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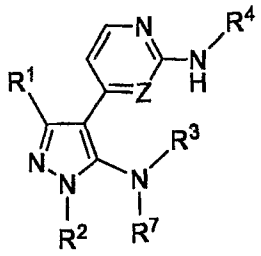
(54) Title: 4-PYRIMIDINE-5-AMINO-PYRAZOLE COMPOUNDS



(I)

(57) Abstract: The present invention relates to compounds with the formula (I), or a pharmaceutically acceptable salt thereof, wherein: -Z- is -C- or -N-; and R^1, R^2, R^3, R^4 and R^7 are as defined in the specification. The invention also relates to pharmaceutical compositions comprising the compounds of formula (I) and methods of treating a condition that is mediated by the modulation of JNK, the method comprising administering to a mammal an effective amount of a compound of formula (I).

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4-PYRIMIDINE-5-AMINO-PYRAZOLE COMPOUNDS

Field of the Invention

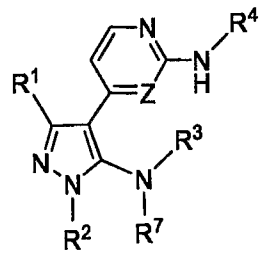
The present invention relates to novel substituted 4-pyrimidine-5-amino-pyrazole compounds of formula (I), to pharmaceutical compositions comprising the compounds, as well as to the use of the compounds in the preparation of a medicament for use in the treatment or prevention of a disease or medical condition mediated through c-Jun N-terminal kinases (JNKs), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity.

Background of the Invention

Mammalian cells respond to extracellular stimuli by activating signaling cascades that are mediated by members of the mitogen-activated protein (MAP) kinase family, which include the c-Jun N-terminal kinases (JNKs), also known as stress activated protein kinase (SAPK). Three distinct genes, JNK1, JNK2, JNK3 have been identified and at least ten different splicing isoforms of JNKs exist in mammalian cells [Gupta et al., EMBO J., 15:2760-70 (1996)]. While JNK1 and JNK2 express in many tissues, JNK3 specifically expresses in the brain. Thus, JNK3 has a potential to be particularly involved in nervous function. The JNK signal transduction system of stress response MAP kinase family system is activated by changes in osmotic pressure, DNA damage, anisomycine, heat shock, ultraviolet radiation, ischemia, inflammatory cytokines and the like and various stress stimulations relating to apoptosis induction, it is considered to constitute a major intracellular information transduction path responsible for stress response (Biochemica et Biophysica Acta, vol. 1333, pp. F85-F104 (1997)). From an experiment using a JNK1 deletion mouse, JNK is reported to be an important mediator involved in obesity and insulin resistance (Nature, vol. 420, pp. 333-336 (2002)). Pyrazole compounds including those described in WO03/049542 have been known in the preparation of a medicament for use in the treatment or prevention of a disease or medical condition mediated through c-Jun N-terminal kinases (JNKs).

Summary of the Invention

The present invention relates to a compound of formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

-Z- is -C- or -N-;

R^1 is H or halo;

R^2 is H, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$amino$(CR^5R^6)_v$, $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

R^3 is H, $(C_1\text{-}C_6)$alkyl, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$amino$(CR^5R^6)_v$, $-(C=O)\text{-}O\text{-}R^5$, $-(C=O)\text{-}NR^5R^6$, $-S(O)_kNR^5R^6$, $-S(O)_j(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10}$aryl), $-(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_q(C=O)(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_qS(O)_j(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v$(4-12)-membered heterocyclyl;

Or optionally, R^2 together with the –N- to which R^3 and R^7 are attached to form a ring A, which is a (5-8)-membered heterocyclyl;

Provided that when R^2 together with the –N- to which R^3 and R^7 are attached to said ring A (5-8)-membered heterocyclyl, R^7 is a bond, and R^3 may be absent;

Or optionally, R^3 together with R^7 and the –C- to which R^3 and R^7 are attached to form a ring B, which is a (3-8)-membered heterocyclyl;

R^4 is $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

each of R^5 and R^6 are independently selected from H, $(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6\text{-}C_{10})$aryl, and $-(CR^8R^9)_p$(4-12)-membered heterocyclyl;

R^7 is H or $(C_1\text{-}C_6)$alkyl;

