 0, 2 5, 1H), 6 36 (d *J* = 5 0 1H), 5 77 (dd, *J* = 9 5, 2 5, 1H) 4 56 (d, *J* = 6 0 2H), 4 11 (t, *J* = 6 0, 1H)
279		364 10	N-(4-(2-(2-hydroxyphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 6	m/z 365 3 [M+H]+	(d_6-Acetone 300 MHz) δ 9 64 (br s 1H) 9 24 (br s, 1H) 8 14 (d, *J* = 5 5, 1H), 7 99 (br s 1H), 7 93 (d, *J* = 8 5 2H), 7 73 (dd, *J* = 8 0, 1 5, 1H), 7 60 (d *J* = 8 5, 2H), 6 90-9 82 (m, 2H), 6 72 (ddd *J* = 8 0 6 5, 2 5, 1H), 6 50 (dd, *J* = 17 0 9 5, 1H), 6 40 (d, *J* = 5 5, 1H), 6 40 dd, *J* = 17 0 2 5, 1H) 5 77 (dd, *J* = 9 5, 2 5, 1H)
280		392 13	N-(4-(2-(3-(hydroxymethyl)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 4	m/z 394 3 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 62 (br s, 1H), 8 25 (br s, 1H), 8 00 (d, *J* =0 5, 1H), 7 90 (d, *J* = 9 0, 2H), 7 56 (d, *J* = 9 0, 2H), 7 34-7 30 (m 1H), 7 24-7 23 (m, 1H), 6 93 (dd, *J* = 8 0, 7 5, 1H), 6 82-6 78 (m 1H), 6 52 (dd, *J* = 17 0, 9 5, 1H), 6 41 (dd, 17 0, 2 5, 1H), 5 78 (dd, *J* = 9 5, 2 5, 1H), 4 47 (d, *J* = 5 5 2H), 3 95 (t, *J* = 5 5, 1H), 2 19 (d, *J* = 0 5 3H)
281		378 12	N-(4-(2-(3-hydroxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 5	m/z 379 3 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 61 (br s 1H) 8 20 (br s 1H), 7 99 (d, *J* = 1 0, 1H), 7 96 (br s, 1H) 7 89 (d *J* = 8 5 2H) 7 54 (d, *J* = 8 5 2H), 6 94 (ddd *J* = 8 5 2 0 1 0, 1H), 6 86 (ap t, *J* = 2 0 1H) 6 79 (ap t, *J* = 8 0, 1H), 6 52 (dd, *J* = 17 0, 9 5, 1H) 6 40 (dd, *J* = 17 0, 2 5, 1H) 6 30 (ddd *J* = 8 0 2 0, 1 0, 1H), 5 77 (dd *J* = 10 0 2 5, 1H) 2 18 (d

							J = 0 5, 3H)
282		378 12	N-(4-(2-(4-hydroxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 5	m/z 379 4 [M+H]+	(d6-Acetone, 300 MHz) δ 9 65 (br s, 1H) 8 05 (br s, 1H), 7 94 (s, 1H), 7 90 (d, J = 8 5 2H) 7 77 (br s, 1H), 7 54 (d, J = 8 5, 2H), 7 15 (d, J = 9 0m 2H), 6 57-6 52 (m, 3H), 6 40 (dd, 17 0, 2 5, 1H) 5 77 (dd J = 10 0, 2 5, 1H), 2 16 (s, 3H)
283		408 13	N-(4-(2-(3-hydroxy-4-methoxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 6	m/z 409 4 [M+H]+	(d6-Acetone, 300 MHz) δ 9 66 (br s, 1H), 8 05 (br s, 1H), 7 95 (d, J = 0 5, 1H), 7 92 (d, J = 8 5, 2H) 7 55 (d J = 8 5, 2H), 7 22 (br s, 1H), 6 83 (dd J = 9 0, 2 5 1H), 6 53 (dd, J = 17 0, 10 0, 1H), 6 50 (d, J = 8 0, 1H), 6 40 (dd, J = 17 0 2 0, 1H), 5 77 (dd, J = 10 0 2 0 1H), 3 68 (s 3H), 2 17 (d, J = 0 5, 3H)
284		406 11	N-(4-(2-(benzo[d][1 3]dioxol-5-ylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	7 0	m/z 407 4 [M+H]+	(d6-Acetone, 300 MHz) δ 9 58 (br s, 1H), 8 21 (br s 1H) 7 96 (s, 1H) 7 90 (d, J = 8 5, 2H), 7 53 (d J = 8 5, 2H), 6 96 (d, J = 2 0, 1H), 6 77 (dd J = 8 5, 2 0, 1H), 6 53 (dd, J = 17 0, 9 5, 1H), 6 50 (d, J = 8 5, 1H), 6 41 (dd, J = 17 0, 2 0, 1H), 5 81 (s 2H) 5 77 (dd J = 9 5, 2 0 1H) 2 17 (d, J = 0 5 3H)
285		455 11	N-(4-(5-methyl-2-(4-(methylsulfonamido)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 5	m/z 456 3 [M+H]+	(d6-DMSO, 300 MHz) δ 10 37 (br s, 1H), 9 31 (br s, 1H) 9 19 (br s 1H) 8 06 (d J = 0 5 1H) 7 85 (d, J = 8 5 2H), 7 55 (d, J = 8 5, 2H), 7 17 (d J = 9 0, 2H), 6 79 (d, J = 9 0, 2H) 6 49 (dd, J = 17 0 10 0, 1H) 6 29 (dd, J = 17 0 2 0, 1H), 5 80 (dd J = 10 0, 2 0, 1H), 2 80 (s, 3H), 2 15 (s, 3H)
286		475 20	N-(4-(2-(4-(4-(hydroxymethyl)piperidin-1-yl)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 4	m/z 476 3 [M+H]+	(d-Chloroform, 300 MHz) δ 7 83 (s,1H) 7 82 (d, J = 7 5, 2H), 7 54 (d J = 8 5, 2H) 6 94 (d, J = 9 0 2H), 6 65 (d, J = 9 0, 2H), 6 50 (dd, J = 17 0, 3 0 1H), 6 42 (dd, J = 17 0, 8 5, 1H), 5 81 (dd, J = 8 5 3 0, 1H), 3 48 (d, J = 6 5, 2H), 3 44 (br d, J = 12 5 2H), 2 57 (d ap t, J = 12 0, 3 0 2H), 2 20 (s, 3H) 1 79 (br d, J = 12 5, 2H), 1 58 (br s, 1H) 1 39 (ddd, J = 12 5, 3 5, 0 5, 1H), 1 29 (ddd J = 12 5 4 0, 1 0, 1H)
287		378 12	N-(4-(2-(2-hydroxyphenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	E	10 1	m/z 379 3 [M+H]+	(d6-Acetone, 300 MHz) δ 9 64 (br s, 1H), 8 01 (d, J = 1 0, 1H), 7 92 (d, J = 9 0, 2H), 7 66 (br s, 1H) 7 56 (d J = 9 0, 2H), 7 43 (dd, J = 8 0 1 5 1H) 6 78 (dd, J = 8 0, 2 0, 1H), 6 67 (ddd, J = 8 0, 8 0 1 5, 1H), 6 52 (dd, J = 17 0, 9 5, 1H) 6 54-6 48 (m 1H), 6 41 (dd J = 17 0, 2 5, 1H) 5 77 (dd J = 9 0 2 5, 1H) 2 20 (d J = 1 0 3H)

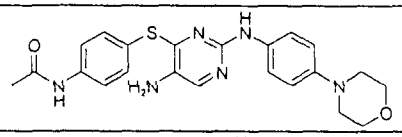
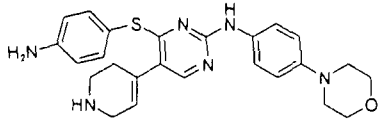
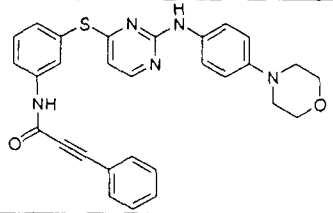
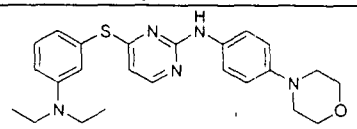
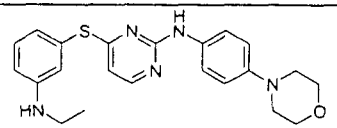
288		455 11	N-(4-(5-methyl-2-(3-(methylsulfonamido)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 6	m/z 456 3 [M+H]+	(d-Chloroform, 300 MHz) δ 7 72 (s, 1H), 7 62 (d, J = 8 5, 2H), 7 36 (d, J = 8 5, 2H) 6 91 (ddd, J = 8 0 2 0 1 0, 1H), 6 81 (ap t, J = 2 0, 1H), 6 76, (ap t, J = 8 0, 1H), 6 56 (ddd, J = 8.0, 2 0, 1 0, 1H), 6 27 (d, J = 4 5 1H), 6 26 (d, J = 7 5, 1H), 5 62 (dd, J = 7 5, 4 5, 1H), 2 74 (s, 3H), 2 03 (d, J = 0 5, 3H)
289		446 10	N-(4-(5-methyl-2-(3-(trifluoromethoxy)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 7	m/z 447 3 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 64 (br s, 1H), 8 64 (br s 1H), 8 05 (d, J = 0 5, 1H), 7 91 (d, J = 8 5, 2H), 7 65 (d, J = 8 5, 2H), 7 44 (ddd, J = 8 0, 2 0, 1 0, 1H), 7 36 (br s, 1H), 7 07 (ap t, J = 8 0, 1H), 6 71 (ddd, J = 8 0, 2 0, 1 0, 1H), 6 52 (dd J = 17 0 10 0, 1H), 6 41 (dd, J = 17 0, 2 5, 1H), 5 78 (dd J = 9 5, 2 5, 1H) 2 20 (d, J = 0 5, 3H)
290		491 20	N-(4-(5-methyl-2-(4-(2-morpholinoethoxy)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	D	4 5	m/z 492 4 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 72 (br s, 1H), 8 14 (br s, 1H), 7 95 (d, J = 0 5, 1H), 7 94 (d, J = 9 0, 2H) 7 56 (d, J = 9 0, 2H), 7 56 (d, J = 9 0, 2H), 7 17 (d J = 9 0, 2H), 6 59 (d, J = 9 0, 2H), 6 56 (dd, J = 17 0, 9 5, 1H), 6 45 (dd, J = 17 0, 2 5, 1H), 5 83 (dd, J = 9 5, 2 5, 1H), 3 96 (t, J = 5 5, 2H) 3 61 (m, 4H), 2 65 (t, J = 5 5, 2H), 2 49 (m 4H)
291		491 24	N-(4-(2-(4-(3-(diethylao)propoxy)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	D	4 6	m/z 492 4 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 83 (br s, 1H) 8 14 (br s, 1H), 7 95 (d, J = 9 0, 2H), 7 94 (d, J = 1 0, 1H) 7 56 (d, J = 9 0, 2H), 7 17 (d, J = 9 0, 2H), 6 59 (d J = 9 0, 2H), 6 56 (dd, J = 17 0, 9 5, 1H) 6 45 (dd, J = 17 0 2 5, 1H), 5 83 (dd, J = 9 5 2 5, 1H), 3 96 (t, J = 5 5 2H), 3 61 (m, 4H), 2 65 (t J = 5 5 2H) 2 49 (m, 4H)
292		517 21	ethyl 1-(4-(4-(4-acrylamidophenylthio)-5-methylpyrimidin-2-ylao)phenyl)piperidine-4-carboxylate	C	7 4	m/z 518 4 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 80 (br s, 1H), 8 04 (br s, 1H), 7 95 (d, J = 8 5, 2H), 7 92 (s, 1H), 7 54 (d J = 8 5, 2H) 7 08 (d, J = 9 0, 2H), 6 61 (d, J = 9 0 2H), 6 57 (dd, J = 17 0, 9 5, 1H), 6 46 (dd, J = 17 0, 2 5, 1H), 5 81 (dd, J = 9 5, 2 5, 1H), 4 12 (q, J = 7 0, 2H), 3 44 (d t, J = 13 0, 3 5, 2H), 2 59 (d t J = 12 0, 2 5, 2H) 2 35 (t t J = 11 5 4 0, 1H) 2 17 (s, 3H), 1 92 (br dd J = 13 5 3 5, 2H), 1 73 (br ddd, J = 24 0, 11 5, 3 5, 2H), 1 25 (t, J = 7 0 3H)
293		485 12	N-(4-(2-(4-methoxy-3-(methylsulfonamido)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 7	m/z 486 3 [M+H]+	(d_6-Acetone 300 MHz) δ 9 72 (br s, 1H) 8 38 (br s 1H) 7 97 (d J = 0 5 1H), 7 93 (d J = 9 0 2H) 7 57 (d J = 9 0, 2H), 7 22 (d, J = 2 5, 1H), 7 22 (dd, J = 9 5 2 5, 1H), 6 59 (d J = 9 5, 1H) 6 54 (dd J = 17 0 9 5, 1H), 6 41 (dd J = 17 0 2 0 1H) 5 78 (dd, J = 9 5 2 0, 1H) 3 74 (s 3H) 2 92 (s 3H) 2 18 (d J = 0 5 3H)

294		469 12	N-(4-(5-methyl-2-(4-(methylsulfonamidomethyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 6	m/z 470 3 [M+H]+	(d-Chloroform & d4-Methanol, 300 MHz) δ 7 87 (d, J = 0 5, 1H), 7 77 (d, J = 8 5, 2H), 7 55 (d, J = 8 5 2H), 7 09 (d, J = 9 0, 2H), 7 01 (d, J = 9 0, 2H) 6 51 (s, 1H), 6 49 (d, J = 4 0, 1H), 5 84 (dd J = 8 0, 4 0 1H) 4 11 (s, 2H) 2 72 (s, 3H), 2 22 (d J = 0 5, 3H)
295		447 17	N-(4-(2-(4-(3-hydroxypyrrolidin-1-yl)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 5	m/z 448 3 [M+H]+	(d6-DMSO, 300 MHz) δ 10 51 (br s, 1H), 8 95 (br s, 1H), 7 97 (d, J = 0 5, 1H), 7 89 (d, J = 8 5, 2H) 7 54 (d, J = 8 5, 2H), 6 93 (d, J = 8 5, 2H), 6 51 (dd, J = 17 0 10 0, 1H), 6 32 (dd, J = 17 0, 2 0 1H), 5 82 (dd, J = 10 0, 2 0, 1H), 4 84 (br s, 1H) 4 30 (br s, 1H), 3 23 (dd, J = 10 5, 5 5, 1H), 3 12 (br d, J = 5 0, 1H), 3 04 (dd, J = 8 5, 4 0, 1H), 2 89 (br d, J = 10 5, 1H), 2 12 (s, 3H), 1 96-1 90 (m 1H), 1 81-1 74 (m, 1H)
296		485 12	N-(4-(2-(3-methoxy-4-(methylsulfonamido)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 6	m/z 486 2 [M+H]+	(d6-Acetone & d6-DMSO, 300 MHz) δ 9 95 (br s 1H), 8 73 (br s, 1H), 8 03 (d, J = 1 0, 1H), 7 90 (d J = 8 5, 2H), 7 71 (br s, 1H), 7 53 (d, J = 8 5, 2H) 7 10 (d, J = 2 0, 1H), 7 04 (dd, J = 8 5, 2 5 1H), 6 96 (d, J = 8 5, 1H) 6 55 (dd, J = 17 0, 10 0 1H) 6 37 (dd, J = 17 0, 2 5, 1H), 5 74 (dd J = 10 0 2 0 1H), 3 72 (s, 3H), 2 85 (s, 3H), 2 19 (d, J = 1 0, 3H)
297		528 11	N-(4-(2-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	7 2	m/z 529 2 [M+H]+	(d6-Acetone, 300 MHz) δ 9 69 (br s, 1H) 8 58 (br s, 1H), 8 04 (d, J = 0 5, 1H), 7 93 (d, J = 8 5, 2H), 7 60 (d, J = 9 0, 2H), 7 43 (s, 4H), 7 08 (br s, 1H), 6 52 (dd, J = 17 0, 10 0, 1H), 6 41 (dd, J = 17 0 2 5, 1H), 5 78 (dd, J = 9 5, 2 5 1H), 2 21 (d J = 0 5, 3H)
298		495 14	N-(4-((2-(4-(1,1-dioxo-1λ6,4-thiomorpholin-4-yl)phenylao)-5-methylpyrimidin-4-yl)sulfanyl)phenyl)prop-2-enamide	C	6 6	m/z 496 3 [M+H]+	(d6-DMSO, 300 MHz) δ 10 52 (br s, 1H), 9 16 (br s, 1H), 7 87 (d, J = 8 5, 2H), 7 56 (d, J = 8 5, 2H) 7 03 (d, J = 9 0, 2H), 6 56 (d, J = 9 0, 2H), 6 53 (dd, J = 17 0, 9 5, 1H) 6 37 (dd, J = 17 0, 2 5, 1H), 5 88 (dd, J = 9 5, 2 5, 1H), 3 51-3 48 (m, 4H) 3 05-3 01 (m, 4H), 2 14 (s, 3H)
299		461 19	N-(4-(2-(4-(3-hydroxypiperidin-1-yl)phenylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylamide	C	6 5	m/z 462 3 [M+H]+	(d6-Acetone, 300 MHz) δ 9 74 (br s, 1H), 8 04 (br s, 1H), 7 95 (d, J = 9 0, 2H), 7 93 (d, J = 0 5 1H) 7 55, (d, J = 9 0, 2H), 7 10 (d J = 9 0, 2H) 6 62 (d, J = 9 0, 2H), 6 57 (dd, J = 17 0 9 5, 1H), 6 45 (dd, J = 17 0, 2 5, 1H), 5 80 (dd, J = 9 5, 2 5 1H) 3 72-3 70 (m 2H), 3 45-3 39 (m, 1H) 3 22-3 15

							(m, 1H), 2 66-2 49 (m, 2H), 2 18 (d, J = 0 5, 3H) 1 95-1 75 (m 2H), 1 64-1 52 (m 1H), 0 90-0 86 (m 1H)
300		447 17	N-(4-(5-methyl-2-(2-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylam ide	C	7 4	m/z 448 3 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 71 (br s, 1H) 8 23 (br s, 1H0, 8 04 (d, J = 0 5, 1H), 7 96 (d, J = 8 5 2H) 7 66-7 63 (m, 1H), 7 57 (d, J = 9 0, 2H), 7 13-7 09 (m, 1H), 6 81-6 76 (m, 2H), 6 53 (dd, J = 17 0, 10 0, 1H), 6 41 (dd, J = 17 0, 2 5, 1H), 5 77 (dd, J = 10 0, 2 5, 1H), 3 80-3 77 (m, 4H), 2 80-2 77 (m 4H), 2 21 (d, J = 0 5, 3H)
301		436 16	N-(4-(2-(3-(3-hydroxypropoxy)phen ylao)-5-methylpyrimidin-4-ylthio)phenyl)acrylam ide	C	6 6	m/z 437 3 [M+H]+	(d_6-Acetone, 300 MHz) δ 9 62 (br s,1H), 8 24 (br s, 1H), 8 01 (d, J = 0 5, 1H), 7 89 (d, J = 9 0, 2H) 7 54 (d, J = 9 0, 2H), 7 33 (ddd, J = 8 0, 2 0, 1 0 1H), 6 95 (ap t, J = 2 0, 1H), 6 87 (ap t, J = 8 0 1H), 6 52 (dd, J = 17 0, 9 5, 1H), 6 41 (dd, J = 17 0, 2 5, 1H), 6 39 (ddd, J = 8 0, 2 5, 1 0 1H), 4 00 (t, J = 6 5, 2H), 3 70 (ddd, J = 11 5, 6 0, 5 0 2H), 3 59 (dd, J = 5 5, 5 0, 1H), 2 19 (d, J = 0 5 3H), 1 92 (quin J =6 5, 2H)
302		368 09	4-(3-methoxyphenylthio)-5-methyl-N-(3-nitrophenyl)pyrimidin-2-ae	C	7 9	m/z 369 2 [M+H]+	(d_6-DMSO, 300 MHz) δ 9 92 (br s, 1H), 8 18 (d, J = 1 0, 1H), 8 11 (ap t, J = 2 0, 1H), 7 69 (ddd J = 8 0 2 0, 0 5, 1H), 7 63 (ddd, J = 8 0, 2 0 1 0, 1H) 7 46-7 40 (m, 1H), 7 20-7 14 (m, 3H), 7 09 (ap t J = 8 5, 1H), 3 73 (s, 3H), 2 18 (d, J = 0 5 3H)
303		372 04	4-(3-chlorophenylthio)-5-methyl-N-(3-nitrophenyl)pyrimidin-2-ae	C	8 3	m/z 373 2/37 5 2 [M+H]+	(d_6-DMSO, 300 MHz) δ 9 90 (br s, 1H), 8 20 (d, J = 1 0, 1H), 8 14 (ap t, J = 2 5, 1H), 7 71-7 51 (m 6H), 7 14 (ap t, J = 8 5, 1H), 2 19 (d, J = 0 5, 3H)
304		342 07	N1-(4-(4-chlorophenylthio)-5-methylpyrimidin-2-yl)benzene-1,3-diae	I	11 5	m/z 343 2/34 5 2 [M+H]+	(d_6-Acetone, 300 MHz) δ 8 05 (br s, 1H) 8 00 (d, J = 0 5, 1H), 7 62 (d, J = 8 5, 2H), 7 54 (d, J = 8 5 2H) 6 73 (ap t, J = 8 0, 1H), 6 64 (ap t, J = 2 0, 2H), 6 60 (ddd, J = 8 0, 2 0, 1 0, 1H), 6 22 (ddd, J = 8 0, 2 0, 1 0, 1H), 2 17 (d, J = 0 5, 3H)
306		511 07	N-(4-(5-bromo-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylam ide	C	7 24	m/z 511 2/51 3 2 [M+H]+	^{1}H-NMR (300MHz, $CDCl_3$) δ 10 53 (s, 1H), 9 50 (s 1H) 7 89 (d, J = 8 7Hz, 2H) 7 57 (d, J = 8 7Hz 2H) 6 94 (bd, J = 8 8Hz, 2H), 6 54-6 45 (m, 3H), 6 33 (dd, J = 16 9,2 1Hz, 1H), 5 86 (dd, J = 9 9,2 1Hz 1H) 3 64 (m, 4H), 2 85 (m, 4H)

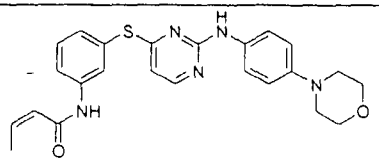
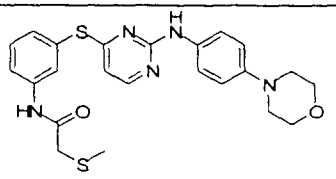
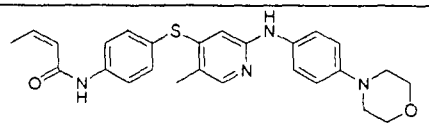
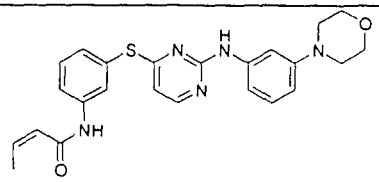
307		509 19	N-(4-(2-(4-morpholinophenylao)-5-phenylpyrimidin-4-ylthio)phenyl)acrylamide	C	7 41	m/z 510 3 [M+H]+	^{1}H-NMR (300MHz D_6-DMSO) δ 9 43 (s 1H) 8 13 (s 1H) 7 91 (d J = 8 7Hz 2H) 7 59-7 53 (m 6H) 7 47 (m 1H) 7 05 (bd J = 8 7Hz 2H) 6 56 6 51 (m 3H) 6 38 (dd J = 16 9 1 9Hz 1H) 5 90 (dd J = 10 0 1 9Hz 1H) 3 69 (m 4H) 2 91 (m 4H)
308		457 06	4-(4-aophenylthio)-5-bromo-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 24	m/z 458 3/460 2 [M+H]+	^{1}H-NMR (300MHz D_6-DMSO) δ 7 94 (bs 1H) 7 14 (d J = 8 5Hz 2H) 7 01 (d J = 9 0Hz 2H) 6 65 (d J = 8 5Hz 2H) 6 57 (d J = 9 0Hz 2H) 3 71 (m 4H) 2 90 (m 4H)
309		505 04	4-(4-aophenylthio)-5-iodo-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 23	m/z 506 2 [M+H]+	^{1}H-NMR (300MHz D_6-DMSO) δ 9 36 (s 1H) 8 27 (s 1H) 7 17 (d J = 8 5Hz 2H) 7 06 (d J = 9 0Hz 2H) 6 68 (d J = 8 5Hz 2H) 6 65 (d J = 9 0Hz 2H) 5 73 (bs 2H) 3 72 (m 4H) 3 00 (m 4H)
310		456 17	4-(4-aophenylthio)-N-(4-morpholinophenyl)-5-(pyridin-4-yl)pyrimidin-2-ae	C	6 29	m/z 457 3 [M+H]+	^{1}H NMR (300MHz D_6-DMSO) δ 9 50 (s 1H) 8 66 (d J = 6 0Hz 2H) 8 14 (s 1H) 7 60 (d J = 6 0Hz 2H) 7 17 (d J = 8 5Hz 2H) 7 13 (d J = 9 2Hz 2H) 6 68 (d J = 8 5Hz 2H) 6 67 (d J = 9 2Hz 2H) 3 71 (m 4H) 3 01 (m 4H)
311		445 17	4-(4-aophenylthio)-N-(4-morpholinophenyl)-5-(1H-pyrazol-4-yl)pyrimidin-2-ae	F	5 73	m/z 446 3[M+H]+	^{1}H-NMR (300MHz D_6-acetone) δ 12 57 (b 1H) 8 53 (bs 1H) 8 14 (s 1H) 7 92 (bs 2H) 7 25 (d J = 8 6Hz 4H) 6 86-6 75 (m 4H) 5 34 (bs 2H) 3 75 (m 4H) 3 07 (m 4H)
312		560 26	tert-butyl 4-(4-(4-aophenylthio)-2-(4-morpholinophenylao) pyrimidin-5-yl)-5 6-dihydropyridine-1(2H)-carboxylate	F	7 45	m/z 561 4[M+H]+	^{1}H-NMR (300MHz D_6-acetone) δ 8 21 (bs 1H) 7 87 (s 1H) 7 24 (d J = 8 6Hz 2H) 7 23 (d J = 9 0Hz 2H) 6 81 (d J = 8 6Hz 2H) 6 77 (d J = 9 0Hz 2H) 5 86 (m 1H) 5 24 (bs 2H) 4 07 (m 2H) 3 74 (m 4H) 3 64 (t J = 5 6Hz 2H) 3 07 (m 4H) 2 46 (m 2H) 1 49 (s 9H)

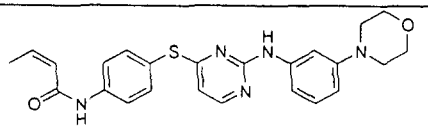
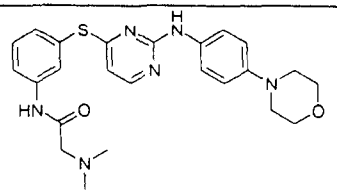
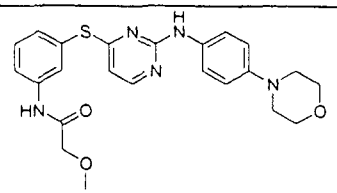
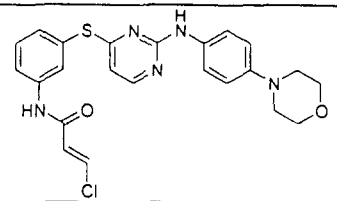
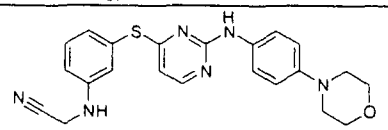
313		559 05	N-(4-(5-iodo-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	7 15	m/z 560 2 [M+H]+	^{1}H-NMR (300MHz, D_6-DMSO) δ 10 54 (s, 1H) 9 45 (s, 1H), 8 33 (s, 1H), 7 88 (d, J = 8 7Hz 2H), 7 56 (d, J = 8 7Hz, 2H), 6 92 (bd, J = 9 0Hz, 2H) 6 54-6 43 (m, 3H) 6 33 (dd, J = 16 9,2 0Hz, 1H) 5 86 (dd J = 9 9,2 0Hz, 1H) 3 63 (m 4H) 2 85 (m, 4H)
314		466 14	N-(4-(2-(4-morpholinophenylao) -5-nitropyrimidin-4-ylthio)phenyl)acetamide	C	6 45	m/z 467 3 [M+H]+	^{1}H-NMR (300MHz, D_6-acetone) δ 10 41 (bs, 1H), 10 24 (bs, 1H), 9 03 (s, 1H), 7 86 (d, J = 8 7Hz 2H), 7 50 (d, J = 8 7Hz, 2H), 7 05 (d, J = 9 2Hz 2H) 6 54 (d J = 9 2Hz, 2H), 3 75 (m, 4H), 2 97 (m, 4H), 2 12 (s, 3H)
315		467 12	N-(4-(5-chloro-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	7 01	m/z 468 3/47 0 3 [M+H]+	^{1}H-NMR (300MHz, D_6-DMSO) δ 10 56 (bs, 1H) 9 53 (bs, 1H), 8 23 (s, 1H), 7 90 (d, J = 6 8Hz, 2H), 7 58 (d, J = 8 6Hz, 2H), 6 94 (bd, J = 9 0Hz 2H), 6 54-6 44 (m, 3H), 6 33 (dd, J = 16 9,2 1Hz 1H), 5 87 (dd, J = 10 0,2 1Hz, 1H), 3 62 (m 4H) 2 85 (m, 4H)
316		645 23	N-(4-(5-chloro-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-3-(4-morpholinophenylao) propanamide	C	7 14	m/z 646 3/64 8 3 [M+H]+	^{1}H-NMR (300MHz, D_6-DMSO) δ 10 36 (bs 1H) 9 52 (bs, 1H), 8 23 (s, 1H), 7 81 (d J = 8 7Hz 2H), 7 55 (d, J = 8 7Hz, 2H), 6 98 (d, J = 8 7Hz 2H), 6 77 (d, J = 8 9Hz, 2H), 6 57 (d J = 8 9Hz 2H), 6 51 (d, J = 8 7Hz, 2H), 5 22 (m 1H), 3 65 (m 4H), 3 45-3 25 (m, 12H), 2 86 (m 4H)
317		641 28	N-(4-(5-methoxy-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-3-(4-morpholinophenylao) propanamide	C	6 59	m/z 642 4 [M+H]+	^{1}H-NMR (300MHz, D_6-DMSO) δ 10 32 (bs, 1H), 9 02 (bs, 1H), 8 02 (s, 1H), 7 79 (d, J = 8 7Hz 2H), 7 50 (d, J = 8 9Hz, 2H), 6 99 (d J = 9 2Hz 2H) 6 77 (d, J = 8 9Hz, 2H), 6 57 (d, J = 8 7Hz 2H), 6 50 (d, J = 9 2Hz, 2H), 5 20 (m, 1H), 3 87 (s 3H), 3 70 (m, 4H), 3 47-3 27 (m, 12H), 2 87 (m 4H)
318		413 11	4-(4-aophenylthio)-5-chloro-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 05	m/z 414 2/41 6 3 [M+H]+	^{1}H-NMR (300MHz, D_6-acetone) δ 8 46 (bs, 1H) 8 05 (s, 1H), 7 26 (d, J = 8 5Hz, 2H), 7 20 (d, J = 9 0Hz, 2H), 6 84 (d, J = 8 5Hz 2H), 6 78 (d J = 9 0Hz, 2H), 5 37 (bs, 2H), 3 73 (m 4H) 3 05 (m 4H),
319		409 16	4-(4-aophenylthio)-5-methoxy-N-(4-morpholinophenyl)pyrimidin-2-ae	C	6 41	m/z 410 3 [M+H]+	^{1}H-NMR (300MHz, D_6-acetone) δ 8 00 (bs 1H) 7 88 (s, 1H), 7 23 (d, J = 8 3Hz, 2H) 7 22 (d J = 9 0Hz, 2H), 6 82 (d, J = 8 3Hz 2H) 6 76 (d J = 9 0Hz 2H) 5 26 (bs 2H) 3 91 (s 3H) 3 74 (m 4H) 3 04 (m, 4H)

320		436 17	N-(4-(5-ao-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetamide	C	5 21	m/z 437 3 [M+H]+	^{1}H-NMR (300MHz, D_6-DMSO) δ 10 28 (bs, 1H) 8 66 (bs, 1H) 7 77 (d, *J* = 8 7Hz, 2H), 7 77 (s, 1H), 7 50 (d, *J* = 8 7Hz, 2H), 6 97 (d, *J* = 9 1Hz, 2H), 6 48 (d, *J* = 9 1Hz, 2H), 4 47 (bs, 2H) 3 73 (m, 4H), 3 24 (m, 4H), 2 10 (s, 3H)
321		460 20	4-(4-aophenylthio)-N-(4-morpholinophenyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-2-ae	C	0 89	m/z 461 3 [M+H]+	^{1}H-NMR (300MHz, $CDCl_3$) δ 7 87 (s, 1H) 7 35 (d *J* = 8 6Hz, 2H), 7 06 (d, *J* = 9 0Hz, 2H), 6 84 (bs, 1H), 6 78 (d, *J* = 8 6Hz, 2H), 6 75 (d, *J* = 9 0Hz 2H), 5 92 (m, 1H), 3 97 (bs, 2H), 3 90 (m, 4H), 3 58 (m 2H), 3 16 (t, *J* = 5 6Hz 2H), 3 12 (m 4H), 2 44 (m, 2H)
322		507 17	N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-3-phenylpropiolamide	C	7 5	m/z 508 2 [M+H]+	^{1}H-NMR (300 MHz, CD_3OD) δ 8 06 – 7 92 (m 2H), 7 86 (t, *J* = 1 8, 1H) 7 68 – 7 57 (m, 2H) 7 55 – 7 32 (m, 5H), 7 27 – 7 14 (m, 2H), 6 75 (d *J* = 9 0, 2H), 6 49 (d, *J* = 5 4, 1H), 3 88 – 3 73 (m 4H), 3 13 – 2 96 (m 4H)
323		435 21	4-(3-(diethylao)phenylthio) -N-(4-morpholinophenyl)pyrimidin-2-ae	C	8 0	m/z 436 3 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 9 36 (s 1H) 8 09 (d, *J* = 5 3 1H), 7 42 (d *J* = 9 0 2H) 7 29 (dd *J* = 7 4 8 8, 1H), 6 93 – 6 64 (m, 4H) 6 25 (d *J* = 5 4 1H), 3 82 – 3 62 (m, 4H), 3 06 – 2 89 (m, 4H) 1 06 (t, *J* = 7 0, 6H)
324		407 18	4-(3-(ethylao)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-ae	C	7 3	m/z 408 3 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 9 36 (s, 1H), 8 09 (d, *J* = 5 3, 1H), 7 42 (d, *J* = 9 0, 2H), 7 21 (t, *J* = 7 8, 1H) 6 81 – 6 70 (m, 5H), 6 25 (d, *J* = 5 3, 1H), 5 87 (t, *J* = 5 3 1H), 3 83 – 3 64 (m 4H), 3 08 – 2 96 (m, 6H), 1 14 (t, *J* = 7 1, 3H)

325		461 19	(E)-2-methyl-N (3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-enamide	C	7 0	m/z 462 3 [M+H]+	^{1}H-NMR (300 MHz DMSO) δ 9 83 (s 1H) 9 57 (s 1H) 8 12 (d J = 5 3 1H) 7 99 – 7 94 (m 2H) 7 46 (t J = 8 2 1H) 7 38 – 7 22 (m 3H) 6 71 (d J = 9 0 2H) 6 44 (dd J = 1 5 6 9 1H) 6 37 (d J = 5 2 1H) 3 79 – 3 64 (m 4H) 3 04 – 2 90 (m 4H) 1 83 – 1 79 (m 3H) 1 79 – 1 72 (m 3H)
326		450 15	N1-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)oxalamide	C	6 2	m/z 451 3 [M+H]+	^{1}H-NMR (300 MHz DMSO) δ 10 82 (s 1H) 9 37 (s 1H) 8 29 (s 1H) 8 17 (t J = 1 8 1H) 8 14 – 8 06 (m 2H) 7 99 (s 1H) 7 50 (t J = 7 9 1H) 7 43 – 7 33 (m 1H) 7 29 (d J = 8 8 2H) 6 69 (d J = 9 0 2H) 6 40 (d J = 5 2 1H) 3 82 – 3 62 (m 4H) 3 05 – 2 88 (m 4H)
327		449 15	N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-2-oxopropanamide	C	6 8	m/z 450 2 [M+H]+	
328		532 23	2-(morpholinomethyl)-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 533 3 [M+H]+	^{1}H-NMR (500 MHz DMSO) δ 11 11 (s 1H) 9 39 (d J = 12 9 1H) 8 14 (d J = 5 3 1H) 7 96 – 7 92 (m 2H) 7 52 (t J = 8 1 1H) 7 40 – 7 26 (m 3H) 6 72 (d J = 8 7 2H) 6 43 (br s 1H) 6 06 (d J = 1 5 1H) 5 64 (d J = 1 2 1H) 3 73 (t J = 4 8 4H) 3 56 (t J = 4 3 4H) 3 29 (t J = 4 8 4H) 2 99 (m 4H) 2 42 (s 3H)

329		422 15	1-(3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)urea	C	6 0	m/z 423 3 $[M+H]^+$	^{1}H-NMR (500 MHz DMSO) δ 9 38 (s 1H), 8 83 (s, 1H), 8 12 (d, J = 5 3, 1H), 7 76 (t, J = 1 8, 1H) 7 60 (d, J = 8 1, 1H), 7 42 – 7 32 (m, 3H) 7 18 – 7 12 (m 1H) 6 76 (d J = 9 0, 2H) 6 35 (br s 1H) 5 94 (s, 2H), 3 80 – 3 69 (m, 4H), 3 08 – 2 95 (m 4H)
330		532 23	1-morpholino-2-((3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenylao)methyl)prop-2-en-1-one	C	6 5	m/z 533 4 $[M+H]^+$	^{1}H-NMR (500 MHz DMSO) δ 9 38 (s 1H) 8 10 (d, J = 5 3, 1H) 7 43 (d, J = 8 9, 2H), 7 25 (t, J = 7 8, 1H), 6 90 – 6 68 (m, 5H) 6 41 (t, J = 6 4 1H) 6 23 (d J = 4 9 1H), 5 38 (s, 1H) 5 10 (s 1H) 3 90 (d, J = 6 3 2H), 3 78 – 3 69 (m, 4H), 3 56 – 3 38 (m 4H) 3 06 – 2 97 (m, 4H)
331		445 16	N-(3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)but-2-ynamide	C	6 7	m/z 446 4 $[M+H]^+$	^{1}H-NMR (300 MHz DMSO) δ 10 81 (s, 1H), 9 37 (s, 1H), 8 12 (d, J = 5 3, 1H) 7 88 (s, 1H) 7 83 (d J = 7 9, 1H), 7 47 (t, J = 7 9, 1H), 7 38 – 7 21 (m, 3H), 6 70 (d J = 9 0 2H), 6 39 (d J = 5 1 1H) 3 79 – 3 67 (m, 4H), 3 07 – 2 92 (m, 4H), 2 03 (s, 3H)
332		455 12	2-chloro-N-(3-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	6 7	m/z 457 3/459 3 $[M+H]^+$	^{1}H-NMR (300 MHz DMSO) δ 10 53 (s, 1H) 9 40 (s, 1H), 8 12 (d, J = 5 3, 1H), 7 92 – 7 77 (m 2H) 7 51 (t, J = 8 0, 1H), 7 37-7 28 (m, 3H), 6 71 (d J = 8 9, 2H), 6 37 (d, J = 4 8, 1H), 4 25 (s 2H) 3 72 (t J = 4 8 4H), 2 98 (t J = 4 8 4H)

333		447 17	(Z)-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-enamide	C	6 8	m/z 448 4 [M+H]+	δ 10 17 (s, 1H) 9 37 (s, 1H) 8 12 (d, *J* = 5 3 1H) 7 91 (m, 2H), 7 47 (t, *J* = 8 1, 1H), 7 29 (m, 3H) 6 70 (d, *J* = 8 9, 2H), 6 41 (d, *J* = 4 8, 1H), 6 24 (dd, *J* = 7 2, 11 4, 1H), 5 98 (dd, *J* = 1 8, 11 4 1H), 3 72 (t, *J* = 4 8, 4H), 2 98 (t *J* = 4 8 4H) 2 11 (dd, *J* = 1 6, 7 2, 3H)
334		467 14	2-(methylthio)-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetamide	C	6 5	m/z 468 3 [M+H]+	^{1}H-NMR (500 MHz, DMSO) δ 10 28 (s 1H), 9 39 (s 1H), 8 13 (d, *J* = 5 2, 1H), 7 91 (s, 1H), 7 83 (d, *J* = 8 1, 1H), 7 49 (t, *J* = 8 0 1H) 7 32 (d, *J* = 7 5 3H), 6 73 (d, *J* = 8 4, 2H), 6 39 (s, 1H), 3 81 – 3 66 (m, 4H), 3 27 (s, 2H), 3 09 – 2 95 (m, 4H) 2 14 (s, 3H)
335		461 19	(Z)-N-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-enamide	C	7 1	m/z 462 3 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 35 (s 1H), 9 12 (s 1H), 8 00 (s, 1H), 7 85 (d, *J* = 8 7, 2H) 7 51 (d, *J* = 8 6, 2H), 6 98 (d, *J* = 9 0, 2H), 6 47 (d, *J* = 9 1, 2H), 6 33 (dd, *J* = 7 2, 11 4, 1H), 6 06 (dd *J* = 1 7 11 5, 1H), 3 65 (t, *J* = 4 5, 4), 2 87 (t, *J* = 4 5, 4H) 2 17 (dd *J* = 1 5, 7 2, 3H), 2 12 (s, 3H)
336		447 17	(Z)-N-(3-(2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-enamide	C	7 0	m/z 448 3 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 18 (s, 1H), 9 48 (s, 1H) 8 17 (d *J* = 5 3, 1H), 7 99 (s, 1H), 7 78 (d *J* = 7 1 1H), 7 47 (t, *J* = 7 9 1H) 7 31 (d *J* = 7 8 1H), 7 20 (s, 1H), 7 08 (d, *J* = 9 3, 1H), 6 97 (l, *J* = 8 1 1H) 6 51 (dd, *J* = 1 5, 8 3 1H), 6 32 (d, *J* = 5 3, 1H), 6 24 (dd, *J* = 7 2, 11 4, 1H), 5 99 (dd *J* = 1 7 11 4 1H), 3 79 – 3 65 (m 4H), 3 11 – 2 95 (m 4H) 2 10 (dd *J* = 1 5 7 2, 3H)

337		447 17	(Z)-N-(4-(2-(3-morpholinophenylao) pyrimidin-4-ylthio)phenyl)but-2-enamide	C	7 0	m/z 448 3 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 26 (s 1H), 9 46 (s, 1H) 8 14 (d, *J* = 5 3 1H), 7 80 (d, *J* = 8 7 2H) 7 56 (d *J* = 8 6 2H), 7 21 (s, 1H), 7 09 (d *J* = 7 7 1H), 7 04 – 6 91 (m, 1H), 6 51 (dd, *J* = 1 8 8 3 1H), 6 35 – 6 20 (m, 2H), 6 04 (dd, *J* = 1 7 11 5 1H), 3 83 – 3 64 (m, 4H), 3 09 – 2 94 (m, 4H), 2 13 (dd, *J* = 1 5, 7 2, 3H)
338		464 20	2-(dimethylao)-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetamide	D	7 7	m/z 465 4 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 9 94 (s 1H) 9 37 (s, 1H) 8 12 (d, *J* = 5 3, 1H), 7 98 (d *J* = 1 7 1H) 7 92 (d, *J* = 8 3, 1H), 7 46 (t, *J* = 7 9, 1H), 7 38 – 7 22 (m, 3H), 6 71 (d, *J* = 9 0, 2H), 6 36 (d, *J* = 4 9, 1H) 3 78 – 3 67 (m, 4H), 3 06 (s, 2H) 3 03 – 2 92 (m 4H), 2 24 (s, 6H)
339		451 17	2-methoxy-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acetamide	C	6 4	m/z 452 3 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 9 98 (s 1H) 9 37 (s, 1H), 8 12 (d, *J* = 5 3, 1H), 7 99 (t, *J* = 1 7 1H) 7 93 (d, *J* = 7 9, 1H), 7 47 (t, *J* = 7 9, 1H) 7 31 (d *J* = 8 9, 3H), 6 72 (d, *J* = 9 0, 2H), 6 36 (d, *J* = 4 9 1H), 3 99 (s, 2H) 3 78 – 3 66 (m, 4H) 3 35 (s 3H), 3 07 – 2 93 (m, 4H)
340		467 12	(E)-3-chloro-N-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 468 3/47 0 3 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 42 (s, 1H), 9 38 (s, 1H), 8 12 (d, *J* = 5 3, 1H), 7 95 – 7 81 (m, 2H) 7 50 (t, *J* = 7 9, 1H), 7 43 (d, *J* = 13 2, 1H), 7 37 – 7 24 (m, 3H), 6 70 (d, *J* = 9 0, 2H), 6 60 (d, *J* = 13 2, 1H), 6 40 (d, *J* = 4 3, 1H), 3 72 (t, *J* = 4 8 4H), 2 97 (t, *J* = 4 8, 4H)
341		418 16	2-(3-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)acetonitrile	C	6 5	m/z 419 3 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 9 37 (s 1H), 8 10 (d, *J* = 5 3, 1H) 7 41 (d, *J* = 9 0 2H), 7 34 (t *J* = 7 9 1H) 7 06 – 6 86 (m, 3H), 6 78 (d, *J* = 9 1 2H), 6 56 (t *J* = 6 6, 1H) 6 26 (d, *J* = 5 2 1H) 4 31 (d *J* = 6 8, 2H) 3 86 – 3 62 (m 4H) 3 10 –