any carbon atoms of said ring A, ring B, and the $(C_1\text{-}C_6)$alkyl, the (3-10)-membered cycloalkyl, the $(C_6\text{-}C_{10})$aryl and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^3, R^4, R^5, and R^6 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, R^{9a}, $-(CR^8R^9)_q\text{-}(C=O)\text{-}R^8$, $-(CR^8R^9)_q\text{-}(C=O)\text{-}R^{9a}$, $-(CR^8R^9)_q\text{-}(C=O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_q\text{-}(C=O)\text{-}O\text{-}R^{9a}$, $-O\text{-}(C=O)\text{-}R^8$, $-O\text{-}(C=O)\text{-}R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C=O)\text{-}R^9$, $-NR^8\text{-}(CR^8R^9)_q(C=O)R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C=O)\text{-}O(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}(CR^8R^9)_q(C=O)\text{-}OR^9$, $-NR^8\text{-}(C=O)NR^8R^9$, $-NR^8\text{-}(C=O)NR^8R^{9a}$, $-NR^8\text{-}(C=O)\text{-}(C=O)\text{-}NR^8R^9$, $-NR^8\text{-}(C=O)\text{-}(C=O)\text{-}NR^8R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)\text{-}NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{9a}$, $-S(O)_j(C_1\text{-}C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}S(O)_kR^{9a}$, $-NR^8\text{-}S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any carbon atoms of each of the foregoing R^{10} $(C_1\text{-}C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6\text{-}C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O\text{-}CF_3$, $-O\text{-}CHF_2$, $-O\text{-}CH_2F$, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, R^{14}, $-O\text{-}R^{14}$, $-(C=O)\text{-}R^8$, $-(C=O)\text{-}R^{14}$, $-(C=O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-(C=O)\text{-}O\text{-}R^{14}$, $-O\text{-}(C=O)\text{-}R^8$, $-O\text{-}(C=O)\text{-}R^{14}$, $-NR^8(C=O)\text{-}R^9$, $-NR^8(C=O)\text{-}R^{14}$, $-(C=O)\text{-}NR^8R^9$, $-(C=O)\text{-}NR^8R^{14}$, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, $-NR^8OR^{14}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1\text{-}C_6)$alkyl, $-S(O)_jR^{14}$, $NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, $NR^{14}\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, and $-NR^8\text{-}S(O)_kR^{14}$;

any nitrogen atoms of said ring A, ring B, and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{10}, R^{11} and R^{14} are optionally substituted with R^{12} substituents each independently selected from $(C_1\text{-}C_6)$alkyl, $-(C=O)-R^8$, $-(C=O)-R^{14a}$, $-(C=O)-O-(C_1\text{-}C_6)$alkyl, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14a}$, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14a}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} $(C_1\text{-}C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6\text{-}C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6\text{-}C_{10}$aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(C=O)-R^8$, $-(C=O)-O-(C_1\text{-}C_6)$alkyl, $-O-(C=O)-R^8$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1\text{-}C_6)$alkyl, and $-NR^8S(O)_k(C_1\text{-}C_6)$alkyl;

each R^8 and R^9 are independently H or $(C_1\text{-}C_6)$alkyl;

each R^{9a}, R^{14}, and R^{14a} are independently $-(CR^8R^9)_v$(3-10)-membered cycloalkyl, $-(CR^8R^9)_v(C_6\text{-}C_{10})$aryl, or $-(CR^8R^9)_v$(4-12)-membered heterocyclyl;

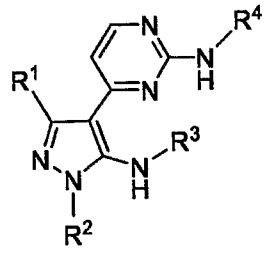
p, q, and v are each independently 0, 1, 2, 3, 4, or 5;

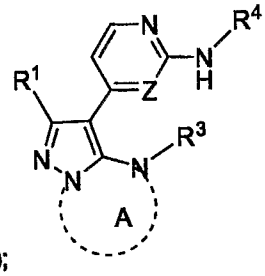
n and j are each independently 0, 1, or 2;

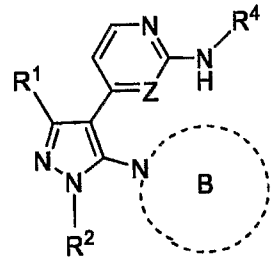
w is 0, 1, 2, or 3, and

k is 1 or 2.

In another embodiment, the invention relates to compounds of the formula (I) selected from the group consisting of:


(Ia);

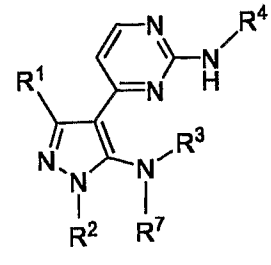

(Ib); and


(Ic);

or a pharmaceutically acceptable salt thereof, wherein:

-Z-; Ring A, Ring B, R^1, R^2, R^3, R^4 and R^7 are as defined above.

In another embodiment, the invention relates to compounds of the formula (Ia):


(Ia);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or halo;

R^2 is H, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, (C_1-C_6)alkoxy, (C_1-C_6)amino$(CR^5R^6)_v$, (C_1-C_6)alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

R^3 is H, (C_1-C_6)alkyl, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, (C_1-C_6)alkoxy, (C_1-C_6)amino$(CR^5R^6)_v$, $-(C=O)-O-R^5$, $-(C=O)-NR^5R^6$, $-S(O)_kNR^5R^6$, $-S(O)_j(C_1-C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10}$aryl), $-(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_q(C=O)(C_1-C_6)$alkyl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v(C_6-C_{10})$aryl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_qS(O)_j(C_1-C_6)$alkyl, $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v$(4-12)-membered heterocyclyl;