342		467 12	(E)-3-chloro-N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 9	m/z 468 3 [M+H]+	2 89 (m 4H)	^{1}H-NMR (300 MHz DMSO) δ 10 56 (s 1H) 9 36 (s 1H) 8 10 (d J = 5 2 1H) 7 82 (d J = 8 6 2H) 7 58 (d J = 8 5 2H) 7 51 (d J = 13 1 1H) 7 16 (d J = 8 0 2H) 6 67 (d J = 13 2 1H) 6 59 (d J = 8 7 2H) 6 55 – 6 44 (m 1H) 3 81 – 3 57 (m 4H) 3 00 – 2 82 (m 4H)
343		481 13	(E)-3-chloro-N-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 2	m/z 482 3 [M+H]+		^{1}H-NMR (300 MHz DMSO) δ 10 59 (s 1H) 9 13 (s 1H) 8 00 (s 1H) 7 84 (d J = 8 6 2H) 7 61 – 7 48 (m 3H) 6 96 (d J = 8 9 2H) 6 69 (d J = 13 2 1H) 6 44 (d J = 9 0 2H) 3 76 – 3 57 (m 4H) 2 92 – 2 78 (m 4H) 2 12 (s 3H)
344		467 14	2-(methylthio)-N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acetamide	C	6 6	m/z 468 3 [M+H]+		^{1}H-NMR (300 MHz DMSO) δ 10 36 (s 1H) 9 35 (s 1H) 8 10 (d J = 5 3 1H) 7 84 – 7 70 (m 2H) 7 63 – 7 50 (m 2H) 7 29 (d J = 8 8 2H) 6 70 (d J = 9 0 2H) 6 37 (d J = 5 2 1H) 3 82 – 3 61 (m 4H) 3 32 (s 2H) 3 10 – 2 89 (m 4H)
345		481 16	N-(4-(5-methyl-2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)-2-(methylthio)acetamide	C	6 9	m/z 482 2 [M+H]+		^{1}H-NMR (300 MHz DMSO) δ 10 39 (s 1H) 9 09 (s 1H) 8 01 (d J = 0 6 1H) 7 78 (d J = 8 7 2H) 7 54 (d J = 8 7 2H) 7 04 (d J = 9 0 2H) 6 51 (d J = 9 1 2H) 3 81 – 3 64 (m 4H) 3 33 (s 2H) 2 94 – 2 89 (m 4H) 2 22 (s 3H) 2 13 (s 3H)
346		467 12	(Z)-3-chloro-N-(4-(2-(4-morpholinophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 6	m/z 468 3/47 0 3 [M+H]+		^{1}H-NMR (300 MHz DMSO) δ 10 50 (s 1H) 9 34 (s 1H) 8 10 (d J = 5 3 1H) 7 82 (d J = 8 7 2H) 7 57 (d J = 8 7 2H) 7 21 (d J = 8 6 2H) 7 01 (d J = 8 0 1H) 6 63 (d J = 9 0 2H) 6 57 (d J = 8 0 1H) 6 51 – 6 42 (m 1H) 3 69 (t J = 4 8 4H) 2 94 (t J = 4 8 4H)

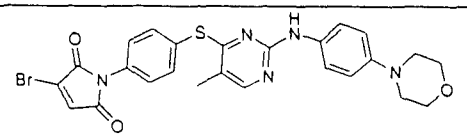
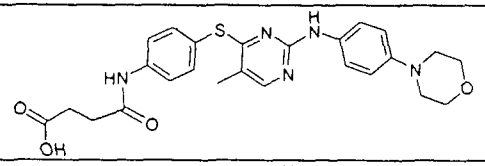
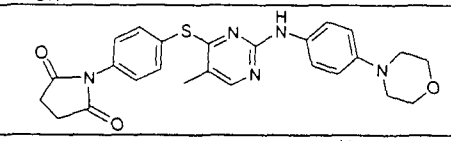
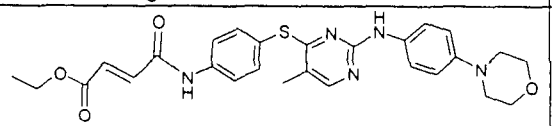
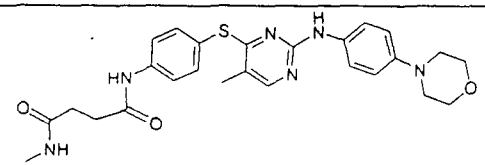
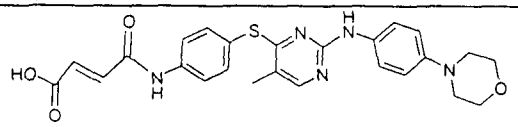
347		469 13	N-(4-(5-chloro-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)propion amide	C	7 1	m/z 470 2/47 2 2 [M+H]+	^{1}H-NMR (300 MHz, DMSO) δ 10 29 (s 1H) 9 49 (s, 1H), 8 23 (s, 1H), 7 82 (d, J = 8 7, 2H), 7 54 (d J = 8 6 2H) 6 99 (d, J = 8 9, 2H), 6 51 (d J = 9 1 2H), 3 71 (t, J = 4 8, 4H), 2 93 (t, J = 4 8, 4H) 2 39 (q J = 7 5, 2H), 1 12 (t, J = 7 5 3H)
348		382 07	N-(4-(2-(3-chlorophenylao)pyrim idin-4-ylthio)phenyl)acrylam ide	C	7 4	m/z 383 2 [M+H]+	1H NMR (300 MHz, Acetone) ı ı 9 63 (br s, 1H), 8 76 (br s, 1H), 8 17 (d, J = 5 5, 1H) 7 90 (m 3H) 7 58 (m, 3H), 7 20 (m, 1H), 6 93 (m, 1H), 6 54-6 36 (m, 3H) 5 77 (dd, J = 9 4 2 5, 1H)
349		509 08	3-(3-chlorophenylao)-N-(4-(2-(3-chlorophenylao)pyrim idin-4-ylthio)phenyl)propana mide	C	8 1	m/z 511 2/51 3 2 [M+H]+	^{1}H NMR (300 MHz, Acetone) δ 9 54 (br s 1H) 8 75 (br s, 1H), 8 16 (d, J = 5 4, 1H), 7 84 (d, J = 8 7, 3H), 7 57 (d, J = 8 7, 3H), 7 14 (dt J = 8 1 27 9, 2H), 6 92 (dd, J = 1 1, 7 9, 1H), 6 74 – 6 54 (m, 3H), 6 41 (d, J = 5 3, 1H), 5 38 (m, 1H) 3 55 (q, J = 6 4 2H) 2 78 – 2 69 (m, 2H)
350		348 10	N-(4-(2-(phenylao)pyrimidin-4-ylthio)phenyl)acrylam ide	C	6 9	m/z 349 2 [M+H]+	1H NMR (300 MHz, Acetone) δ 9 66 (br s, 1H), 8 57 (br s, 1H) 8 13 (d, J = 5 3, 1H), 7 93 (d J = 8 7, 2H), 7 60 (m, 4H), 7 25 – 7 14 (m, 2H), 6 89 (t, J = 7 4 1H), 6 59 – 6 32 (m, 3H) 5 78 (dd J = 2 5, 9 5, 1H)
351		441 16	3-(phenylao)-N-(4-(2-(phenylao)pyrimidin-4-ylthio)phenyl)propana mide	C	7 5	m/z 442 3 [M+H]+	1H NMR (300 MHz Acetone) δ 9 56 (br s 1H) 8 56 (br s, 1H), 8 12 (d, J = 5 5, 1H), 7 85 (d, J = 8 7, 2H), 7 58 (m 4H), 7 22-7 08 (m, 4H) 6 89 (m, 1H), 6 68 (m, 2H), 6 60 (m, 1H), 5 04 (br s 1H), 3 53 (m, 2H) 2 75 (m, 2H)
352		427 08	N-(4-(2-(4-sulfamoylphenylao)p yrimidin-4-ylthio)phenyl)acrylam ide	C	6 2	m/z 428 2 [M+H]+	1H NMR (300 MHz, DMSO) δ10 46 (s 1H), 10 03 (s, 1H), 8 24 (d, J = 5 0, 1H), 7 87 (d, J = 8 7, 2H) 7 70-7 56 (m, 6H), 7 08 (s, 2H), 6 53-6 27 (m 3H), 5 82 (dd, J = 10 0, 1 8, 1H)
353		382 07	N-(4-(2-(4-chlorophenylao)pyrim idin-4-ylthio)phenyl)acrylam ide	C	7 3	m/z 383 2/38 5 2 [M+H]+	1H NMR (300 MHz, Acetone) δ9 65 (s, 1H) 8 68 (s, 1H), 8 14 (d, J = 5 3, 1H), 7 93 (d, J = 8 8, 2H) 7 60 (m, 4H), 7 16 (d, J = 9 2, 2H) 6 53-6 39 (m 3H), 5 78 (dd, J = 9 9, 1 9, 1H)
354		391 09	N-(4-(2-(3-cyano-4-fluorophenylao)pyrimi din-4-ylthio)phenyl)acrylam ide	C	7 0	m/z 392 2 [M+H]+	1H NMR (300 MHz DMSO) δ10 42 (s 1H) 9 99 (s 1H), 8 22 (d, J = 5 3, 1H), 8 00 (b s 1H) 7 84 (d, J = 8 8 3H), 7 60 (d, J = 8 8, 2H), 7 27 (m 1H) 6 50-6 30 (m 3H) 5 82 (dd J = 9 9 1 9 1H)

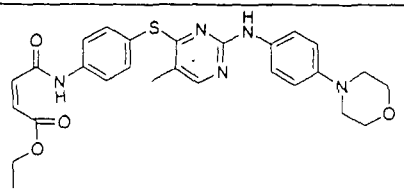
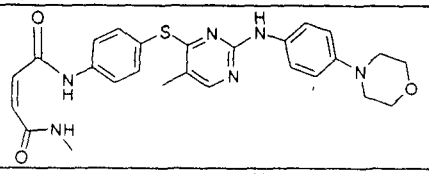
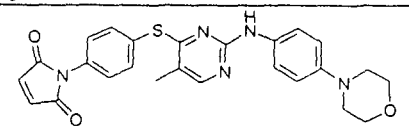
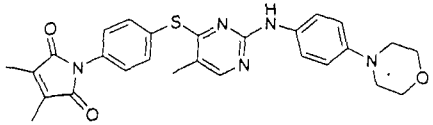
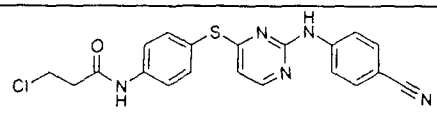
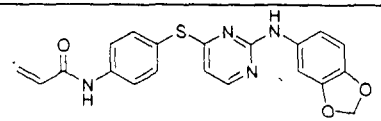
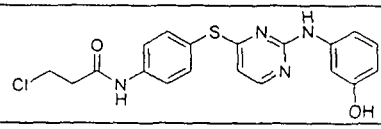
355		417 16	N-(4-(2-(3-(pyrrolidin-1-yl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 5	m/z 418 3 [M+H]+	
356		406 11	methyl 3-(4-(4-acrylamidophenylthio)pyrimidin-2-ylao)benzoate	C	7 0	m/z 407 2 [M+H]+	1H NMR (300 MHz, Acetone) δ9 64 (br s, 1H) 8 82 (s, 1H), 8 29 (br s, 1H), 8 17 (d, J = 5 5, 1H) 7 99-7 85 (m, 3H), 7 58 (m, 3H), 7 30 (m, 1H), 6 54-6 37 (m, 3H), 5 78 (dd, J = 9 2, 2 8 1H), 3 87 (s, 3H)
357		406 11	methyl 4-(4-(4-acrylamidophenylthio)pyrimidin-2-ylao)benzoate	C	6 9	m/z 407 2 [M+H]+	1H NMR (300 MHz, Acetone) δ9 68 (br s, 1H), 8 94 (br s, 1H), 8 19 (d, J = 5 2, 1H), 7 96 (m 2H), 7 81 (m, 2H), 7 69-7 58 (m, 4H), 6 60-6 38 (m, 3H) 5 80 (dd, J = 9 6 2 5, 1H), 3 81 (s, 3H)
358		557 17	methyl 4-(4-(4-(3-(4-(methoxycarbonyl)phenylao)propanamido)phenylthio)pyrimidin-2-ylao)benzoate	C	7 4	m/z 558 3 [M+H]+	
359		362 12	N-(4-(2-(p-tolylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 2	m/z 363 4 [M+H]+	1H NMR (500 MHz, Acetone) δ 9 67 (s, 1H), 8 43 (s 1H), 8 10 (d, J = 5 3, 1H), 7 92 (d, J = 8 7, 2H) 7 58 (d, J = 8 7 2H), 7 45 (d, J = 8 3, 2H), 6 99 (d J = 8 3, 2H), 6 59 – 6 35 (m, 3H), 5 78 (dd J = 2 1, 10 0, 1H), 2 22 (s, 3H)
360		469 19	3-(p-tolylao)-N-(4-(2-(p-tolylao)pyrimidin-4-ylthio)phenyl)propanamide	C	7 9	m/z 470 4 [M+H]+	
361		393 09	N-(4-(2-(3-nitrophenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 0	m/z 394 2 [M+H]+	

362		531 13	3-(3-nitrophenylao)-N-(4-(2-(3-nitrophenylao)pyrimidin-4-ylthio)phenyl)propanamide	C	7 6	m/z 532 3 [M+H]+	
363		497 16	N-(4-(2 (3-(N isopentylsulfamoyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 4	m/z 498 4 [M+H]+	^{1}H NMR (300 MHz Acetone) δ 9 68 (s 1H) 8 92 (s 1H) 8 27 – 8 12 (m 2H) 7 93 (m 3H) 7 61 (d J = 8 7 2H) 7 37 (m 2H) 6 59 – 6 22 (m 4H) 5 78 (dd J = 2 5 9 6 1H) 3 02 – 2 91 (m 2H) 1 64 (m 1H) 1 40 (m 2H) 0 83 (d J = 6 6 6H)
364		427 08	N-(4-(2-(3-sulfamoylphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 1	m/z 428 3 [M+H]+	
365		510 15	N-(4-(2 (3-(4-methylpiperazin-1-ylsulfonyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 6	m/z 511 3 [M+H]+	
366		517 12	N-(4-(2-(3-(N-benzylsulfamoyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 1	m/z 518 4 [M+H]+	
367		497 12	N-(4-(2-(4-(morpholinosulfonyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 7	m/z 498 3 [M+H]+	
368		517 12	N-(4-(2-(4-(N-benzylsulfamoyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 2	m/z 518 3 [M+H]+	

369		459 14	N-(4-(2-(1-(cyclopropylsulfonyl)piperidin-4-ylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 5	m/z 460 3 [M+H]+	
370		510 15	N-(4-(2-(4-(4-methylpiperazin-1-ylsulfonyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 4	m/z 511 3 [M+H]+	
371		497 16	N-(4-(2-(4-(N-isopentylsulfamoyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	7 3	m/z 498 2 [M+H]+	
372		497 12	N-(4-(2-(3-(morpholinosulfonyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	9 7	m/z 498 2 [M+H]+	
373		527 13	N-(4-(2-(3-methoxy-4-(morpholinosulfonyl)phenylao)pyrimidin-4-ylthio)phenyl)acrylamide	E	9 43	m/z 528 3 [M+H]+	
374		457 09	N-(4-(2-(3-methoxy-4-sulfamoylphenylao)pyrimidin-4-ylthio)phenyl)acrylamide	C	6 1	m/z 458 2 [M+H]+	^{1}H NMR (300 MHz DMSO) δ 10 46 (s 1H) 9 99 (s 1H) 8 26 (d J = 5 4 1H) 7 88 (d J = 8 7 2H) 7 70 – 7 43 (m 4H) 7 27 (dd J = 1 9 8 7 1H) 6 84 (s 2H) 6 58 – 6 24 (m 3H) 5 88 – 5 72 (m 1H) 3 83 (s 3H)

375		465 16	(1S 2R)-2-fluoro-N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)cyclopr opanecarboxamide	C	6 8	m/z 466 3 [M+H]+	
376		447 17	N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)cyclopr opanecarboxamide	C	6 7	m/z 448 3 [M+H]+	
377		472 17	1-cyano-N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)cyclopr opanecarboxamide	C	6 8	m/z 473 3 [M+H]+	
378		499 12	2-chloro-2-fluoro-N-(4-(2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)cyclopr opanecarboxamide	C	7 1	m/z 500 3 [M+H]+	
379		583 06	4-(4-(5-bromo-2-chloropyrimidin-4-ylao)phenylthio)-5-methyl-N-(4-morpholinophenyl)pyr imidin-2-ae	E	10 9	m/z 584 2/58 6 2/588 2 [M+H]+	1H NMR (300MHz DMSO) δ 9 51 (s 1H) 8 62 (s 1H) 8 02 (s 1H) 7 95 (d J = 8 7 2H) 7 60 (d J = 8 7 2H) 7 01 (d J=9 1 2H) 6 46 (d J = 9 1 2H) 3 57 (m 4H) 2 72 (m 4H) 2 14 (s 3H)
380		491 16	(Z)-4-(4-(5 methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)-4-oxobut-2-enoic acid	G	6 1	m/z 492 3 [M+H]+	1H NMR (300MHz DMSO) δ 11 04 (br s 1H) 9 13 (s 1H) 8 01 (s 1H) 7 83 (d J = 8 7 2H) 7 55 (d J = 8 7 2H) 6 98 (d J = 9 1 2H) 6 48 6 36 (m 4H) 3 68 (m 4H) 2 88 (m 4H) 2 13 (s 3H)
381		569 07	(E)-3-bromo-4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)-4-oxobut-2-enoic acid	G	6 2	m/z 570 2/57 2 2 [M+H]+	1H NMR (300MHz DMSO) δ 9 14 (s 1H) 8 02 (s 1H) 7 80 (d J = 8 7 2H) 7 54 (d J = 8 7 2H) 6 96 (d J = 9 1 2H) 6 74 (s 1H) 6 46 (d J = 9 1 2H) 3 70 (m 4H) 2 89 (m 4H) 2 13 (s 3H)

382		551 06	3-bromo-1-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-1H-pyrrole-2,5-dione	C	7 3	m/z 552 2/554 2 [M+H]+	1H NMR (300 MHz, Acetone) δ 8 0 1 (s 1H) 7 76 (d J = 8 4, 2H), 7 62 (d, J = 8 4, 2H) 7 48 (s, 1H) 7 21 (d, J = 8 8, 2H), 6 69 (d, J = 9 2 2H) 3 74 (m 4H), 2 98 (m, 4H), 2 08 (s 3H)
383		493 18	4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)-4-oxobutanoic acid	D	4 6	m/z 494 3 [M+H]+	1H NMR (300MHz, DMSO) δ12 15 (br S 1H), 10 32 (s, 1H) 9 09 (s, 1H), 8 00 (s, 1H) 7 77 (d J = 8 7, 2H), 7 51 (d, J = 8 7, 2H), 7 02 (d J = 9 0 2H), 6 50 (d, J = 9 0, 2H), 3 72 (m, 4H), 2 92 (m 4H), 2 59 (m, 4H), 2 13 (s, 3H)
384		475 17	1-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)pyrrolidine-2,5-dione	E	9 1	m/z 476 3 [M+H]+	1H NMR (300MHz, DMSO) δ9 14 (s, 1H), 8 07 (s 1H), 7 73 (d, J = 8 7, 2H), 7 46 (d, J = 8 7, 2H). 7 13 (d, J = 9 1, 2H), 6 61 (d, J = 9 1. 2H), 3 70 (m 4H), 2 93 (m, 4H), 2 83 (s 4H) 2 16 (s, 3H)
385		519 19	(E)-ethyl 4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)-4-oxobut-2-enoate	C	7 2	m/z 520 3 [M+H]+	1H NMR (300MHz, DMSO) δ 10 93 (s 1H) 9 12 (s 1H), 8 01(s, 1H), 7 89 (d, J = 8 8, 2H) 7 58 (d J = 8 8, 2H), 7 28 (d J = 15 4, 1H), 6 97 (d J = 9 2, 2H), 6 79 (d, J = 15 4 1H) 6 45 (d J = 9 2 2H) 4 26 (q J = 7 1, 2H), 3 62 (m, 4H) 2 84 (m 4H), 2 14 (s, 3H,), 1 28 (t, J = 7 1, 3H)
386		506 21	N1-methyl-N4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)succinamide	C	6 0	m/z 507 3 [M+H]+	1H NMR (300MHz, DMSO) d 10 3 1(S, 1H), 9 09 (s 1H), 8 00 (s 1H) 7 77 (d, J = 9 2, 2H) 7 5 1(d J = 8 3, 2H), 7 02 (d, J = 8 3, 2H), 6 49 (d, J = 9 2 2H), 3 72 (br s, 4H), 2 92 (br s, 4H), 2 59 (m, 4H) 2 44 (d, J = 7 5 2H), 2 13(s, 3H)
387		491 16	(E)-4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)-4-oxobut-2-enoic acid	D	4 8	m/z 492 3 [M+H]+	1H NMR (300MHz, DMSO) d 10 53 (s, 1H), 9 09 (s, 1H), 8 00 (s, 1H), 7 90 (d, J = 8 8, 2H), 7 52 (d. J = 8 8, 2H), 6.96 (d, J = 9 2, 2H) 6 69 (d, J = 3 6 2H), 6 45 (d, J = 9 2 2H) 3 65 (m, 4H) 2 84 (m 4H) 2 13 (s 3H)

388		519 19	(Z)-ethyl 4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenylao)-4-oxobut-2-enoate	C	7 0	m/z 520 3 [M+H]+	1H NMR (300MHz DMSO) δ 10 65 (s, 1H) 9 10 (s, 1H) 8 00 (s, 1H), 7 82 (d, J = 8 7 2H) 7 55 (d J = 8 7 2H), 6 98 (d, J = 9 1, 2H), 6 58-6 33 (m 4H), 4 16 (m, 2H,), 3 69 (m, 4H) 2 88 (m 4H) 2 13 (s, 3H), 1 19 (t, 3H)
389		504 19	N1-methyl-N4-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)maleamide	C	6 5	m/z 505 3 [M+H]+	1H NMR (300MHz, DMSO) d 12 31 (s, 1H), 9 10 (s, 1H) 8 79 (m, 1H), 8 01 (s 1H), 7 82 (d, J = 8 7 2H), 7 55 (d, J = 8 7, 2H), 6 99 (d J = 9 2, 2H), 6 46 (d J = 9 2 2H) 6 38 (d J = 12 8 1H) 6 28 (d, J = 12 8, 1H) 3 66 (m 4H) 2 86 (m 4H) 2 72 (d J = 5 0, 3H) 2 14 (s 3H)
390		473 15	1-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-1H-pyrrole-2,5-dione	C	6 9	m/z 474 3 [M+H]+	1H NMR (300MHz, DMSO) δ9 18 (s, 1H), 8 06 (s, 1H), 7 73 (d, 2H), 7 56 (d, 2H), 7 29 (s, 2H), 7 08 (d, 2H), 6 53 (d, 2H), 3 67 (m 4H) 2 87 (m 4H) 2 16 (m 3H)
391		501 18	3,4-dimethyl-1-(4-(5-methyl-2-(4-morpholinophenylao) pyrimidin-4-ylthio)phenyl)-1H-pyrrole-2,5-dione	C	7 6	m/z 502 3 [M+H]+	1H NMR (300MHz DMSO δ9 14 (s 1H), 8 05 (s 1H), 7 71 (m, 2H) 7 55 (m, 2H), 7 08 (d, J = 9 1 2H), 6 56 (d, J = 9 1, 2H), 3 67 (m, 4H), 2 88 (m 4H), 2 16 (s, 3H), 2 02 (s, 6H)
392		409 08	3-chloro-N-(4-(2-(4-cyanophenylao)pyrimidin-4-ylthio)phenyl)propanamide	C	7 0	m/z 410 1 / 412 1 [M+H]+	
393		392 09	N-(4-(2-(benzo[d][1,3]dioxol-5-ylao)pyrimidin-4-ylthio)phenyl)acrylamide	E and H	8 3	m/z 392 3 M+	^{1}H NMR (300 MHz, d_6-DMSO) δ10 46 (br s, 1H), 9 47 (s, 1H), 8 12 (d J = 5 2, 1H) 7 84 (d, J = 8 7, 2H), 7 57 (d, J = 8 7 2H), 7 16-7 15 (m 1H), 6 92 (dd, J = 8 5, 2 2, 1H), 6 66 (d, J = 8 2, 1H) 6 50 (dd, J = 10 0, 6 9, 1H), 6 33 (s, 1H), 6 31-6 27 (m 1H), 5 88 (s, 2H), 5 80 (dd, J = 10 1 1 9 1H)
394		400 08	3-chloro-N-(4-(2-(3-hydroxyphenylao)pyrimidin-4-ylthio)phenyl)propanamide	C	6 4	m/z 401 3 / 403 3 [M+1]+	

The term "C_{1-6}alkyl" refers to straight chain or branched chain hydrocarbon groups having from 1 to 6 carbon atoms Examples include ethyl, propyl, isopropsl. butyl. isobutyl, sec-butyl, tert-butyl. pentyl. neopentyl and hexyl.

The term "C_{1-6}alkylene" is the divalent equivalent of "Ci-$_6$alkyl".

The term "C_{2-6}alkenyT" refers to straight chain or branched chain hydrocarbon groups having at least one double bond of either E or Z stereochemistry where applicable and 2 to 6 carbon atoms. Examples include vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

The term "C_{2-6}alkynyl" refers to straight chain or branched chain hydrocarbon groups having at least one triple bond and 2 to 4 carbon atoms. Examples include ethynyl, 1- or 2-propynyl, 1-, 2- or 3- butynyl and methyl-2-propynyl.

The term "Cs-gcycloalkyl" refers to non-aromatic cyclic hydrocarbon groups having from 3 to 8 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "aryl" refers to single, polynuclear, conjugated or fused residues of aromatic hydrocarbons. Examples include phenyl, biphenyl, terphenyl, quaterphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl. dibenxanthracenyl and phenanthrenyl. 5 to 7 membered monocyclic aromatic ring systems such as phenyl are preferred.

The term "heterocyclyl" refers to saturated or unsaturated, monocyclic or polycyclic hydrocarbon groups containing at least one heteroatom atom selected from the group consisting of consisting of N, O, S and SO_2.

Suitable heterocyclyls include N-containing heterocyclic groups, such as, unsaturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl;

saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl, imidazolidinyl, piperidino or piperazinyl;

unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl or tetrazolopyridazinyl;

unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, such as, pyranyl or furyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms, such as, thienyl;

unsaturated 3 to 6-membered heteromonocyclic group containing I to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, isoxazolyl or oxadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 ox) gen atoms and 1 to 3 nitrogen atoms. such as. morpholinyl:

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl or benzoxadiazolyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms. such as, thiazolyl or thiadiazolyl:

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolidinyl; and

unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms. such as. benzothiazolyl or benzothiadiazolyl.

Preferred heterocyclyls are 5 to 7 membered saturated or unsaturated heterocyclyls having 1 to 4 heteroatoms independently selected from N, O, S and SO_2 such as morpholino, piperidinyl, piperazinyl, pyrrolidinyl and 1,3-thiazolidine 1. 1- dioxide or 8 to 10 membered bicyclic ring systems having 1 to 5 heteroatoms independently selected from N, O, S and SO_2.

The term "halogen" refers to fluorine, chlorine, bromine and iodine

The term "substituted or unsubstituted" refers to a group that may or may not be further substituted with one or more groups selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, Ci_{-6} alkylaryl, aryl, heterocyclyl, halo, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{2-6}alkenyl, haloC_{2-6}alkynyl, haloaryl, haloheterocyclyl, hydroxy, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, aryloxy, heterocyclyloxy, carboxy, haloCi_{-6}alkoxy, haloC_{2-6}alkenyloxy, haloC_{2-6}alkynyloxy, haloaryloxy, nitro, nitroC_{1-6},alkyl, nitroC_{2-6}alkenyl, nitroaryl, nitroheterocyclyl, azido, amino, C_{1-6}alkylamino, C_{2-6}alkenylamino, C_{2-6}alkynylamino, arylamino, heterocyclylamino acyl, C_{1-6}alkylacyl. Q^alkenylacyl, C_{2-6}alkynylacyl, arylacyl, heterocycylylacyl, acylamino, acyloxy, aldehydo, C_{1-6}alkylsulphonyl, arylsulphonyl, C_{1-6}alkylsulphonylamino, arylsulphonylamino, C_{1-6}alkylsulphonyloxy, arylsulphonyloxy, C_{1-6}alkylsulphenyl, C_{2-6}alklysulphenyl. arylsulphenyl, carboalkoxy, carboaryloxy, mercapto, C_{1-6}alkylthio, arylthio, acylthio, cyano and the like. Preferred substituents are selected from the group consisting of Ci_{-4} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, , Ci_{-6} alkylaryl, aryl, heterocyclyl, halo, haloaryl, haloheterocyclyl, hydroxy, C_{1-4} alkoxy, aryloxy, carboxy, amino, C^alkylacyl, arylacyl, heterocyclylacyl, acylamino, acyloxy, C_{1-6}alkylsulphenyl, arylsulphonyl and cyano.

The compounds of the invention may also be prepared as salts which are pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts. Examples of

pharmaceutically acceptable salts include salts of pharmaceutical ɪ\ acceptable cations such as sodium, potassium lithium, calcium magnesium, ammonium and alkylammonium, acid addition salts of pharmaceutically acceptable inorganic acids such as hydrochloric, orthophosphoric sulfuric, phosphoric, nitric, carbonic boric sulfamic and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric tartaric maleic, hydroxymaleic, fumaric citric, lactic mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulfonic, iπhalomethanesulfonic, toluenesulfonic, benzenesulfonic isethionic salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric pantothenic, tannic, ascorbic, valeric and orotic acids Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety

The salts may be formed by conventional means, such as by reacting the free base form of the compound with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin

Where a compound possesses a chiral center the compound can be used as a purified enantiomer or diastereomer, or as a mixture of any ratio of stereoisomers It is however preferred that the mixture comprises at least 70%, 80%, 90%, 95%, 97 5% or 99% of the preferred isomer, where the preferred isomer gives the desired level of potency and selectivity

This invention also encompasses prodrugs of the compounds of formula I The invention also encompasses methods of treating disorders that can be treated by the inhibition of protein kinases, such as JAK comprising administering drugs or prodrugs of compounds of the invention For example, compounds of formula I having free ammo, amido, hydroxy or carboxylic acid groups can be converted into prodrugs Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (eg, two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy and carboxylic acid groups of compounds of the invention The amino acid residues include the 20 naturally occurring ammo acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylh ɪstɪdɪne, norvlm, beta-alanine, gamma-aminobuty πc acid, citrulline, homocysteine, homose πne, ornithine and methioine sulfone Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of compounds of the present invention through the carbonyl carbon

prodrug sidechain Prodrugs also include phosphate derivatives of compounds (such as acids, salts of acids, or esters) joined through a phosphorus-oxygen bond to a free hydroxyl of compounds of formula 1. Prodrugs may also include N-oxides, and S-oxides of appropriate nitrogen and sulfur atoms in formula I.

This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of protein kinases, such as JAK kinases comprising administering drugs or prodrugs of compounds of the invention

Process of making compounds

Compounds are generally prepared in a 3-step process starting from a dihaloheterocycle.

The first step is a nucleophilic aromatic substitution to generate a monothio-monohalo intermediate.

The nucleophilic aromatic substitution is typically carried out by addition of a thiol to the di-ha!ogenated heterocycle in a solvent such as water, methanol, ethanol, isopropanol, tert-butanol, dioxane, THF, DMF, ethoxyethanol, toluene or xylene or a solvent mixture comprising 2-3 solvents selected from those listed above. The reaction is typically performed at room temperature to elevated temperature in the presence of excess amine or a non-nucleophilic base such as triethylamine or diisopropylethylamine, or an inorganic base such as potassium hydroxide, potassium carbonate or sodium hydroxide or sodium carbonate. Alternatively the thiol may be introduced through in situ generation of a thiolate from a protected thiol species or from reduction of a thiocyanate. Protected thiol species may be, for example, thiosilicones, which may be deprotected with a fluoride anion.

The thiols employed in the first step of the synthesis of these compounds are obtained commercially or are prepared using methods well known to those skilled in the art. Thus for example, an aromatic or heteroaromatic bromide or iodide can be converted to the corresponding thiol by a palladium catalysed reaction between triisopropylsilylthiol and the halide following the method of Soderquist (Soderquist, 1994), or related methods.

The second step is a nucleophilic aromatic substitution to generate the required monoamino-monothio product.

The nucleophilic aromatic substitution is typically carried out by addition of a primary or secondary amine to the mono-halogenated heterocycle in a solvent such as ethanol, isopropanol, tert-butanol, dioxane, THF, DMF, ethoxyethanol, toluene or xylene. The reaction is typically performed at elevated temperature in the presence of excess amine or a non-nucleophilic base such as triethylamine or

diisoprop\ lethylami πe. or an inorganic base such as potassium carbonate or sodium carbonate. The reaction may also be performed under acidic conditions in solvents such as dioxane, ethanol or isopropanol. with acids such as p-toluenesulfonic acid and HCI With either acidic or basic conditions, the reactions may be performed under pressure using for example microwave heating.

Alternatively, the amino substituent may be introduced through a transition metal catalysed amination reaction. Typical catalysts for such transformations include $Pd(OAc)_2/P(t\text{-}Bu)_3$, $Pd_2(dba)_3$/BfNAP and $Pd(OAc)_2$/BINAP. These reactions are typically carried out in solvents such as toluene or dioxane, in the presence of bases such as caesium carbonate or sodium or potassium /<?/7-butoxide at temperatures ranging from room temperature to reflux.

The products formed from either reaction step may be further derivatised using techniques known to those skilled in- the art. Alternatively, derivatisation of the mono-halo intermediate may be undertaken prior to reaction of the second halo substituent. Those skilled in the art will appreciate that the order of the reactions described for the syntheses above may be changed in certain circumstances and that certain functionalities may need to be derivatised (i.e. protected) in certain instances for the reactions described above to proceed with reasonable yield and efficiency. The types of protecting functionality are well-known to those skilled in the art and are described for example in Greene (Greene, T., Wuts, P. (1999) *Protective Groups in Organic Synthesis.* Wiley-lnterscience; 3rd edition.).

The leaving group may be any suitable known type such as those disclosed in J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure" 4lh Edition, pp 352-357, John Wiley & Sons, New York, 1992 which is incorporated herein by reference. Preferably, the leaving group is halogen, more preferably chlorine.

JAK Inhibition

The compounds of formula I have activity against protein kinases, particularly the JAK kinases and most particularly selective activity against JAKl, JAK2 or JAK3 kinases or combinations thereof. A JAK2 inhibitor is any compound that selectively inhibits the activity of JAK2. A JAK3 inhibitor is any compound that selectively inhibits the activity of JAK3. A JAK 1/JAK2 selective inhibitor is any compound that selectively inhibits both JAKl and JAK2. One activity of both JAK2 and JAK3 is to phosphorylate a STAT protein. Therefore an example of an effect of a JAK2 or JAK3 inhibitor is to decrease the phosphorylation of one or more STAT proteins. The inhibitor may inhibit the phosphorylated form of JAK2 or JAK3 or the non-

phosphor}'lated form of JAK2 or JAK3

Selective and Irreversible Inhibition of JAK3

A PTK catalyses the transfer of a phosphate group from a molecule of ATP to a tyrosine residue located on a protein substrate. The inhibitors known in the art are usually competitive with either the ATP or the protein substrate of the kinase (Levitzki 2000). Since the concentration of ATP in a cell is normally very high (millimolar), compounds that are competitive with ATP may lack in vivo activity since it is unlikely that said compounds can reach the concentrations within the cell that are necessary to displace the ATP from its binding site

An alternative approach which has been attempted in relation to EGFR is to design or select compounds which bind to EGFR TK in an irreversible manner. Such compounds are disclosed in Fry 1998; Discafani 1999; Smaill 1999; Smaill 2000; Tsou 2001; Smaill 2001; Wissner 2003. These compounds function as irreversible inhibitors by virtue of the fact that they can form covalent bonds to amino acid residues located at the active site of the enzyme which results in enhanced potency of the compounds in vitro and in the inhibition of growth of human tumors in in vivo models of cancer. A further benefit of such irreversible inhibitors when compared to reversible inhibitors, is that irreversible inhibitors can be used in prolonged suppression of the tyrosine kinase, limited only by the normal rate of receptor turnover.

Alignment of the four members of the JAK family of protein tyrosine kinases reveals that within the amino acids that comprise the ATP-binding pocket of these kinases there are very few amino acid differences that could be used to target potential inhibitors towards one family member or another. Interestingly, JAK3 alone amongst this sub-family of kinases possesses a Cysteine residue close to the front lip of the ATP-binding cavity (Cys 963). By targeting this Cysteine with a functionality bearing an alkylating group such as a Michael acceptor, or other such group that can react reversibly or irreversibly with the thiol moiety of this Cysteine residue, highly selective JAK3 inhibition can be achieved.

Pharmaceutical Compositions

The present invention provides pharmaceutical compositions comprising at least one of the compounds of the formula I and a pharmaceutically acceptable carrier. The carrier must be "pharmaceutically acceptable" means that it is compatible with the other ingredients of the composition and is not deleterious to a subject. The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or

diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavours, etc.) according to techniques such as those well known in the art of pharmaceutical formulation (See, for example, Remington: *The Science and Practice of Pharmacy*, 21st Ed., 2005. Lippincott Williams & Wilkins).

The compounds of the invention may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular; intra(trans)dermal, or intracisternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray or insufflation; topically, such as in the form of a cream or ointment ocularly I the form of a solution or suspension; vaginally in the form of pessaries, tampons or creams; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps.

The pharmaceutical compositions for the administration of the compounds of the invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. These methods generally include the step of bringing the compound of formula I into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the compound of formula I into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the compound of formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any

method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents such as sweetening agents, flavouring agents, colouring agents and preserving agents, e.g. to provide pharmaceutically stable and palatable preparations. Tablets contain the compound of formula 1 in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the compound of formula I is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the compound of formula I is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the compound of formula I in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a

mineral oil such as liquid paraffin The oily suspensions may contain a thickening agent for example beeswax, hard paraffin or cetyl alcohol Sweetening agents such as those set forth above and flavoring agents may be added to provide a palatable oral preparation These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the compound of formula I in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above Additional excϕients, for example sweetening, flavoring and coloring agents, may also be present

*1*he pharmaceutical compositions of the invention may also be in the form of oιl-in-water emulsions The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate The emulsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenteral ly-acceptable diluent or solvent, for example as a solution in 1,3-butane diol Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono- or diglyceπdes In addition, fatty acids such as oleic acid find use in the preparation of injectable formulations

For administration to the respiratory tract, including intranasal administration, the active compound may be administered by any of the methods and formulations employed in the art for administration to the respiratory tract

Thus in general the active compound may be administered in the form of a solution or a suspension or as a dr\ powder

Solutions and suspensions will generally be aqueous, for example prepared from water alone (for example sterile or pyrogen-free water) or water and a physiologically acceptable co-solvent (for example ettianol, propylene glycol or polyethylene glycols such as PEG 400).

Such solutions or suspensions may additionally contain other excipients for example preservatives (such as benzalkonium chloride), solubilising agents/surfactants such as polysorbates *(eg.* Tween 80. Span 80, benzalkonium chloride), buffering agents. isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers Suspensions may additionally contain suspending agents (for example microcrystalline cellulose and carboxymethyl cellulose sodium)

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the subject administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurised pack with a suitable propellant. such as a chlorofluorocarbon (CFC), for example dichlorodifluoromethane, trichlorofiuoromethane or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of active compound may be controlled by provision of a metered valve.

Alternatively the active compound may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form, for example in capsules or cartridges of eg. gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the active compound will generally have a small particle size, for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronisation.

When desired. formulations adapted to give sustained release of the active compound may be employed.

The active compound may be administered by oral inhalation as a free-flow powder via a 'Oiskhaler '' (trade mark of Glaxo Group Ltd) or a meter dose aerosol inhaler.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug Such materials are cocoa butter and polyethylene glycols

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

For application to the eye, the active compound may be in the form of a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride, or chlorohexidine and thickening agents such as hypromellose may also be included.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilisers, preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines, both natural and synthetic. Methods to form liposomes are known in the art.

Efficacy of this class of compounds may be applicable to drug eluting stents. Potential applications of drug eluting stents with these compounds include pulmonary artery stenosis, pulmonary vein stenosis, as well as coronary artery stenosis. Drug eluting stents may also be used in saphenous vein grafts or arterial grafts or conduits Drug eluting stents that release this class of compounds may also be applicable for treating stenoses of the aorta or peripheral arteries, such as the iliac artery, the femoral artery or the popliteal artery. The compound may be bound to the drug eluting stent by

any of various methods known in the field. Examples of such methods include polymers. phosphoryi choline, and ceramics The compound may also be impregnated into a bioabsorbable stent.

The active compounds may also be presented for use in the form of veterinary compositions, which may be prepared, for example, by methods that are conventional in the art. Examples of such veterinary compositions include those adapted for.

(a) oral administration, external application, for example drenches (e.g aqueous or non-aqueous solutions or suspensions); tablets or boluses: powders. granules or pellets for admixture with feed stuffs; pastes for application to the tongue;

(b) parenteral administration for example by subcutaneous, intramuscular or intravenous injection, e.g. as a sterile solution or suspension; or (when appropriate) by intramammary injection where a suspension or solution is introduced in the udder via the teat;

(c) topical applications, e.g. as a cream, ointment or spray applied to the skin, **or**

(d) rectally or intravaginally, e.g. as a pessary, cream or foam.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

Examples of other therapeutic agents include the following: endothelin receptor antagonists (eg ambrisentan, bosentan, sitaxsentan), PDE-V inhibitors (eg sildenafil, tadalafil, vardenafil), Calcium channel blockers (eg amlodipine, felodipine, varepamil, diltiazem, menthol), prostacyclin, treprostinil, iloprost, beraprost, nitric oxide, oxygen. heparin, warfarin, diuretics, digoxin, cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RJB, anti-CD2. anti-CD3 (OK.T-3), anti-CD4, anti-CD80, anti-CD86, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CDl 54), fusion proteins constructed from CD40 and gp39 (CD401g and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), cholesterol biosynthesis inhibitors such as HMG CoA

reductase inhibitors (lovastatin and simvastatin). non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. aspirin. acetaminophen. leflunomide, deoxyspergualin. cyclooxygenase inhibitors such as celecoxib. steroids such as prednisolone or dexamethasone, gold compounds, beta-agonists such as salbutamol, LABA's such as salmeterol, leukotriene antagonists such as montelukast, antiproliferative agents such as methotrexate, FK506 (tacrolimus. Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine. VP-16, etoposide, fludarabine, doxorubin, adriamycin, amsacπne, camptothecin, cytarabine, gemcitabine. fluorodeoxyuridine, melphalan and cyclophosphamide, antimetabolites such as methotrexate, topoisomerase inhibitors such as camptothecin. DNA alkylators such as cisplatin, kinase inhibitors such as sorafenib, microtubule poisons such as paclitaxel, TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, hydroxy urea and rapamycin (sirolimus or Rapamune) or derivatives thereof.

When other therapeutic agents are employed in combination with the compounds of the present invention they may be used for example in amounts as noted in the Physician Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Methods of Treatment

The compounds of formula 1may be used in the treatment of kinase associated diseases including JAK kinase associated diseases such immunological and inflammatory diseases including organ transplants; hyperproliferative diseases including cancer and myeloproliferative diseases; viral diseases; metabolic diseases; and vascular diseases.

Generally, the term "treatment" means affecting a subject, tissue or cell to obtain a desired pharmacological and/or physiological effect and include: (a) preventing the disease from occurring in a subject that may be predisposed to the disease, but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or (c) relieving or ameliorating the effects of the disease, i.e., cause regression of the effects of the disease.

The term "subject" refers to any animal having a disease which requires treatment with the compound of formula I.

In addition to primates, such as humans, a variety of other mammals can be treated using the compounds, compositions and methods of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species

can be treated However, the invention can also be practiced in other species, such as avian species (e g.. chickens).

The term "administering" should be understood to mean providing a compound of the invention to a subject in need of treatment.

The term "kinase associated diseases" refers to a disorder or disorders that directly or indirectly result from or are aggravated by aberrant kinase activity, in particular JAK kinase activity- and/or which are alleviated by inhibition of one or more of these kinase enzymes.

In a preferred embodiment the kinase associated disease state involves one or more of the JAK kinases. JAKI, JAK2. JAK3 or TYK2 In a particularly preferred embodiment, the disease involves JAK2 or JAK3 kinase. Such diseases include, but are not limited to, those listed in the Table below.