R^4 is (C_1-C_6)alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

each of R^5 and R^6 are independently selected from H, (C_1-C_6)alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6-C_{10})$aryl, and $-(CR^8R^9)_p$(4-12)-membered heterocyclyl;

R^7 is H or (C_1-C_6)alkyl;

any carbon atoms of the (C_1-C_6)alkyl, the (3-10)-membered cycloalkyl, the (C_6-C_{10})aryl and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^3, R^4, R^5, and R^6 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, $-(CR^8R^9)_q-(C=O)-R^8$, $-(CR^8R^9)_q-(C=O)-R^{9a}$, $-(CR^8R^9)_q-(C=O)-O-(C_1-C_6)$alkyl, $-(CR^8R^9)_q-(C=O)-O-R^{9a}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-R^9$, $-NR^8-(CR^8R^9)_q(C=O)R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-O(C_1-C_6)$alkyl, $-NR^8-(CR^8R^9)_q(C=O)-OR^9$, $-NR^8-(C=O)NR^8R^9$, $-NR^8-(C=O)NR^8R^{9a}$, $-NR^8-(C=O)-(C=O)-NR^8R^9$, $-NR^8-(C=O)-(C=O)-NR^8R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)-NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{9a}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8-S(O)_k(C_1-C_6)$alkyl, $-NR^8-S(O)_kR^{9a}$, $-NR^8-S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any carbon atoms of each of the foregoing R^{10} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O-CF_3$, $-O-CHF_2$, $-O-CH_2F$, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{14}, $-O-R^{14}$, $-(C=O)-R^8$, $-(C=O)-R^{14}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-O-R^{14}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{14}$, $-NR^8(C=O)-R^9$, $-NR^8(C=O)-R^{14}$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, $-NR^8OR^{14}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{14}$, $NR^8-S(O)_k(C_1-C_6)$alkyl, $NR^{14}-S(O)_k(C_1-C_6)$alkyl, and $-NR^8-S(O)_kR^{14}$;

any nitrogen atoms of the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{10}, R^{11} and R^{14} are optionally substituted with R^{12} substituents each independently selected from (C_1-C_6)alkyl, $-(C=O)-R^8$, $-(C=O)-R^{14a}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14a}$, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14a}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} $(C_1\text{-}C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6\text{-}C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6\text{-}C_{10}$aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(C=O)\text{-}R^8$, $-(C=O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-O\text{-}(C=O)\text{-}R^8$, $-NR^8(C=O)\text{-}R^9$, $-(C=O)\text{-}NR^8R^9$, $-(C=O)\text{-}NR^8R^{14}$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1\text{-}C_6)$alkyl, and $-NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl;

each R^8 and R^9 are independently H or $(C_1\text{-}C_6)$alkyl;

each R^{9a}, R^{14}, and R^{14a} are independently $-(CR^8R^9)_v$(3-10)-membered cycloalkyl, $-(CR^8R^9)_v(C_6\text{-}C_{10})$aryl, or $-(CR^8R^9)_v$(4-12)-membered heterocyclyl;

p, q, and v are each independently 0, 1, 2, 3, 4, or 5;

n and j are each independently 0, 1, or 2;

w is 0, 1, 2, or 3.

In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is unsubstituted $(C_1\text{-}C_6)$alkyl, such as isopropyl.

In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is $(C_1\text{-}C_6)$alkyl, such as methyl, ethyl, or butyl, substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, R^{9a}, $-(CR^8R^9)_q\text{-}(C=O)\text{-}R^8$, $-(CR^8R^9)_q\text{-}(C=O)\text{-}R^{9a}$, $-(CR^8R^9)_q\text{-}(C=O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_q\text{-}(C=O)\text{-}O\text{-}R^{9a}$, $-O\text{-}(C=O)\text{-}R^8$, $-O\text{-}(C=O)\text{-}R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C=O)\text{-}R^9$, $-NR^8\text{-}(CR^8R^9)_q(C=O)R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C=O)\text{-}O(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}(CR^8R^9)_q(C=O)\text{-}OR^9$, $-NR^8\text{-}(C=O)NR^9$, $-NR^8\text{-}(C=O)NR^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)\text{-}NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_k\ NR^8R^{9a}$, $-S(O)_j(C_1\text{-}C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}S(O)_kR^{9a}$, $-NR^8\text{-}S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$.

In another sub-embodiment, R^{10} is independently selected from $(C_1\text{-}C_6)$alkoxy, R^{9a}, $-NR^8\text{-}(CR^8R^9)_q(C=O)\text{-}O(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}(CR^8R^9)_q(C=O)\text{-}OR^9$, $-NR^8\text{-}(CR^8R^9)_q(C=O)OR^{9a}$, $-NR^8R^{9a}$, $-NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}S(O)_kR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$.

Within the foregoing embodiment and sub-embodiment, any carbon atoms of each of the foregoing R^{10} $(C_1\text{-}C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6\text{-}C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O\text{-}CF_3$, $