Activation of the JAK/STAT pathway in various pathologies

Disease Type	Cell Types Involved	Cytokines involved	JAK Kinase Involved	Characteristics
Atopy Allergic Asthma, Atopic Dermatitis (Eczema), Allergic Rhinitis,	Mast Cells, Eosinophils, T-Cells, B-Cells,	IL-4, IL-5, IL-6, IL-7, IL-13	JAK1, JAK2, JAK3, Tyk2	T-cell activation of B-cells followed by IgE mediated activation of resident Mast cells and Eosinophils
CMH Allergic Contact Dermatitis, hypersensitivity pneumonitis	T-cells, B-cells, macrophages, neutrophils	IL-2, IL-4, IL-5, IL-6, IL-10, IFNγ, TNF, IL-7, IL-13,	JAK1, JAK2, JAK3, Tyk2	B cell and/or T_{DH} cell activation Macrophage/granulocyte activation
AutoImmune Diseases Multiple sclerosis, Glomerulonephritis Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, Juvenile Arthritis, Sjögren's Syndrome, Scleroderma Polymyositis, Ankylosing Spondylitis, Psoriatic Arthritis	B-Cells, T cells, monocytes, Macrophages, Neutrophils, Mast Cells, Eosinophils,	IL-2, IL-4, IL-5, IL-6, IL-7, Il-10, IL-13, IFNγ, TNF, GM-CSF; G-CSF,	JAK1, JAK2, JAK3, Tyk2	Cytokine Production (e.g.TNFα/β , IL-1, CSF-1, GM-CSF), T-cell Activation, B cell activation, JAK/STAT activation
Transplantation				

Allograft Rejection GvHD	T cells, B cells, macrophages	IL-2, IL-4, IL-5, IL-7, IL-13, TNF	JAK1, JAK2, JAK3,	Macrophage/T cell mediated necrosis, Tc cell mediated apoptosis, and B cell/Ig mediated opsonization/necrosis of foreign graft
Viral Diseases				
Epstein Barr Virus (EBV)	Lymphocytes	Viral Cytokines, IL-2,	JAK1, JAK2, JAK3	JAK/STAT Mediation
Hepatitis B	Hepatocytes			
Hepatitis C	Hepatocytes			
HIV	Lymphocytes			
HTLV I	Lymphocytes			
Varicella-Zoster Virus (VZV)	Fibroblasts			
Human Papilloma Virus (HPV)	Epithelial cells			
Hyperproliferative diseases-cancer				
Leukemia	Leucocytes	Various Autocrine cytokines, Intrinsic Activation	JAK1, JAK2, JAK3	Cytokine production, JAK/STAT Activation
Lymphoma.	Lymphocytes			
Multiple Myeloma	various			
prostate cancer	various			
breast cancer	various			
hodgkins lympohoma	various			
B-cell chronic lymphocytic leukemia	various			
lung cancer	various			
hepatoma	various			
metastatic myeloma	various			
glioma	various			
Myeloproliferative Diseases Polycythemia rubra vera, primary myelofibrosis,	Hematopoietic	Interleukin-3, erythropoietin, thrombopoietin	JAK2 mutation	JAK/STAT activation

thrombocythemia, essential thrombocythemia, idiopathic myelofibrosis, chronic myelogenous leukemia				
Vascular Disease Hypertension, Hypertrophy, Heart Failure, Ischemia, Pulmonary arterial hypertension	Endothelial cells, smooth muscle cells including pulmonary artery smooth muscle cells, cardiac myocytes, fibroblasts, endothelial cells	IL6, angiotensin II, LIF, TNFalpha, serotonin, caveolin1	JAK1, JAK2, TYK2	JAK/STAT activation
Metabolic disease Obesity, metabolic syndrome	Adipocytes, pituitary cells, neurons, monocytes	Leptin	JAK2	JAK/STAT activation

The term "immunological and inflammatory disease" refers to an immunological, inflammatory or autoimmune disease, including but not limited to rheumatoid arthritis, polyarthritis, rheumatoid spondylitis, osteoarthritis, gout, asthma, bronchitis, allergic rhinitis, chronic obstructive pulmonary disease, cystic fibrosis, inflammatory bowl disease, irritable bowl syndrome, mucous colitis, ulcerative colitis. diabrotic colitis, Crohn's disease, autoimmune thyroid disorders , gastritis, esophagitis. hepatitis, pancreatitis, nephritis, psoriasis, eczema, acne vulgaris, dermatitis, hives, multiple sclerosis, Alzheimer's disease, Lou Gehrig's disease, Paget's disease, sepsis, conjunctivitis, neranl catarrh, chronic arthrorheumatism, systemic inflammatory response syndrome (SIRS), polymyositis, dermatomyositis (DM), Polaritis nodoa (PN), mixed connective tissue disorder (MCTD), Sjoegren's syndrome, Crouzon syndrome, achondroplasia, systemic lupus erythematosus, scleroderma, vasculitis, thanatophoric dysplasia, insulin resistance, Type I diabetes and complications from diabetes and metabolic syndrome.

The term "hyperproliferative diseases" includes cancer and myeloproliferative disease states such as cellular-proliferative disease states, including but not limited to: Cardiac : sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma,

hmphoma. chondromatous hanlartoma. mesothelioma, Gastrointestinal esophagus (squamous cell carcinoma adenocarcinoma, leiomyosarcoma lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma. hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), Genitourinary tract kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostrate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma. choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma), Liver hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, Bone osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfrorna (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors, Nervous system skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma), Gynecological uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgermmoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma [embryonal rhabdomyosarcoma]), fallopian tubes (carcinoma), Hematologic blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, myelodysplastic syndrome), Hodgkm's disease, non-Hodgkm's lymphoma [malignant lymphomaj, ɕi malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Adrenal glands neuroblastoma, and Myleoprohferative diseases such as polycythemia rubra vera, primary myelofibrosis, thrombocythemia, essential thrombocythemia (ET), agnoneic myeloid

metaplasia (AMM). also referred to as idiopathic myelofibrosis (IMF), and chronic myelogenous leukemia (CML).

The term "vascular diseases" refers to diseases including but not limited to cardiovascular diseases, hypertension, hypertrophy, hypercholesterolemia. hyperlipidemia, thrombotic disorders, stroke, Raynaud's phenomenon, POEMS syndrome, angina, ischemia, migraine, peripheral arterial disease, heart failure, restenosis, atherosclerosis, left ventricular hypertrophy, myocardial infarction, ischemic diseases of heart, kidney, liver and brain, and pulmonary arterial hypertension.

Preferred diseases for JAK2 selective inhibitors include immunological and inflammatory diseases such as auto-immune diseases for example atopic dermatitis, asthma, allergic rhinitis, rheumatoid arthritis, juvenile arthritis, Sjogren's syndrome, scleroderma, polymyositis, ankylosing spondylitis, psoriatic arthritis, cell mediated hypersensitivity for example allergic contact dermatitis and hypersensitivity pneumonitis, Crohn's disease, psoriasis, Crouzon syndrome, achondroplasia, systemic lupus erythematosus, scleroderma, mixed connective tissue disease, vasculitis, thanatophoric dysplasia and diabetes; hyperproliferative disorders such as cancer for example prostate cancer, colon cancer, breast cancer, liver cancer such as hepatoma, lung cancer, head and neck cancer such as glioma, skin cancer such as metastatic melanoma, leukemia, lymphoma, multiple myeloma and myleoproliferative diseases such as polycythemia rubra vera, myelofibrosis, thrombocythemia, essential thrombocythemia (ET), agnoneic myeloid metaplasia (AMM), also referred to as idiopathic myelofibrosis (IMF), and chronic myelogenous leukemia (CML) ; and vascular diseases such as hypertension, hypertrophy, stroke, Raynaud's phenomenon, POEMS syndrome, angina, ischemia, migraine, peripheral arterial disease, heart failure, restenosis, atherosclerosis and pulmonary arterial hypertension.

Preferred diseases for compounds which selectively inhibit both JAKI and JAK2 are hyperproliferative diseases such as cancer for example prostate cancer, colon cancer, breast cancer, liver cancer such as hepatoma, lung cancer, head and neck cancer such as glioma, skin cancer such as metastatic melanoma, leukemia, lymphoma and multiple myeloma.

Preferred diseases for selective inhibitors of JAK3 are immunological and inflammatory diseases including autoimmune diseases such as systemic lupus erythematosus, mixed connective tissue disease, scleroderma, multiple sclerosis, autoimmune neuritis, rheumatoid arthritis, psoriasis, insulin resistance, Type I diabetes and complications from diabetes, metabolic syndrome, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, and other indications where immunosuppression may be desirable such as organ

transplants and graft vs host disease. Furthermore specific inhibitors of JAK.3 may find application for therapeutic treatments for hyperproliferative diseases such as leukaemia and lymphoma where JAK3 is hyperactivated.

The compounds of formula may also be used in a method of suppressing the immune system of a subject. In one embodiment, the method of suppressing the immune system is to modify the immune system response to a transplant into the subject. More preferably, the transplant is an organ transplant or tissue transplant.

Preferably, the method of suppressing the immune system is for the treatment of disease states selected from Atopy, such as Allergic Asthma, Atopic Dermatitis (Eczema), and Allergic Rhinitis; Cell Mediated Hypersensitivity, such as Allergic Contact Dermatitis and Hypersensitivity Pneumonitis; Autoimmune Diseases, such as Multiple sclerosis, Glomerulonephritis,Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, Juvenile Arthritis, Sjogren's Syndrome, Scleroderma Polymyositis, Ankylosing Spondylitis, Psoriatic Arthritis, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, Juvenile Arthritis, Sjogren's Syndrome, Scleroderma, Polymyositis, Ankylosing Spondylitis, Psoriatic Arthritis, Ulcerative Colitis, Crohn's disease; Other autoimmune diseases such as Type I diabetes, autoimmune thyroid disorders, and Alzheimer's disease; Transplantation related diseases, such as Allographt Rejection, and graft vs host disease; Viral Diseases, such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV), Human Papilloma Virus (HPV), Cancer, such as Leukemia, Lymphoma and Prostate Cancer.

Dosages

The term "therapeutically effective amount" refers to the amount of the compound of formula I that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

In the treatment or prevention of conditions which require kinase inhibition an appropriate dosage level will generally be about 0.0 1 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0,

15.0 20.0. 25.0. 50.0. 75.0. 100.0, 150.0. 200.0, 250.0. 300.0, 400.0. 500.0. 600 0. 750.0, 800.0, 900 0. and 1000.0 milligrams of the active ingredient. The dosage may be selected, for example to any dose within any of these ranges, for therapeutic efficacy and/or symptomatic adjustment of the dosage to the patient to be treated. The compounds will preferably be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be understood that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

In order to exemplify the nature of the present invention such that it may be more clearly understood, the following non-limiting examples are provided.

EXAMPLES

Compound Synthesis

The compounds of the invention may be prepared by methods well known to those skilled in the art; and as described in the synthetic and experimental procedures shown below for selected compounds.

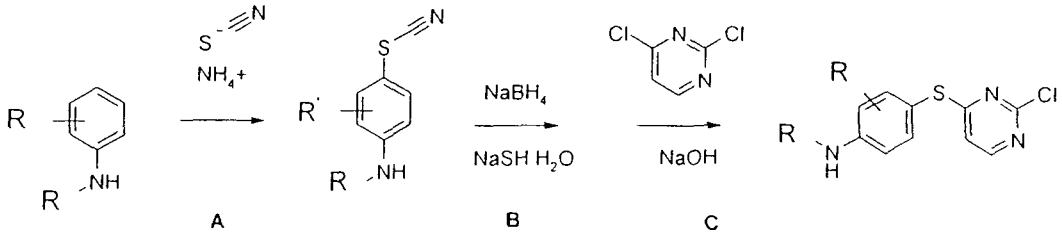
Definitions:

PyBOP	benzotriazole-1-yloxytripyrrolidinophosphonium hexafluorophosphate
DMF	*N*,*N*-dimethylformamide
DMAP	4-Dimethylaminopyridine
DCM	dichloromethone
NMP	l-methyl-2-pyrorrolidinone
n-PrOH	n-propanol
ACN	acetonitrile
EDCHCl	l-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride
HOBT	*N*-hydroxybenzotriazole
TEA	triethylamine
DIPEA	diisopropylethylamine
p-TsOH	/7-toluene sulfonic acid
HATU	o-(7-azabenzotriazol-l-yl)- *N*,*N*,*N*',*N*'-tetrarnethyluronium hexafluorophosphate

THF tetrahydrofuran

General Examples

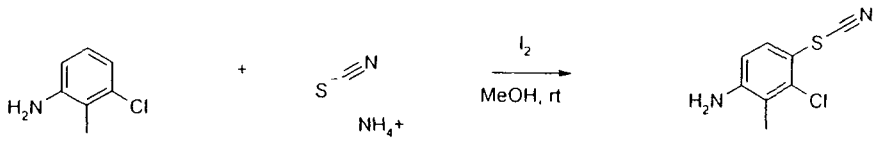
Synthesis of thiocyanates from anilines and subsequent reduction and reaction with dichloropyrimidine



Step A

4-amino-2-chloro-3-methylphenyl thiocyanate

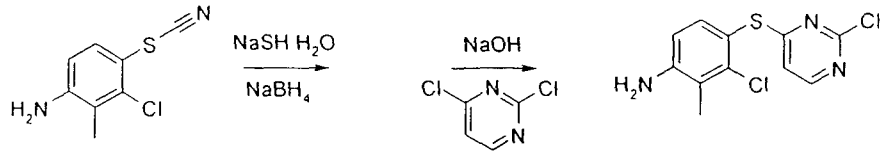
(J.S. Yadav, B.V. Subba Reddy, U.V. Subba Reddy and A.D Krishna "Iodine/MeOH as a novel and versatile reagent system for the synthesis of α-ketothiocyanates" *Tetrahedron Letters,* Volume 48, Issue 30, 23 July 2007, Pages 5243-5246)



To a stirred solution of ammonium thiocyanate (1.61 g, 0.02 mo!) and iodine (1.79 g, 7.1 mmol) in methanol was added 3-chloro-2-methylaniline (0.84 mL, 7.1 mmol) dropwise. The mixture was allowed to stir at room temperature for 2 days after which time water (50 mL) was added and the mixture was extracted with dichloromethane (4 x 50 mL). The extracts were washed with a 15% aqueous solution of sodium thiosulfate (100 mL) then dried (Na_2SO_4) and the solvent removed *in vacuo* to afford 4-amino-2-chloro-3-methylphenyl thiocyanate as a brown-solid (1.26g, 90%). Material was used crude in subsequent steps

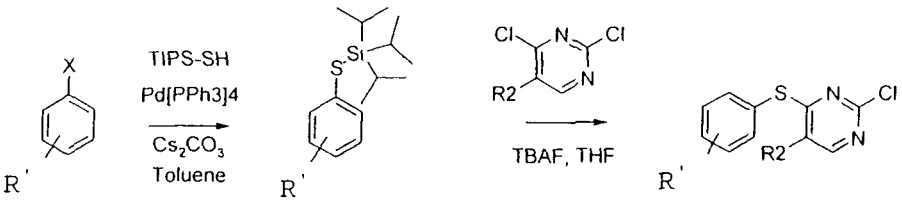
Step B,C

3-chloro-4-[(2-chloropyrimidin-4-yl)thio]-2-methylaniline



Crude 4-amino-2-chloro-3-methylphenyl thiocyanate (600 mg, 3.0 mmol) was dissolved in a mixture of methanol: water (2: 1, 22 mL) and cooled to 0^0C. Sodium hydrosulfide monohydrate (338 mg, 4.6 mmol) and sodium borohydride (447 mg, 11.8 mmol) were added then the mixture was allowed to warm to room temperature and stir overnight. After this time sodium hydroxide (96 mg, 2.4 mmol) was added followed by 2,4-dichloropyrimidine (360 mg, 2.4 mmol) and the mixture allowed to stir for a further 24 h. The methanol was removed *in vacuo* and then the mixture was extracted with ethyl acetate. The extracts were dried (Na_2SCM) and evaporated then the residue was purified by flash chromatography to afford 3-chloro-4-[(2-chloropyrimidin-4-yl)thio]-2-methylaniline (353 mg, 41%).

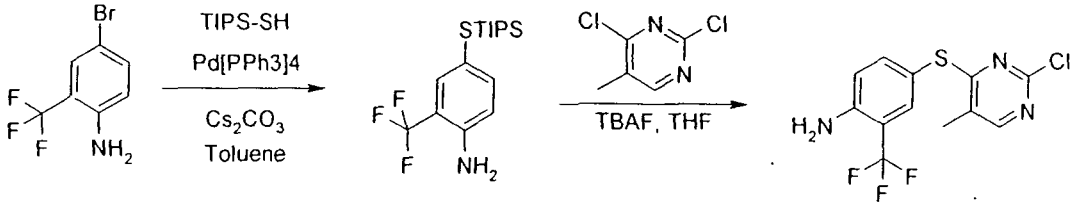
Synthesis of Thiols from **Aryl Halides and subsequent** reaction **with** Dichloropyriniidine



X=Cl, Br, I

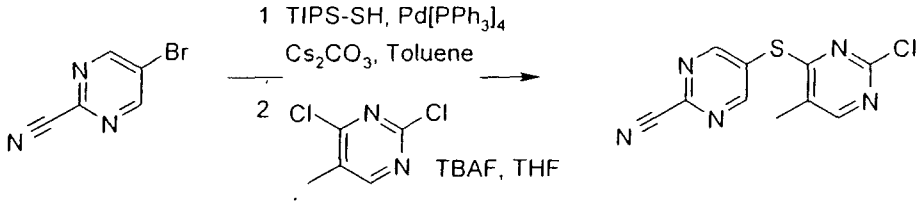
Example I

4-[(2-chloro-5-methylpyrimidin-4-yl)thio]- 2-(trifluoromethyl)aniIine



A mixture of $Pd[PPh_3J_4$ (75 mg. 0 065 mmol) and Cs_2CO_3 (550 mg. 1.69 mmol) was evacuated and purged with nitrogen Toluene (12 mL) was then added followed by 4-bromo-2-(trifluoromethyl)aniline (187 µL. 1.33 mmol) and Triisopropylsilanethiol (TIPS-SH) (363 µL, 1.69 mmol). The mixture was heated at 100^0C for 24 h then cooled to room temperature. Saturated aqueous NH_4CI (5 mL) was added then diluted with water and extracted twice with EtOAc. The combined extracts were washed with water, brine then dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude TIPS thiophenol as a dark red oil (675 mg). This oil was dissolved in THF (13 mL), 2,4-dichloro-5-methylpyr umid ine (190 µL. 1.62 mmol) was added and the solution was cooled to O^0C. Tetrabutyl ammonium fluoride (TBAF) (1.0 M in THF, 2.6 mL, 2.6 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 3 h. Water was added and the mixture was extracted three times with EtOAc. The combined extracts were washed with water, brine then dried (Na_2SO_4). Solvent removal under reduced pressure and the resulting residue was purified by silica gel chromatography with 30% EtOAc/Petrol as eluent to give 4-[(2-chloro-5-methy!pyrimidin-4-yl)thio]-2-(trifluoromethyl)aniline (410 mg, 95%). ^{1}H NMR ($CDCI_3$, 300 MHz) δ 8.07 (d, *J* = 0.9 Hz, 1 H), 7.58 (d, *J* = 2.4 Hz, 1 H), 7.43 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 4.43 (*br* s, 2 H), 2.25 (d, *J* = 0.6 Hz, 3 H); LRMS (ESI): *m/z* calcd for $[M+H]^+$ 320.0, found 320.2.

Example II:



A mixture of 4-bromo-2-cyanopyrimidine (280 mg, 1.52 mmol), $Pd[PPh_3J_4$ (86 mg, 0.074 mmol) and Cs_2CO_3 (628 mg, 1.93 mmol) was evacuated and purged with nitrogen. Toluene (15 mL) was then added followed by TIPS-SH (413 µL, 1.92 mmol). The mixture was heated at 100^0C for 22 h and the resulting orange suspension was then cooled to O^0C. 2,4-Dichloro-5-methylpyrimidine (267 µL, 2.28 mmol) was then added followed by tetrabutyl ammonium fluoride (1.0 M in THF. 3.8 mL, 3.8 mmol) dropwise. The mixture was stirred at O^0C for 30 min then allowed to warm to room temperature and stirred for 6 h. The reaction was quenched with saturated aqueous NH_4CI and the mixture was extracted three times with EtOAc. The combined extracts

were washed with water, brine then dried (Na_2SO_4). Solvent removal under reduced pressure and purification by silica gel chromatography with 100% dichloromethane then 1% EtOAc/dichloromethane as eluent gave 5-(2-chloro-5-methylpy πmidin-4-ylthio)pyrimid ιne-2-carbonitrile (327 mg, 82%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.97 (s, 2H), 8.25 (s, IH), 2.35 (s, 3H); Std LC-MS; rt 6.30 mm. *m/z* 264. 1 [M+H]+; purity 96% at 254 nm.

Example 1

2-Chloro-4-(phenylthio)pyrimidine

To a stirred solution of 2,4-dichloropyrimidine (1.00 g, 6.7 1 mmol) in absolute ethanol (10 mL), was added sodium salt of benzenethiol (0.89 g, 6.73 mmo!)in small portions The mixture was stirred at room temperature for 2 hours, then at 40 ^{0}C for 16 hours. It was diluted with ethyl acetate (20 mL), and filtered. The filtrate was concentrated in vacuo, and the residue was flash chromatographed on silica gel using ethyl acetate:petroleum ether (1:99—+25:75) as eluant to give the desired product (498 mg, 36%).

1H-n.m.r. ($CDCI_3$). δ 6.62 (d, 1H, J=5.4 Hz, pyrimidine-H), 7.47-7.54 (m, 3H^Ar-H),. 7.59-7.62 (m, 2H, Ar-H), 8.18 (d, 1H, J=5.4 Hz, pyrimidine-H).

The minor-isomer, 4-chloro-2-(phenylthio)pyrimidinewas also obtained (274 mg, 20%). 1H-n.m.r. ($CDCI_3$): δ 7.58-7.63 (m, 2H,,Ar-H), 7.69-7.73 (m, IH, Ar-H), 8.03 (d, IH. J=4.8 Hz, pyrimidine-H), 8.06-8.09 (m, 2H, Ar-H), 8.92 (d, IH, J=4.8 Hz, pyrimdine-H).

Example 2

Methyl 4-(2-chloropyrimidin-4-ylthio)benzoate

To a sodium hydroxide (2.38g, 59mmol) solution in methanol (50 mL) and water (5 mL), was added dropwise a solution of methyl 4-mercaptobenzoate (9.00 g, 54 mmol) in methanol (100 mL). The mixture was stirred at room temperature for 1 hour, to this was added methanol solution (100 mL) of 2, 4-dichlorpyrimidine (8.77g, 59 mmol) over 5 minutes. The whole was stirred at room temperature for 16 hours. Methanol was removed in vacuo, and the residue was partitioned between ethyl acetate (20OmL) and water (100 mL). The organic layer was separated and dried (Na_2SO_4). Removal of the solvent in vacuo yielded the product (14.6Og, 97%).

Example 3a

4-(2-Chloropyrimidin-4-ylthio)benzenamine

To a suspension of sodium hydride (60% dispensed in mineral oil, 0.97 g, 24 mmol) in anhydrous tetrahydrofuran (80 mL), was added 4-aminobenzenethiol (2.77 g. 22 mmol) dissolved in tetrahydrofuran (20 mL) over 5 minutes. The mixture was stirred at room temperature for 30 minutes, to this was added a solution of 2,4-dichloropyrimidine (3.00g, 20 mmol) dissolved in tetrahydrofuran (20 mL) over 5 minutes. The resulting mixture was stirred at room temperature for 64 hours, diluted with ethyl acetate (100 mL), washed with water and brine. After being dried (Na_2SO_4), the organic solution was concentrated in vacuo. The residue was flash chromatographed on silica gel using 5% of acetone in dichloromethane as eluant to give the product (3.60 g, 75%).

Example 3b

4-[(2-chloro-5-methylpyrimidin-4-yl)thio]aniline

Sodium hydroxide (2.38 g, 5.9 mmol) was dissolved in water (10 mL), 4-aminothiophenol (6.77 g, 5.4 mmol) was added as a solution in methanol (25 mL) and the reaction was stirred at room temperature for 30 minutes. 2,4-Dichloro-5-methylpyrimidine (7.05 g, 4.3 mmol) was slowly added as a solution in methanol (25 mL) and the reaction was stirred at room temperature for a further 1 hour during which time a precipitate formed. This precipitate was isolated by filtration, washed with minimum ice cold diethyl ether and dried under vacuum to give 4-[(2-chloro-5-methylpyrimidin-4-yl)thio]aniline (8.49 g, 92%).

Example 4

3-(2-Chloropyrimidin-4-ylthio)benzenamine

In a procedure analogous to Example 3, reaction of 4-aminobenzenethiol (4.62 g, 37 mmol) and 2,4-dichloropyrimidine (5.00 g, 34 mmol) furnished the product (7.98 g, 100%).

Example 5

2-Chloro-4-(pyrimidin-2-ylthio)pyrimidine

In a procedure analogous to Example 3, reaction of pyrimidine-2-thiol (41 5 mg, 3 70 mmol) and 2,4-dichloropyrimidine (500 mg, 3.36 mmol) furnished the product (705 mg. 93%)

Example 6

Nl-(4-(phenylthio)py π midin-2-yl)benzene-l,3-diamine

To a stirred mixture of **2-chloro-4-(phenylthio)pyrimidine** (300 mg, 1.35 mmol) and diisopropylethylamine (0.35 mL, 2.02 mmol) in 2-ethoxyethanol (2 mL), was added 1,3-phenylenediamine (291 mg, 2.70 mmol) in one portion. The whole was heated under reflux for 20 hours. The mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), washed with water and brine. The organic solution was dried (Na_2SO_4), concentrated in vacuo. The residue was flash chromatographed on silica gel using ethyl acetate:petroleum ether (20:80—+50:50) as eluant to give the product (167 mg, 42%).

Example 7

Nl-(4-(pyridin-2-ylthio)pyrimidin-2-yl)benzene-l,3-diamine

In a procedure analogous to Example 6, reaction of 2-chloro-4-(pyridin-2-ylthio)pyrimidine (100 mg, 0.45 mmol) and 1,3-phenylenediamine (193mg, 1.78 mmol) furnished the product (40 mg, 30%).

Example 8

Methyl 4-(2-(4-morpholinophenylamino)pyrimidin-4-yIthio)benzoate **(Compound 66)**

To a stirred mixture of **methyl** 4-(2-chloropyrimidin-4-ylthio)benzoate (3.80g, 14 mmol) and 4-morpholinoaniline (2.89 g, 16 mmol) in 1,4-dioxane (100 mL), was added p-toluensulfonic acid monohydrate (2.57 g, 14 mmol) in one portion. The whole was heated at 100 ^{0}C for 16 hours, cooled to room temperature, and poured into water (200 mL). The precipitate was collected by filtration, washed repeatedly with 2% aqueous

citric acid, water, and ethyl acetate It was then dried under high vacuum to afford the product (2 90 g. 51%)

Example 9

N-(4-(2-(4-morpholinophenylamino)pyrimidin-4-ylthio)phenyl)acrylamide **(Compound 25)**

In a procedure analogous to Example 8. reaction of N-(4-(2-chloropyrimidin-4-ylthio)phenyl)acrylamide (540 mg, 1 85 mmol) and 4-morpholinoaniline (400 mg, 2.24 mmol) furnished the product.(430 mg. 54%)

Example 10

N-(3-(2-(4-morpholinophenylamino)pyrimidin-4-ylthio)phenyl)acrylamide (Compound **23)**

In a procedure analogous to Example 8, reaction of N-(3-(2-chloropyrimidin-4-y!thio)phenyl)acrylamide (1. 10 g, 3 77 mmol) and 4-morpholinoaniline (806 mg, 4.52 mmol) furnished the product (690 mg, 43%)

lH-n.m.r. ($CDCI_3$): δ P84, book 155

Example 11

N-(3-(2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylthio)phenyl)acrylamide (Compound **51)**

In a procedure analogous to Example 8, reaction of N-(3-(2-chloropyrimidin-4-ylthio)phenyl)acrylamide (100 mg, 0.34 mmol) and 3,4,5-trimethoxyaniline (75 mg, 0.41 mmol) furnished the product (20 mg, 14%)

Example 12

(E)-N-(3-(2-(4-morpholinophenylamino)pyrimidin-4-ylthio)phenyl)but-2-enamide (Compound **54)**

In a procedure analogous to Example 8, reaction of (E)-N-(3-(2-chloropyrimidin-4-ylthio)phenyl)but-2-enamide (103 mg, 0.26 mmol) and 4-morpholinoaniline (47 mg, 0 26 mmol) furnished the product (8 1 mg, 69%).

Example 13

Methyl 3-(2-(4-morpholinophenylamino)pyrimidin-4-ylthio)benzoate (Compound 48)

In a procedure analogous to Example 8, reaction of methyl 3-(2-chIoropyrim ıdm-4-ylthio)benzoate (3 10 mg, 1.84 mmol) and 4-morpholinoaniline (394 mg. 2.2 1 mmol) furnished the product (4 10 mg, 87%).

Example 14

4-(4-(lH-tetrazo!-l-yl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-amine **(Compound** 80)

In a procedure analogous to Example 8, reaction of 4-(4-(lH-tetrazol-I-yl)phenylthio)-2-chloropyrimidine (100 mg, 0.34 mmol) and 4-morpholinoaniline (75 mg, 0 4 1 mmol) furnished the product (56 mg, 38%).

Example 15

N-(3-(4-(phenylthio)pyrimidin-2-ylamino)phenyl)acrylamide (Compound **16)**

To a stirred solution of **Nl-(4-(phenylthio)pyrimidin-2-yl)benzene-l,3-diamine** (80 mg, 0.27 mmol) and acrylic acid (37 µL, 0.54 mmol) in anhydrous dichloromethane (2 mL), was added l-[3-(dimethylamino)propyl]-3-ethyIcarbodiimide hydrochloride salt (78 mg, 0 4 1 mmol), triethylamine (1 14 µL, 0.82 mmol) and 4-pyrrolidinopyridine (5 mg). The resulting mixture was stirred at room temperature under nitrogen atmosphere for 16 hours. It was diluted with dichloromethane (20 mL), washed with water, 2.0 Maqueous sodium carbonate solution, and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was flash chromatographed on silica gel using ethyl acetate:petro!eum ether (5O:5O→ 100:0) as eluant to give the desired product (3 1 mg, 33%).

Example 16

N-(3-(4-(phenylthio)pyrimidin-2-ylamino)phenyl)-2-cγanoacetamide (Compound 17)-

In a procedure analogous to Example 15, reaction of **Nl-(4-(phenylthio)pyrimidin-2-**yl)benzene-l,3-diamine(80 mg, 0.27 mmol) and cyanoacetic acid (46 mg, 0.54 mmol) furnished the product (46 mg, 47%).

Example 17

N-(3-(4-(pyridin-2-ylthio)pyrimidin-2-ylamiπo)phenyl)acrylamide (Compound 2)

In a procedure analogous to Example 15, reaction of **Nl-(4-(pyridin-2-ylthio)pyrimidin-2-yl)benzene-l,3-diamine** (35 mg, 0.12 mmol) and acrylic acid (16 µL, 0.24 mmol) furnished the product (18 mg, 43%).

Example 18

N-(3-(2-(4-morpholinophenylamino)pyrimidin-4-yl(hio)phenyl)-2-cyanoacetamide (Compound **24)**

In a procedure analogous to Example 15, reaction of 4-(3-aminophenylthio)-N-(4-morpholinophenyl)pyrimidin-2-amine (50 mg, 0.13 mmol) and cyanoacetic acid (23 mg, 0.26 mmol) furnished the product (38 mg, 64%).

Example 19

N-(4-(2-(4-morpholinophe πylamino)pyrimidin-4-ylthio)phenyl)-2-cyanoacetamide (Compound **26)**

In a procedure analogous to Example 15, reaction of 4-(4-aminophenylthio)-N-(4-morpholinophenyl)pyrimidin-2-amine (60 mg, 0.16 mmol) and cyanoacetic acid (46 mg, 0.32 mmol) furnished the product (48 mg, 68%).

Example 20

N-(3-(2-chloropyrimidin-4-ylthio)phenyl)acrylamide

In a procedure analogous to Example 15, reaction of 3-(2-chloropyrimidin-4-ylthio)benzenamine (300 mg, 1.26 mmol) and acrylic acid (173 μL, 2.52 mmol) furnished the product (250 mg, 68%).

Example 2 1

N-(4-(2-chloropyrimidin-4-ylthio)phenyl)acrylamide

In a procedure analogous to Example 15, reaction of 4-(2-chloropyrimidin-4-ylthio)benzenamine 2-chloro-4-(4'-aminothiophenyl)pyrirnidine (800 mg, 3.37 mmol) and acrylic acid (463 μL, 6.74 mmol) furnished the product (550 mg, 56%).

Example **22**

N-(4-(4-(4-methoxyphenylthio)pyrimidin-2-ylamino)phenyI)acrylamide **(Compound** 39)

In a procedure analogous to Example 15, reaction of Nl-(4-(4-methoxyphenylthio)pyrimidin-2-y!)benzene-l,4-diamine (80 mg, 0.23 mmol) and acrylic acid (24 μL, 0.46 mmol) furnished the product (48 mg, 55%).

Example 23

N-(4-(4-(4-methoxyphenylthio)pyrimidin-2-ylamino)phenyl)methacrylamide (Compound 41)

In a procedure analogous to Example 15, reaction of Nl-(4-(4-methoxyphenylthio)pyrimidin-2-yl)benzene-l,4-diamine (80 mg, 0.23 mmol) and methacrylic acid (50 mg, 0.46 mmol) furnished the product (42 mg, 47%).

Example 24

N-(4-(2-(4-morpholinophenylamino)pyrimidin-4-ylthio)benzyI)acrylamide (Compound 111)

In a procedure analogous to Example 15, reaction of 4-(4-(aminomethyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-amine (70 mg, 0.18 mmol) and acrylic acid (19 mg, 0.27 mmol) furnished the product (22 mg, 27%).

Example 25

4-(2-(4-Morpholinophenylamino)pyrimidin-4-ylthio)-N-(cyanomethyl)benzamide (Compound 72)

In a procedure analogous to Example 15, reaction of 4-(4-(aminomethyl)phenylthio)-N-(4-morpholinopheny-l)pyrimidin-2-amine (70 mg, 0.18 mmol) and cyanoacetic acid (23 mg, 0.27 mmol) furnished the product (5 mg, 6%)

Example 26

N-(3-(2-(4-morpholinophenylamino)pyrimidin-4-ylthio)benzyl)acrylamide (Compound **112)**

In a procedure analogous to Example 15, reaction of 4-(3-(aminomethyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-amine (60 mg, 0.15 mmoi) and acrylic acid (16 mg, 0.23 mmol) furnished the product (21 mg, 31%).

Example 27

(3-(2-(4-Morpholinophenylamino)pyrimidin-4-ylthio)phenyl)methanol (Compound **62)**

To a stirred mixture of methyl 3-(2-(4-morpholinophenylamino)pyrimidin-4-ylthio)benzoate (4.00 g, 9.46 mmol) in anhydrous tetrahydrofuran, was added lithium aluminum hydride (360 mg, 9.46 mmol) in small portions while the mixture was gently warmed to 40 ^{0}C. The mixture was stirred at this temperature for about 4 hours. It was then cooled on an ice bath, cold 10% aqueous sodium bicarbonate solution was added slowly to quench the reaction. The whole mixture was partitioned between ethyl acetate and 10% aqueous sodium bicarbonate solution. The aqueous layer was re-extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4). Removal of the solvent in vacuo afforded the product (2.50 g, 80%).

Example 28

4-(3-(Bromomethyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-amine (Compound **132)**

To a stirred mixture of tetrabromomethane (370 mg, 1.12mmol) and triphenylphosphine (293 mg, 1.12 mmol) in dichloromethane (10 mL), was added (3-(2-(4-

morpholinophenylamino)pyrimidin-4-ylthio)phe πyl)methanol (400 mg. I 0 1 mmol) portionwise. After being stirred at room temperature for 1 hour. another batch of tetrabromomethane (370 mg, 1. 12mmol) and triphenylphosphine (293 mg. I 12 mmol) was added to the mixture and the whole was stirred at room temperature for I hour Al! of the volatiles were removed in vacuo, and the residue was flash chromatographed on silica gel using ethyl acetate:dichloromethane (0: 1oo→ 10:90) as eluant to give the product (208 mg. 45%)

Example 29

2-(l-(3-(2-(4-Morpholinophenylamino)pyrimidin-4-ylthio)benzyl)-lH-imidazol-4-yl)acetonitrile (Compound 128)

To a stirred mixture of 4-(3-(bromomethyl)phenylthio)-N-(4-morpholinophenyl)pyrimidin-2-amine (100 mg, 0.22 mmol) and 4-cyanomethyl imidazole (47 mg, 0.44 mmol) in dimethyl formamide (2 mL), was added cesium carbonate (154 mg, 0.44 mmol) in one portion. The mixture was stirred at room temperature for 16 hours. It was filtered to remove any inorganic material, and the dimethyl formamide solution was concentrated in vacuo. The residue was column chromatographed on the silica gel using methanol:dichloromethane (4:96) as eluant to give the product (50 mg, 47%).

Example 30

2-(l-(4-(2-(4-Morpholinophenylamino)pyrimidin-4-ylthio)benzyl)-lH-imidazol-4-yl)acetonitrile **(Compound 90)**

In a procedure analogous to Example 29, reaction of 4-(3-(bromomethyl)phenylthio)-N-(4-morpholinopr tenyl)pyrimidin-2-amine (100 mg, 0.22 mmol) and 1,3-imidazole (30 mg, 0.44 mmol) furnished the product (43 mg, 44%).

***Compound** Analysis*

^{1}H NMR data was acquired on a Bruker 300 MHz NMR Spectrometer.

LC-EI-MS **and EI-MS**

General parameters

LC-EI-MS and EI-MS data was acquired on a Waters 2795 Alliance HPLC coupled to a Waters 2996 Photodiode Array Detector and Integrity TMD Electron Impact Mass Spectrometer operating under control of Waters Millenium^{32} software version 4.0 with the settings outlined below.

Mass spectrometer parameters

Helium flow of approximately 0.36 L/min; acquisition mode set to scan: sampling rate of 1 spectra/sec; source temperature 200^{0}C; nebuliser temperature 8O^{0}C; expansion region temperature 75^{0}C; mass range *m/z* 100-550, *m/z* 100-650 or *m/z* 100-700 as required.

HPLC parameters

LC-MS parameters were as described for each of the methods outlined below. EI-MS samples were injected and analysed with no column present, with a solvent flow rate of 0.25 mL/min.

LC-ESI-MS

General parameters

LC-ESI-MS data was acquired on a Waters 2695Xe HPLC coupled to a Waters 2996 Photodiode Array Detector and Waters ZQ Mass Spectrometer operating under electrospray ionization conditions with Masslynx software version 4.1 with the settings outlined below.

Mass spectrometer parameters

Mass range:	*m/z* 100-650		
Scan time:	0.5		
Inter scan delay:	0.1		
Desolvation gas:	500 L/h N_2	Capillary:	+3 3 kV
Cone Gas:	100 L/h N_2	Cone Voltage:	+30 V
Desolvation Temperature:	400 ^{0}C	Extractor:	3 V
Source Temperature:	12O^{0}C	RF lens:	0.0 V

HPLC parameters:

Were as described for each of the methods outlined below.

Specific LC-MS **method details**

Method A (LC-EI-MS)

Solvent Gradient :

Time	% MilliQ water	% ACN	% (0.5% aq formic acid)	Curve
0	90	0	10	-
0.5	90	0	10	6
7.5	0	90	10	6
10.5	0	90	IO	6
11.5	90	0	10	6
14.5	90	0	10	6

Flow rate : 0.25 mL/min

Column Heater : 35 ^{0}C

Column: one of

- Alltima HP C_{18} 2.1 x 150 mm, 5 micron
- XTerra MS C,g, 3.0 x 100 mm, 3.5 micron
- XBridge C_{18}, 3.0 x 100 mm, 3.5 micron

Method B (LC-EI-MS)

Solvent Gradient :

Time	% MilliQ water	% ACN	Curve
0	90	10	-
7	0	100	6
9	0	100	6
10	90	10	6
13	90	IQ	6

Flow rate: 0.25 mL/min

Column: one of

- Alltima HP C_{18} 2.1 x 150 mm, 5 micron
- XTerra MS C_{18}, 3.0 x 100 mm, 3.5 micron
- XBridge Qg, 3.0 x 100 mm, 3.5 micron

Method C **(LC-ESI-MS)**

Solvent Gradient :

Time	% MilhQ water	% ACN	Curve
0	90	IO	1
5	0	100	6
6	0	100	6
7	90	IO	6
10	90	10	6

Flow rate : 0.25 mL/min

Column: XTerra MS ds, 2.1x 50 mm, 3.5 micron

Method D (LC-ESI-MS)

Solvent Gradient :

Time	% MilliQ water	% ACN	% 0.5% formic acid (aq)	Curve
0	90	0	10	1
0 5	90	0	10	I
5 5	0	90	10	I
7 5	0	90	10	6
8 5	90	0	10	6
II 5	90	0	10	6

Flow rate : 0.25 mL/min

Column: XTerra MS Qg, 2.1x 50 mm, 3.5 micron

Method E (LC-ESI-MS)

Solvent Gradient :

Time	% MilliQ water	% ACN	Curve
0	90	10	
7	0	100	6
9	0	100	6
10	90	10	6
13	90	10	6

Flow rate : 0.25 mL/min

Column one of

- Alltima HP C18, 2 1x 150 mm. 5 micron
- XBπdge Cl8. 3 Ox 100 mm. 3 5 micron

Method F (LC-ESI-MS)

Solvent Gradient

Time	% MilliQ water	% ACN	Curve
0	90	10	I
5	0	100	6
6	0	100	6
7	90	10	6
10	90	10	6

Flow rate 0 25 mL/min

Column Alltima HP Cu, 2 1x 150 mm, 5 micron

Method G (LC-ESI-MS)

Solvent Gradient

Time	% MilliQ water	% ACN	% 0 5% formic acid (aq)	Cur\ e
0	90	0	10	I
0 5	90	0	10	I
5 5	0	90	10	1
7 5	0	90	10	6
8 5	90	0	10	6
I1 5	90	0	10	6

Flow rate 0 25 mL/min

Column Alltima HP Cig, 2 1x 150 mm, 5 micron

Method H (EI-MS)

Flow rate 0 25 mL/mιn ACN

Column None

Method I (LC-ESI-MS)

Solvent Gradient

Time.	% MilhQ water	% ACN	Curve
0	90	10	
7	0	- 100	6
9	0	100	6
IO	90	10	6
13	90	10	6

Flow rate : 0.25 mL/min

Column: XTerra MS Cis, 3 0 x 100 mm. 3.5 micron

Example 3 1 - Enzyme Screening

Compound **Dilution**

For screening purposes, compounds (in 100% DMSO) were warmed at 37 degrees for at least 20 minutes before use. A 20 μm stock was initially made in assay buffer, where the final concentration of DMSO was 0.3%. The stocks were then diluted in 384 well Optiplates (Packard) where the final concentration of the compound was 5 M.

Tyrosine Kinase Domain Production

Kinase domains were produced using the following procedures.

JAKl

The kinase domain of human JAKl was amplified from U937mRNA using the polymerase chain reaction with the following primers:

XHOI-JI 5'-CCG CTC GAG ACT GAA GTG GAC CCC ACA CAT-3' [SEQ. ID. NO. 5]

Jl-KPNI 5'-CGG GGT ACC TTA TTT TAA AAG TGC TTC AAA-3' [SEQ. ID. NO. 6]

The JAKl PCR products were cloned into the pDest20 destination vector (Gibco). The JAKI plasmid was then transformed into competent DHlOBac cells (Gibco), and the recombinant baculovirus was prepared via Sf9 insect cell transfection.

JAK2

The kinase domain of human JAK2 was amplified from U937mRN A using the polymerase chain reaction with the following primers:

SALI-jk2 5'-ACG CGT CGA CGG TGC CTT TGA AGA CCG GGA T-B' [SEQ ID NO. 7]

jk2-N0TI 5'-ATA GTT TAG CGG CCG CTC AGA ATG AAG GTC ATT T-3' [SEQ ID. NO. 8]

The JAK2 PCR products were cloned into the pDest20 destination vector (Gibco) The JAK2 plasmid was then transformed into competent DHlOBac cells (Gibco). and the recombinant baculovirus was prepared via Sf9 insect cell transfection.

JAK3

The kinase domain of human JAK3 was amplified from U937mRNA using the polymerase chain reaction with the following primers:

XHOI-J3 5'-CCG CTC GAG TAT GCC TGC CAA GAC CCC ACG-3' [SEQ ID NO. 9]

J3-KPNI 5'-CGG GGT ACC CTA TGA AAA GGA CAG GGA GTG-B ' [SEQ. ID NO. 10]

The JAK3 PCR products were cloned into the pDest20 destination expression vector (Gibco) The JAK3 plasmid was then transformed into competent DHlOBac cells (Gibco), and the recombinant baculovirus was prepared via Sf9 insect cell transfection.

HCK:

The kinase domain of Human hemopoietic cell protein-tyrosine kinase (HCK) between L212 and P505 (accession number M16592) was amplified from U937 mRNA using the polymerase chain reaction.

The PCR product was cloned into the pDest20 destination vector (Gibco). The plasmid was then transformed into competent DHlOBac cells (Gibco) to produce a HCK bacmid. The recombinant baculovirus was prepared via Sf9 insect cell transfection with bacmid DNA.

CSF-IR (FMS)

The kinase domain of human CSFl-R from codon 1553 to Q961 was cloned into the pDest20 expression vector (Invitrogen). The CSFl-R plasmid was then transformed into competent DHlOBac cells (Gibco), and the recombinant baculovirus produced prepared for transfection into Sf9 insect cells.

Large Scale **Production of Kinase Domains**

Baciilovirus preparations from each of the constructs were infected into either one or five litres of Sf9 cells (Invitrogen) grown in SF-900 medium (Invitrogen) to a cell density of approximately 1-2 X IO^6 cells/ml Cells were infected with virus at a MOI of 0.8-3.0. Cells were harvested and lysed Tyrosine kinase domains were purified by affinity chromatography on a glutathione-agarose column (Scientifix Pty. Ltd. catalog #: GSH-200)

FLT-3 tyrosine kinase enzyme was purchased from Upstate Cell Signalling Solutions, CA, USA (flt-3 catalog #. 14-500)

Assay **Protocols**

Kinase assays were performed in 384 well Optiplates (Packard) using an AIphascreen Protein Tyrosine Kinase PYlOO detection kit The compounds were pre-incubated with affinity purified PTK domain in the presence of phosphotyrosine assay buffer (IOmM HEPES, pH 7.5, 10OmM $MgCI_2$, 25mM NaCI. 20OmM sodium vanadate and 0.1% Tween 20) for 20 minutes. The compounds were then incubated with substrate in the presence of ATP. The substrate used was susbtrate-1 with the sequence biotin-EGPWLEEEEEA YGWMDF-NH_2 [SEQ. ID. NO. 13] (final concentration 111LI M). For HCK 80μm ATP was used and incubated for 60 minutes. AIphascreen phosphotyrosine acceptor beads followed by streptavidin donor beads at a concentration of 1/100 in stop buffer were added to each well under subdued light and incubated for 2-3 hours. , The AIphascreen plates were read on a Packard Fusion *Alpha* instrument.

Results

The enzyme assay results for selected compounds are given below in Table 2, where +++ is< 10OnM, ++ is <500nM and + is < 1μM

Example 32 - Cellular screening

Compound Dilution

For screening purposes, compounds were diluted in 96 well plates at a concentration of 20μM. Plates were warmed at 37°C for 30 minutes before the assay was performed.

Establishment of the TEL:JAK2 cell line

The coding region encompassing nucleotides 1-487 of TEL was amplified by PCR using the oligonucleotides 5TEL (5'-GGA GGA TCC TGA TCT CTC TCG CTG TGA GAC-3') [SEQ ID NO 14] and 3TEL (5'-AGGC GTC GAC TTC TTC TTC ATG GTT

CTG-3´) [SEQ ID NO 15] and U937 mRNA as a template. A BamHl restriction site was incorporated into the 5TEL primer, and a Sal I restriction site was incorporated into the 3TEL primer. The regions encompassing the kinase domain of JAK.2 (nucleotides 2994-3914; JAK2F 5´-ACGC GTC GAC GGT GCC TTT GAA GAC CGG GAT-3' [SEQ ID NO 16]; JAK2R 5´-ATA GTT TAG CGG CCG CTC AGA ATG AAG GTC ATT T-3´) [SEQ ID NO 17] and JAK3 (nucleotides 2520-3469; JAK3F 5´-GAA GTC GAC TAT GCC TGC CAA GAC CCC ACG ATC TT-3´) [SEQ ID NO 18] were generated by PCR using Taq DNA polymerase (Gibco/BRL) and 1)937 mRNA as a template. A Sal I restriction site was incorporated into the forward primer of JAK2 and JAK3. a Not I site was incorporated into the JAK2 reverse primer and a Xba I site was added to the reverse primer of JAK3.

A TEL/Jak2 fusion was generated by digestion of the TELPCR product with BamH 1/Sal I restriction enzymes, digestion of the JAK.2 PCR product with Sal I/Not I restriction enzymes, followed by ligation and subcloning of the ligation product into the mammalian expression Vector pTRE 2 (Clontech), which was prepared by digestion with BamH I- Not I restriction enzymes, to give the the TEL/Jak2 fusion plasmid pTELJAK2.

The TEL/Jak3 fusion was prepared by ligation of the JAK3 Sal I/Not I cleaved kinase domain PCR product with the BamH I/Sal I restriction digested TEL product, followed by ligation of the ligation product into the BamH I/Not I digested pTRE2, to give the TEL/Jak3 fusion plasmid pTELJAK3.

The growth factor dependant myelomonocytic cell line BaF3 bearing the pTET-off plasmid (Clontech) was transfected with either pTELJAK2 or pTELJAKJ, and the transfected cells were selected for growth-factor independent cell growth. The BaF3 wild-type cells were cultured in DMEM containing 10% FCS, 10% WEHl 3B conditioned medium. The BaF3 TELJAK cells (BafT_J2 or BafT_J2) were cultured in DMEM 10% Tet-System Approved FBS (without WEHI 3B conditioned medium).

Cellular assays **were performed as follows:**

Cell suspensions were prepared by harvesting cells from culture (the cells used in this test were in late log phase growth with high viability.) Cells were diluted in the appropriate growth medium, as described above, to L Ix final concentration (from 50,000 cell/mL to 200,000 cell/mL, depending on cell line).

Compounds to be tested were added (lOμL, IOX final concentration) to a flat bottomed 96-well plate. The cellular suspension (90μL per well) was then added, and the plate incubated for 40 hr at 37°C, 5% CO_2. Alamar Blue lOμL per well was added and the

plates returned to the incubator for a further 4-6 hours The plates were then read at 544 nm

Results

Cellular assay result are given in table 2 where +++ is <1μM. ++is<5μM and +is <20μM

Table 2

CmpdNo	JAK1 IC50_nM	JAK2 IC50_nM	JAK3 IC50_nM	FMS, FLT3, or HCK IC50_nM	BafT_J2 IC50_nM	BAF3wt IC50_nM	BafT_J3 IC50_nM	CTLL2 IC50_nM
2	>1000	>1000	+++		++	++	+++	++
3	>1000	>1000	+++					++
7		>1000	+++		+	+	++	++
8		>1000	+++		++	+	++	+
13		>1000	+++		+	>20000	>20000	>20000
16		>1000	+++		++	+	+++	++
23	>1000	>1000	+++		+	+	+++	+++
24	>1000	++			+	+	+	+
25	>1000	>1000	+++		>20000	>20000	+++	+++
27	+	++	+		>20000	+	+	++
31		>1000	+++		+	+	+++	+++
38				++ (FMS) ++ (HCK)				
42	>1000	>1000	+++		+	+	++	++
52		>1000		++ (FLT3)	++		++	
62	>1000	++	++	+++ (FLT3)	+	+	+	+
67	+	++	++	+++ (FLT3)	+	+	+	+
68	+	+++	++	++ (FLT3)	+	>20000	+	>20000
74		>1000	+++		>20000	>20000	+++	++
75	++	+	++		+	+	+	+
77	>1000	>1000	+++	++ (FMS)	++	++	+++	+++
82	>1000	>1000	+++	++ (FMS)	++	+	++	+
86		>1000	++		+	++	++	++
87		>1000	+++		++	++	+++	+++
88		>1000	++		++	++	++	+
90		>1000	++		++	+		++
91		>1000	+++		+	>20000	+++	+++
97		>1000	+++		++	+	+++	+++
99		>1000	+++		>20000		+++	
101		>1000	>1000	+++ (FMS)	++	+++	+++	+
104		>1000	+++		>20000	>20000	++	++
105		>1000	+++		+	>20000	+++	+
109	>1000	+	++		+	+	+	>20000
110	>1000	>1000	+++		+	+	+++	++
111	>1000	>1000	+++		+	+	+++	++
112	>1000	>1000	+++		+	>20000	+	+
117		>1000	++		+	++	>20000	+

118		>1000	+++		++	>20000	++	>20000
120		>1000	+++		+	>20000	+++	++
123	>1000	>1000	+++		++	++	++	+
124		>1000	+++	++ (FMS)	>20000	>20000	+++	+++
125		>1000	+++		+	>20000	++	++
126		++	+++		++	>20000	++	++
127		+	++		+	>20000	+	+
131		>1000	+++		+	++	++	+
135		>1000	++		+		>20000	
136		>1000	++		>20000	>20000	>20000	>20000
148		>1000	++		+	+	+	+
149		>1000	++		++	++	++	+
154		>1000	++		++	++	++	++
155	>1000	>1000	+++		+	+	+	++
156	>1000	>1000	+++		++	++	++	++
161		>1000	+++		>20000	>20000	+++	++
162	++	+	+++		+	+	++	++
163	>1000	>1000	+++		>20000	>20000	+++	+++
164		>1000	+++		+	>20000	+++	+++
165	>1000	>1000	++		>20000	>20000	>20000	>20000
166		>1000	++		++	+	+	+
168		>1000	+++					
169	>1000	>1000	+++					
170		>1000	+++					
171		>1000	+++		>20000	>20000	++	+
173	++	++	+++		+	+	+++	+++
176		+	+		++	++	++	++
188		++	+++		>20000	>20000	>20000	>20000
189		>1000	++		+	+	+	>20000
190		++	+++		>20000	>20000	>20000	>20000
191		>1000	++		++	++	++	++
193	>1000	>1000	+++		++	++	+++	+++
194	>1000	>1000	+++		++	++	+++	+++
195		>1000	+++		>20000	>20000	+	>20000
197		>1000	+++		>20000	>20000	>20000	>20000
199		+	++		+	+	+	+
201	>1000	>1000	+++		++	++	++	++
202		+	++		++	+	++	++
203		+	++		+++	+++	+++	+++
204		+	++		++	+	+	+
207		>1000	++		>20000		>20000	
210		>1000	++		>20000	>20000	>20000	>20000
212		++	++		>20000	>20000	>20000	>20000
218		>1000	++		>20000	>20000	+	>20000
219		>1000	++		++	++	++	>20000
220		++	+++		++	++	++	+++
221		>1000	++			+++		+++
222		>1000	++		>20000	>20000	>20000	>20000
223		>1000	++		++	++	+	++
224		+	++		>20000	+	>20000	>20000

225		>1000	++		++	++	++	++
226		>1000	++		++		++	
228		>1000	+++		>20000	>20000	>20000	>20000
229		+	++		+	+	+	+
230	+	++	+++		>20000	>20000	>20000	>20000
231	>1000	>1000	+++		+	>20000	+	+
232		>1000	+++		+		++	
233		>1000	+++		++	++	+++	++
235		>1000	+++		+		+++	
237		>1000	+++		++	+++	+++	+++
238		>1000	+++		++		+++	
239	++	+	+++		++	++	+++	+++
240		>1000	++		++	+++	++	++
241	>1000	>1000	+++		++	+	+++	+++
242		>1000	++		>20000	>20000	+	>20000
243	>1000	>1000	+++		++	++	+++	+++
244		++	+++		++	++	++	++
245		++	++		+++	+++	+++	++
246	>1000	>1000	+++		++		+++	
248	>1000	>1000	+++		+	++	+++	+++
249		>1000	+++		++	++	+++	+++
251		>1000	+++		>20000	>20000	>20000	>20000
252		>1000	+++		>20000	>20000		+++
253		>1000	+++		+	>20000	+++	+++
254		>1000	+++		++	++	+++	+++
255		+	++		+	+	+	>20000
259		>1000	+++		+	+	+++	+++
260		>1000	+++		>20000	>20000	++	++
261	>1000	++	+++		>20000	>20000	+++	+++
262		++	++		+	>20000	>20000	>20000
263		>1000	++		++	++	++	>20000
264		>1000	++		++	++	++	++
267	>1000	>1000	+++		++	++	+++	+++
268	>1000	>1000	+++		>20000	>20000	+++	+++
269		>1000	+++		+		+++	
276		>1000	+++		+	+	+++	+++
277		>1000	+++		++	>20000	+++	+++
278		>1000	+++		++		+++	
279		>1000	+++		+	+	+	+
280	>1000	>1000	+++		+	+	+++	+++
281		>1000	+++		+	+	+++	+++
282		>1000	+++		+	+	+++	+++
283		>1000	+++		+	+	+++	+++
284		>1000	+++		+	+	+++	+++
285	>1000	>1000	+++		++	++	+++	+++
286	>1000	>1000	+++		>20000	>20000	+++	+++
287		>1000	+++		>20000		+	
288	>1000	>1000	+++		+	+	+++	+++
289		>1000	+++		+	>20000	++	+++
290	>1000	>1000	+++		+	++	+++	+++

291	>1000	>1000	+++		++	++	+++	+++
292		>1000	+++		>20000	>20000	++	++
293	>1000	>1000	+++		++	++	+++	+++
294		>1000	+++		>20000	>20000	+++	+++
295	>1000	>1000	+++		>20000	>20000	+++	++
296	>1000	>1000	+++		++	++	+++	+++
297	>1000	>1000	+++		+	+	+++	+++
298		>1000	+++		+	+	+++	+++
299	>1000	>1000	+++		+	+	+++	+++
301		>1000	+++		+	+	+++	+++
306	>1000	>1000	+++		>20000	>20000	+++	+++
307		>1000	+++		>20000	>20000	+	>20000
309		>1000	++		++	++	++	+++
313		>1000	+++		>20000	>20000	+++	++
315		>1000	+++		>20000	>20000	+++	+++
318		>1000	+++		>20000	+	>20000	+
328		>1000	+++		+++	++	++	++
331		>1000	++					
332		>1000	+++		++	++	+++	++
340	>1000	>1000	+++		+	++	+++	++
342		>1000	+++		>20000	>20000	++	+
343		>1000	+++		+	+	++	++
346	>1000	>1000	+++		+++	+++	+++	+
347		>1000	+++		>20000	>20000	+++	++
348		>1000	+++		++		++	
350		>1000	+++		+	>20000	+	+
352		>1000	+++		+	>20000	+	+
353		>1000	+++		+	>20000	++	++
354		>1000	+++		+	+	+	+
355		>1000	+++		+	+	++	++
356		>1000	+++		+	+	++	++
357		>1000	+++		++		++	
361		>1000	+++		++	>20000	++	>20000
363		>1000	+++					
364		>1000	+++		++	+	+++	+++
365		>1000	+++		+	+	++	+
366		>1000	+++		+	+	++	++
367		>1000	+++		+	+	++	+
368		>1000	+++		+	+	++	++
370		>1000	+++		+	+	++	++
371		>1000	+++		+	+	++	++
372		>1000	+++		++	++	++	++
373		>1000	+++		++	++	++	++
374	>1000	>1000	+++		++	++	+++	+
378		>1000	++		+++	+++	+++	>20000
380	>1000	>1000	+++		>20000	>20000	>20000	>20000
381		>1000	++		>20000	>20000	+	+
382	>1000	>1000	+++		+	+	+	+
383		++	+++		+	+	>20000	+
384		++	+++		>20000	>20000	>20000	>20000

385	>1000	>1000	+++		>20000	>20000	+++	++
386		>1000	++		>20000	>20000	>20000	>20000
387		+	+++		>20000	>20000	>20000	>20000
388		++	+++		++	++	++	++
389	>1000	>1000	+++		+	+	+++	+++
390		++	+++		++	++	++	++
393		>1000	+++		+	>20000	+++	++

Additional Enzyme Screening

Further enz>me assa\s were conducted at Upstate Biotechnolog) (Dundee UK) in the *KιπaseP ιofu*e> ᵀᴹ Assay system

The general protocol is as follows All kinases are pre-diluted to a 10x working concentration pπor to addition into the assa\ The composition of the dilution buffer for the kinases is 20 niM MOPS pH 7 0, I in M EDTA, 0 1% β-mercaptoethanol. 0 0 1% Brȷ-35. 5% glycerol, I mg/ml BSA All substrates are dissolved and diluted to working stocks in de-ionised water

The results are outlined in Table 3 expressed as % inhibition

TABLE 3: Percent inhibition at 50OnM

Compound Number	Blk(m)	Bmx(h)	BTK(h)	Flt1(h)	Flt4(h)	KDR(h)
23	97	100	84			
25	71	97	83			
42	59	100	100			100
51	29	100	100			100
59	100	100	100			100
71	49	36	27			90
74	100	100	100			100
77	100	100	100			100
87	100	100	100			100
97	100	100	100			100
99	100	100	100			100
104	30	100	73			
105	100	100	100			100
110	100	100	100			100
111	100	100	100			100
112	100	100	100			100
115	100	100	100			100
118	100	100	100			100
120	100	100	100			100
123	100	100	100			100
124	100	100	100	100	100	100
125	100	100	100			100
126	43	78		93	99	95
131	100	100	100			100
352	100	100	100			100
353	100	100	100			100

350	100	100	100			100
350	100	100	100			100
351	100	100	100			100
354	100	100	100			100
201	100	100	100			100
161	100	100	100			100
357	48	48		76	99	95
233	85	89		99	99	98
162	50	55		82	98	95
163	95	85		83	99	92
237	96	92		98	99	97
165	0	40		43	99	86
164	62	87		44	97	83
364	81	73		97	99	96
135	9	58		96	99	95
235	86	79		86	99	96
238	99	90		97	99	95
307	0	29		19	93	72
168	98	92		66	99	96
170	96	97		74	99	97
241	98	92	88	100	100	97
280	99	98	97	100	100	97
285	97	98	91	95	98	94
173	93	94	93	95	98	96
239	99	99	97	100	100	96
243	99	96	97	100	100	97
286	88	95	74	98	100	94
288	99	100	98	100	100	94
340	99	92	97	100	95	94
374	96	91	96	100	100	96
291	99	99	95	100	100	96
246	97	98	97	100	100	93
267	96	89	94	100	100	94
290	97	97	94	100	100	95
248	92	91	80	95	100	95
293	30	79	55	79	100	95
294	37	92	77	94	100	93
292	10	59	3	67	100	96
231	82	99	91	95	100	99
155	40	86	81	74	99	98
156	41	83	81	80	94	97

Example *33*

The effect of the compounds on tumor initiation, progression and metastasis can be evaluated in relevant *in vivo* animal efficacy models Models could be human tumor xenografts models in immuno-deficient mice, from human tumor cell lines or preferably from primary or metastatic human tumors Other models might be human tumor xenografts grown in orthotopic sites, models of disseminated disease and transgenic or

labeled tume[models Models could also include surgical resection of pπman rumor and evaluation of metastatic disease

Models could be selected to ensure that the molecular drug targeted is expressed Examples of tumors display ing deregulation of the JAK/STAT pathway include prostate carcinoma breast cancer colon carcinoma, including leukemia lymphoma m>eloma oxaπan tumors melanoma, lung carcinoma, glioma, renal-cell tumors Cfficac) can be measured in these models *b*\ various outcomes depending on tumor type (solid leukemia or metastatic) and might include measure of tumor onset tumor growth rate tumor burden tumor growth dela\ tumor cell kill, incidence of metastasis imaging of tumor and invasiveness/metastasis by various approaches including labeled cells or ieagents, survival angiogenesis histopathology

Ί he *in vivo* animal efficacy models might also be used for determination of the additivitv or synergy of the effect of the compounds in combination with other drugs,

Rheumatoid arthritis (RA) is a chronic, destructive inflammatory polyarticular joint disease characterised by passive synovial proliferation and subintimal infiltration of inflammatory cells Although the aetiology remains to be elucidated, it is generally acknowledged that RA is an autoimmune disease and arthritis is a consequence of loss of tolerance against a cartilage specific autoantigen In this context, animal models have been established that evolves around induction of RA by an autoantigen such as 1 type Il collagen-induced arthris (CIA) and 2 a combination of an antigen from gram-ve bacteria (LPS) with a panel of 4 monoclonal antibodies (mAb) A third model of arthritis is the Adjuvant-induced arthritis (AIA) which is performed mainly in rats The underlying mechanism of AIA is still controversial However, a 65 kD myobacterial heat shock protein was shown to share a nonapeptide sequence in the core protein molecule of proteoglycan, and suggests that AIA is also a disease inducible by autologous antigen

In AIA, eight-week old Lewis rats were given Complete Freund's Adjuvant (CFA) prepared by suspending as an emulsion of heat-killed Mycobacterium butyricum in liquid paraffin at 12mg/ml CFA- induced arthritis can be stimulated by injection of 50 µl of CFA emulsion intradermally either in to the footpad or to the base of the tail From day 7 (onset of arthritis), rats are examined daily for clinical arthritic score on a 0-4 scale 0, normal, 1, minimal swelling, 2, medium swelling, 3, severe swelling, and 4 severe and non-weight bearing For each limb, the mid-forpaw, the wrist, the joints of the fingers, the midfoot, the ankle and the joints of the digits are scored giving a maximum clinic! score of 48 per rat The animals are sacrificed on day 17 and the

hindpaw s are amputated and fixed in 7 4^0O formalin After decalcification and embedment in paraffin the limbs are sectioned in a mid-sagittal plane stained b\ eosin and hematoxylin and examined microscopical!} for pannus formation (cartilage and bone erosion and destruction), vascularity (blood vessel formation by CD3 I staining) and mononuclear cell infiltration (T.B and macrophages)

In CIA. DBA/1 mice that bear H-2q MHC haplotype are used as they are more susceptible to CIA In general heterologous collagen is used as the) are more immunogenic/arth πtogenic tha homologous type II collagen The mice are primed with an emulsion consisting of bovine type Il collagen and Complete-Freu πd's Adjuvant at a I I ratio (final concentration = 2 mg/ml) The emulsion (0 ImI) is injected into the tail of each mouse approximately 1-2 cm from the base A whitish bolus beneath the dermis should be visible A type Il collagen booster (200μg per mouse) is given intraperitoneally in PBS on day 2 1 High CIA-susceptible mice (DBA/I) generally develop arthritis 4-5 weeks after initial priming Fully developed arthritis including red and swollen paws, can be observed 3-5 days after the onset and active inflammatory arthritis persists more than 3-4 weeks Although inflammation will eventually subside, joint damage as seen as ankylosis is permanent Assessment of CIA symptoms is essentially similar to the AIA model in which clinical signs is assigned clinical score (0-4) based on the severity of the disease Histological measurements can also be performed on formalin-fixed joints to assess erosin, cellular infiltrates and hyperplasia

In combined LPS-mAB induced Arthritis, a severe and consistent arthritis can be induced in mice by a combination of LPS and mAB cocktail that recognize individual epitopes clustered within an 83 amino acid peptide fragment located within CBl I region of type II collagen This model was developed based on the hypothesis that bacterial toxin(s) absorbed through the GI tract play a synergistic and pathologic role with sub-arthritogenic levels of autoantibodies to type II collagen in triggering RA The advantages of this model are: I. synchronized arthritis (100%) is induced rapidly within 7 days 2. a variety of mouse strains can be used as administration of anti-type II collagen mAB cocktail bypasses the requirement for the host's generation of autoantibodies to type II collagen thus arthritis can be induced in mice that do not possess CIA-susceptible MHC haplotypes and 3. ease of administration of mAB and LPS by either i v. and i.p routes

Inflammmatory Bowel Diseases (IBD) which includes Crohn's disease (CD) and ulcerative colitis (UC) represents a group of chronic disorders characterized by

inflammation of the gastrointestinal tract CD can affect am pan of the digestiv e track whereas UC affects oπl\ the colon and rectum UC causes inflammation and ulcers usualh in the sigmoid colon and rectum Cellular iπfilttates are complex and pro-inflammatory cytokines are evident in CD and UC

An experimental model of UC is established in Balb/C mice by administration of dextran sulphate sodium (3%DSS) isolated from *Leuconostoc spp* into the drinking water The experiment has a relative!) short time-course (8 days) and parameters for assessment of colitis include loss ol body weight, stool consistency, rectal bleeding, shortening of colonic length , crypt damage and cytokine analysis of colonic rings

In CD, Balb/C mice are sensitized at day 0 with 2 x 50 μl of 5 mg/ml of dinitrofluobenzene (DNFB) epicutaneously to shaved abdomen and feet on two consecutive days DNFB is typically solubilised in acetone olive oil (4: 1). On day 5, the mice are challenged intracolonically with 50μl dintrobezene sulphonic acid (DNS) at 6 mg/ml in iθ% ethanol The mice are sacrificed on day 8 Parameters to be measured include suppression of total blood cell number and cell types, mucosal mast cell protease 1 (MMCP-I) in serum, TNFα level in colon homogenate, stool consistency, vascular permeability and number of colonic patches Number of neutrophils and mast cells which are indicative of colonic damage and cellular influx will also be assessed by histological and microscopical examinations

Asthma is restricted (o human species, but animal models are often used to investigate particular aspects of this human disease Bronchial biopsies and bronchoalveolar lavage (BAL) fluid recovered from patients with asthma have been shown to contain an increased number of activated T cells, B cells, eosinophils and mast cells Many patients with asthma are sensitized and have specific immunoglogulin E (IgE) antibodies to one or more inhalant allergens. Atopy is, considered to be a major cause of asthma. In atopic individuals, inhalation of allergens preferentially induces a T-helper 2 cell (Th2) response. In the majority of current models, mice are sensitized by itraperitoneal (ip) injection of ovalbumin (OVA), often together with a Th2 skewed adjuvant, such as alum. In the classical mouse model for asthma, C57/BL6 mice are actively sensitized on day 0 by ip injection of !0μg of OVA absorbed onto I mg of alum. From day 14-21 the mice are exposed daily to aerosolized OVA over a 30 minute period. On day 22, airway inflammation is apparent. BAL fluid recovered from these animals demonstrate an increase in peri-bronchiolar space consisting of mixed cellular infiltrates of mononuclear cells and eosinophils. OVA-specific IgE antibodies can be

demonstrated in the serum of sensitized animals The mononuclear cell population consists mainly of cells of Th2 phenotype secreting cytokines IL-4 and 1L-5 IL-4 promotes isotype switching of B cells towards IgE synthesis and ILo influences the production, maturation and activation of eosinophils.

The compounds can also be tested in a murine model of JAK2 ^{V6l7F}-positive myeloproliferative disease (IVIPD)

Establishment of JAK2 ^{V6l7F}-positive MPD

Bone marrow from male 5-Flurourac il-treated Balb/c mice could be infected with a JAK2-V6 I7F - GFP retrovirus and retroorbitally injected into lethalh irradiated female recipients. From day 21 on the mice could be monitored by daily inspection and twice weekly blood counts + FACS for GFP-positive cells It would be expected that a rise in hematocrit could occur around day 28 and a rise of the white blood cell count around day 40.

Treatment with compounds

Early intervention group- Treatment would start on day 21 with compound or carrier given per oral gavage (12 mice in each group) Mice could be monitored by daily inspection and twice weekly blood counts + FACS for GFP-positive cells Animals would be sacrificed on day 60 8-12 h after the last drug dose. Moribund mice or mice with a white cell count over 200,000/nl or weight loss > 20% could be sacrificed earlier

Late intervention group- Groups of 3 mice could be sacrificed on day 29, 36, 43, 50 and 57 and bone marrow and spleen could be analyzed for reticulin fibrosis. Treatment could start with compound or carrier given per oral gavage as soon as fibrosis is documented in 3/3 mice. Mice could be monitored by daily inspection and twice weekly blood counts + FACS for GFP-positive cells. Animals could be sacrificed after 30 days of therapy 8-12 h after the last drug dose. Moribund mice or mice with a white cell count over 200,000/nl or weight loss > 20% could be sacrificed earlier Animals could be subjected to necropsy.

Analysis of tissues and survival

Liver and spleen weights could be determined. Tissue sections from bone marrow, liver and spleen could be analyzed by HE stain. Marrow and spleens could also be silver-stained to assess reticulin fibrosis. Spleen and marrow cells could be analyzed by FACS for GFP, lineage markers, JAK2 and STAT5 phosphorylation. Blood could be collected by heart puncture and plasma separated and frozen for drug concentration

meabuiement Sur\ i\al between groups could be compared with the Kaplan-Me\er method

Assessment of the acti\ it> of JAK2 inhibitors in colon} -forming assajs of human hematopoietic ceils

Peripheral blood mononuclear cells from patients with MPD (predominant myelofibrosis) with and without JAK2 X6i?l mutation (N = IO for each) and 5 normal controls (commercial supplier) could be isolated b\ densit) gradient centπfugation (Ficoll) CD34+ cells can be selected using commercial kits to enrich for progenitor cells CD34-I cells can be plated in triplicate in methylcellulose supplemented with fetal bovine serum and c\tokmes (ϟ/ CPO) After incubation of the plates for *7* \seeks erythroid and myeloid colon} formation could be assessed under an inverted microscope

Pulmonary Arterial Hypertension

The compounds of formula I can be tested in the dog model of pulmonary hypertension as described in Gust, R and Schuster, D P Experimental Lung Research, 27 1-12, 200 1 They can also be tested in a rabbit model of monocrotaline induced pulmonary hypertension The compounds of formula I can also be tested in humans with pulmonary arterial hypertension The elfect of the compounds of formula 1 can be tested in humans with pulmonary arterial hypertension by measurement of its acute effects on cardiopulmonary hemodynamics The effect of the compounds on right ventricular pressures, pulmonary artery pressures, pulmonary vascular resistance, and cardiac output may be determined The effect of the compounds on the six minute walk time, and maximal oxygen consumption may be determined in humans with PAH The effect of the compounds on quality of life (as measured by a questionnaire), hospitalization, and survival may be determined in humans with PAH In humans PAH may be caused by genetic abnormalities (ιe , primary or familial PAH) or secondary causes such as scleroderma, uncorrected congenital heart disease, mixed collagen vascular disorder, hepatitis C, or other liver disease, HIV infection, or hereditary hemorrhagic teleangiectasia The effect of the compounds may also be tested on human endothelial cells, fibroblasts and/or smooth muscle cell lines for example, determination of IC50 for STAT3 phosphorylation in human pulmonary artery smooth muscle cell lines Cell lines from other species, ie, the rat may also be examined The effect of the compounds on precontracted vascular rings from human blood vessels, or blood vessels from other species, i e, the rat, may be examined For example, rat pulmonary artery rings preconstricted with phenylephrine, or endothehn, or serotonin,

oi \asopressin. angiotensin Il or KCL may be studied to determine the dose response to the compounds for \asorelaxation Other \asoconstrictors may be examined

The effect of the compounds on hypoxia induced pulmonary vasoconstriction ma) be examined A model of hypoxia induced pulmonary hypertension might include study of rats, such as the Fawn-Hooded rat exposed to low oxygen (ıe . 5 percent oxy gen) Another model of hypoxia induced pulmonary hypertension might include the fetal calf maintained in a high altitude chamber

The effect of the compounds may be examined in transgenic models of pulmonary hypertension i e , the BMPR2 knockout mouse treated with IL6. the caveolm l knock out mouse, or the vasoactive intestinal peptide knockout mouse

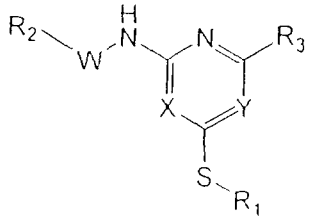
The effect of the compounds on histopathologic changes that occur in both human and animal models of PAH may be measured For example, the compounds may decrease the extent of plexiform lesions in the pulmonary arterioles of diseased lungs The plexiform lesion consists of endothelial cells, smooth muscle cells, and fibroblasts which proliferate and obstruct to a varying degree, the pulmonary arteriolar lumen All publications mentioned in this specification are herein incorporated by reference Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia or elsewhere before the priority date of each claim of this application

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention

CLAIMS

I Λ compound of the general formula I



I

or salts, isomers and/or prodrugs thereof, wherein

X and Y are independently selected from N and CRj.

each R_3 is independently selected from hydrogen, C_{1-6}alkyl, C?^alkenyl, hydroxyl. halogen, nitro, substituted or unsubstituted amino, cyano, nitro, tπfluoromethyl. methoxy, tnfluoromethoxy, aryl and substituted or unsubstituted 5 or 6 membered heterocyclyl containing I to 2 N atoms,

Ri is selected from hydrogen, C_{1-6}alkyl, $C_{1\ 6}$alkylCN, C_{3-8} cycloalkyl. Ci-$_6$alkylenecycloalkyl, ar>'l. C_{1-6}alkylenearyl, heterocyclyl and Ci-$_6$alkyleneheterocyclyl, wherein C,$_{-6}$alkyl, $C_{3\ 8}$cycloalkyl, heterocyclyl and aryl may be optionally substituted with I to 3 substituents selected from R or R_9,

R_9 is independently selected from halogen, substituted or unsubstituted C_{1-6}alkyl, OH, *(O)'*, OCN, substituted or unsubstituted OC,.$_6$alkyl, CN, CF_3.CF_2CN, SCN, $SO_2NR_5R_6$, SR_7, CHO, CO_2R_7, COR^7, $CONR_5R_6$. $CONR_5R_7$, NR_5COR_7, NO_2. NR_5R_6. NR_5CN. CH(CN)NR_5R_6, $NR_5SO_2R_7$, $COCF_3$,-$COCH_2F$, NR_5COCOR_7, NR_5COOR_7, $NR_5CONR_6R_7$, heterocyclyl and COheterocyclyl, wherein each heterocyclyl may be optionally substituted with I to 4 substituents selected from NH_2, CN, OH, CO_2R_7, CH_2CN and 5 membered N-containing heterocyclyl;

R is C$_{1-6}$alkyle πeR_9, OC_{1-6}alkyleneR_9 (except when R_9 is NR_5R_6 or OCi-$_6$alkyl, then R is OC_{2-6}alkyleneR_9), or

R_9 and R together with the groups to which they are attached form a substituted or unsubstituted 5 or 6 membered N-containing heterocyclyl,

R_5 and R_6 are each independently selected from H. C^alkyl, C_{1-6}alkylCN, Q.gcycloalkyl, aryl, heterocyclyl, C_{1-6}alkylene, cycloalkyl, substituted or unsubstituted C_{1-6}alkylene, SO_2C_{1-6}alkyl and C_{1-6}alkylene heterocyclyl, or

R_5 and R_6 together with the nitrogen to which they are attached form a 4-8 membered ring having I to 3 heteroatoms independently selected from NR_8, O, $S(0)_m$ wherein m is O, I or 2 and wherein the ring may be optionally substituted with C_{1-6}alkyl or NR_5R_6;

R_5 is selected from H. $C_{,6}$alkyl. $C_{:6}$alkylene0H C^alk) leneNR,R_{6} $C_{,5}$cycloalkyl and. heterocycl_ I. C_{1_6}alk\ lenecycloalk> I. C_{1-}alk> lenearyl C_{1-6}alkyleneheterocyclyl and C_{1-6}alkyleneCN.

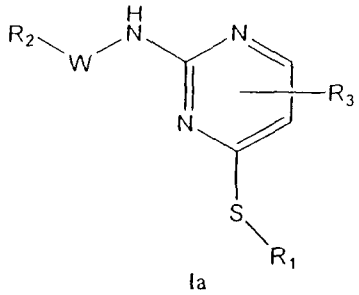
R_7 is selected from H, substituted or unsubstituted C_{1_6}alkyl. substituted or unsubstituted OC_{1-6}alkyl. substituted or unsubstituted SC_{1-6}alkyl. CNOH. C_{1-6}alkyleneCN, substituted or unsubstituted Cj.gcycloalkyl. substituted or unsubstituted aryl. substituted or unsubstituted heterocyclyl.C_{1-6}alkylenecycloalkyl.C_{1-6}alkylenearyl, C_{1_6}alkyleneheterocvclyl. C^alkenyl, $C_{;6}$alkynyl. NR_5R_6 C,^alkyleneNR $_5R_6$ and $C_{,.6}$alkylene0R $_5$,

W is absent, CO. SO_2 or C_{1-6}alkylene,

R_2 is selected from H, C_{1_6}alkyt, C_3gcycloalkyl, aryl and heterocyclyl. each of which may be optionally substituted with I to 4 substituents selected from R and R_9, and wherein each alkenyl and alkynyl may be optionally substituted with I to 3 subsituents independently selected from Ci_{-6}alkyl, CO_2R_7, $CONR_5R_6$, aryl, heterocyclyl, C_{1_6}alklene OH and C_{1_6}alkyleneNH $_2$

2 The compound according to claim I, wherein X is N and Y is CR wherein R_3 is as defined in claim I

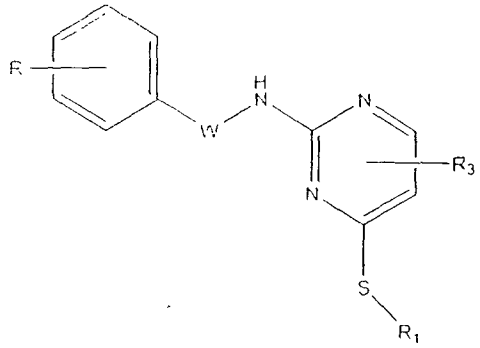
3 The compound according to claim I or claim 2, wherein the compound of formula I has the formula Ia



Ia

wherein W, R_1, R_2 and R_3 are as defined in claim 1

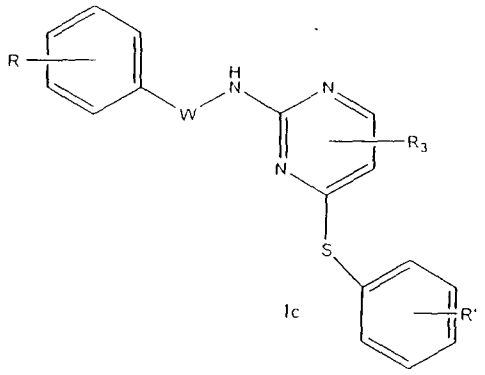
4 The compound according to claim I or claim 2, wherein the compound of formula I has the formula Ib



Ih

wherein W, Ri and R_3 are as defined in claim I and R' is H. R or R_9 as defined in claim I

5 The compound according (o claim I or claim 2, wherein the compound of formula I has the formula Ic



Ic

wherein W, R_3 and R' are as defined in claim 1

6. The compound according to claim 1, wherein W is absent, CO or C_{1-6}alkylene

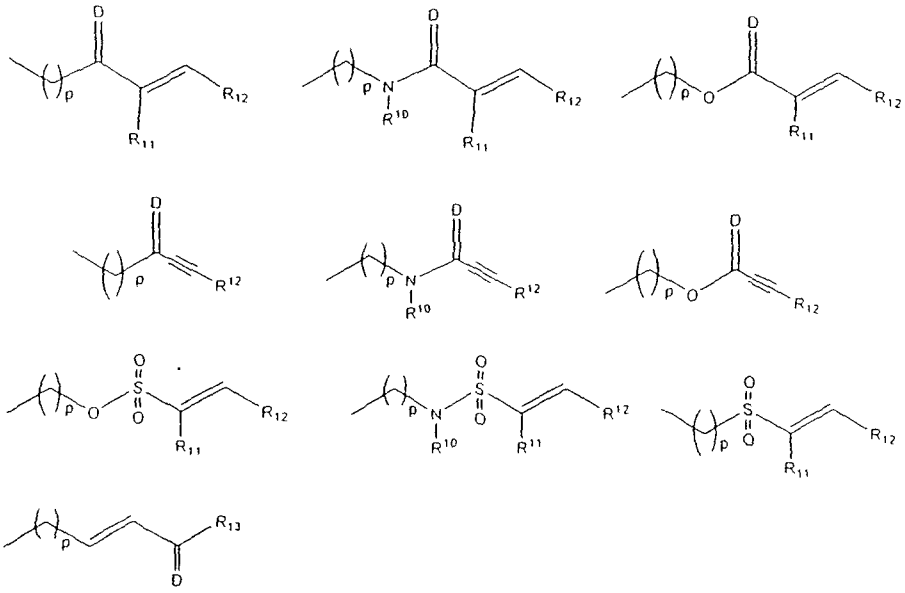
7. The compound according to claim I, wherein Ri is aryl; heterocyclyl; C_{1-6}alkyl, or aryl substituted with one or more substituents selected from NR_5R_6, NR_5COR7, CN, $OC_{,-6}$alkyl, OH, CO_2R_7, $CONRsR_7$, $CONR_5R_6$, $NR_5CO_2R_7$, substituted or unsubstituted C_{1-6}alkyl, SR_7, CHO, substituted or unsubstituted heterocyclyl wherein R_5 to R_7 are as defined in claim I

8. The compound according to claim I, wherein R_2 is aryl; imidazolyl, methylene dioxy phenyl; or aryl substituted with one or more substituents selected from an N-coπtaining 5 or 6 membered heterocyclyl; substituted or unsubstituted OC_{1-6}alkyl,

NR COR- wherein R\ is H and R- is C1-8alkyl C2-8alkenyl C2-8alkynyl or C\ NH- halo CO; R SO2NR2R0 NO NHSOMe CHOHCF-CH, CH2NHSCMUe OH and SH wherein R\ to R- are as defined in claim 1

9 The compound according to claim I wherein R_3 is H, Ci6alk\ I halo C2 6alken\ l ammo u Inch mas be substituted with d_6alken> I c>ano nitro methox) ars l or 5 or 6 membered heterocsds I containing 1 or 2 N atoms which mas be substituted w ilh trimeths lcarboxs

IO The compound according to claim I s\ herein a substituent ol one of R_1 and R_2 is selected horn



wherein

D is O or N,

Rio is selected from H and substituted or unsubstituted Ci^alkyl,

Rn and R_{12} are independently selected from H, substituted or uπsubstituted C1 4alkyl, C1-4alkylNR1,1Ri5, Ci4alkyl0R 8, substituted or unsubstituted aryl or may be joined to form a substituted or unsubstituted 5 to 8 membered ring optionally containing one or more heteroatoms selected from O, S, SO_2 and NR_{10},

Ri_3 is selected from OH, OC_Malkyl, NR,4Rt5,

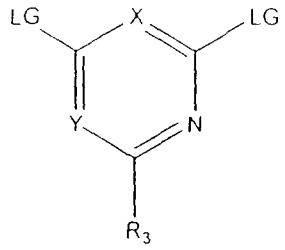
p is Oto 4, and

R_1 and R|, aie independent selected from H substituted or unsubstituied C _alk\ I or ma\ be joined lo form a substituted 5 8 mem bered ring opt ioπall\ contain ing one oi more heteroatoms selected from U S SO and NRm

11 The compound accord ing to cla im I u herei n the compound is a kinase inhibitor

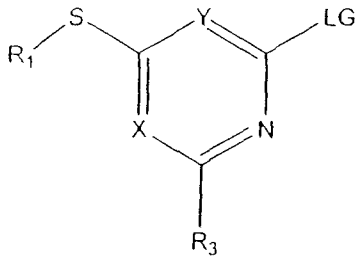
12 A process lor the preparation of the com pound of formula I accord ing to clai m I which comprises the steps of

(a) add ing S-R i where in R, is as defined in cla im I to a compound of form ula II



(I

wherein X, Y and R_3 are as defined in formula I above and LG is a" leaving group to prepare a compound of formula III



III

wherein X, Y, LG, Ri and R_3 are as defined above, and

(b) coupling the compound of formula III with a source of NH-W-R_2 wherein W and R_2 are as defined in claim I

13 A pharmaceutical composition comprising the compound of formula I according to claim I and a pharmaceutically acceptable carrier

14 An implant which comprises the compound of formula I according to claim I

15 A method for the treatment of a kinase associated disease which comprises administering a therapeutically effecme amount of the compound of formula I according to claim I or a pharmaceutical composition according to claim 13 to a subiect in need thereof

16 The method according to claim 15. wherein the kinase associated disease is an immunological or inflammatory disease. h)perproliferat tve disease. viral disease metabolic disease, or vascular disease

17 A method for suppressing the immune bystem of a subject which comprises administering a therapeutically effective amount of the compound oi fotrnula I according to claim I or a pharmaceutical composition according to claim 13

18 A method of inhibiting a kinase in a cell comprising contacting the cell with the compound of formula 1according to claim 1

19 Use of the compound of formula I according to claim I or a pharmaceutical composition according to claim 13 in the manufacture of a medicament for the treatment of a kinase associated disease

20 Use of the compound of formula I according to claim I or a pharmaceutical composition according to claim 13 in the manufacture of a medicament for suppressing the immune system of a subject

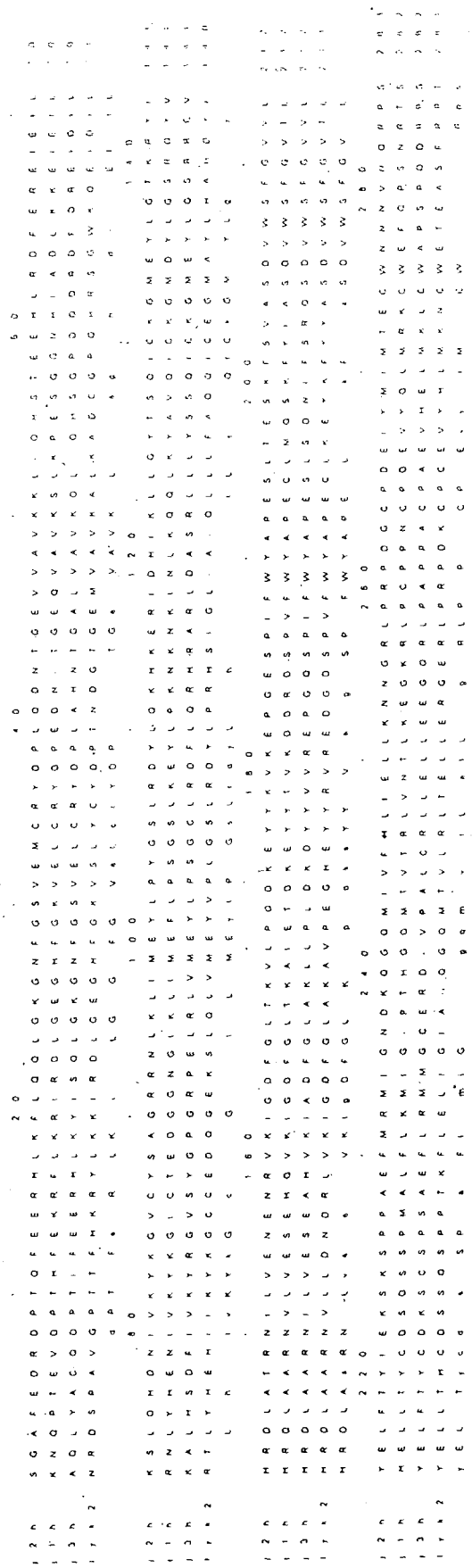


Figure 1

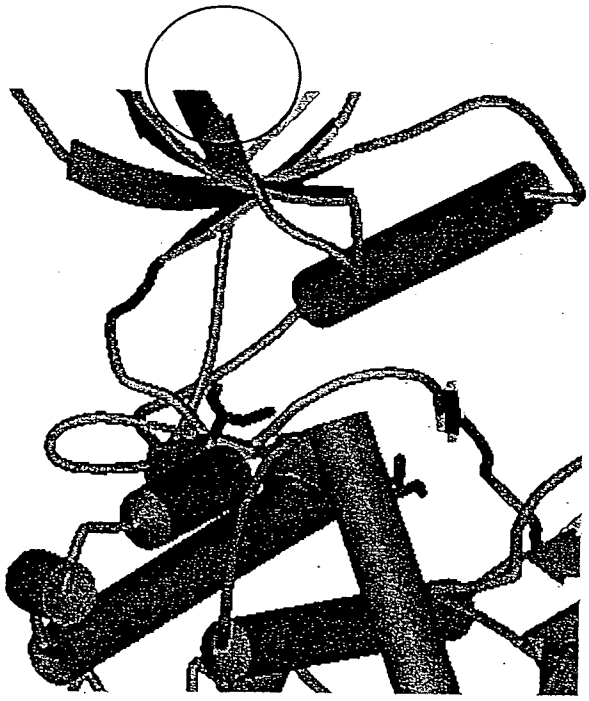


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000103

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07D 239/47(2006.01) *C07D 401/12* (2006.01) *C07D 403/12* (2006.01) *C07D 413/12* (2006.01)
C07D 239/48 (2006.01) *C07D 405/12* (2006.01) *C07D 417/12* (2006.01) ***A61P 9/00*** *(2006.01)*
A61P 37/00 (2006.01) *A61K 31/506* (2006.01) *A 61P 31/12* (2006.01) ***A61P 37/08*** (2006.01)
A61P 3/00 (2006.01) *A61P 35/00 (2006.01)*

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA: Sub-Structure Search based on Formula I

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,974,162 A1 (SANTILLI ET AL) 10 August 1976 See col. 4 lines 5-71ine 47-49, col. 5 and 6	1-4, 6-10, 12 and 13
X	DE 3436380 A1 (BAYER AG) 10 April 1986 See claims and table A and B on pages 45 and 47 respectively	1-3, 6, 7 and 9
X	HIRATA M. et al, "Synthesis of N'-(5-Halogenpyrimidinyl) Sulphanilamide Derivates" Yakugaku Zasshi (1972), 92(3), 288-298 See table 1.	1-4, 6, 7, 9

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 April 2008	- 9 APR 2008

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000103

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 3625168 A1 (BAYER AG) 28 January 1988 See page 13	1-3, 6, 7 and 9
A	WO 2005/039506 A2 (EXELIXIS INC.) 6 May 2005	
A	DE 3205638 A1 (HOECHST AG) 25 August 1983	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2008/000103

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	3974162	NONE					
DE	3436380	NONE					
DE	3625168	EP	0254183	JP	63035565	DK	388087
WO	2005039506	AU	2004283751	CA	2541989	EP	1678168
		US	2007208020				
DE	2005039506	NONE					

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX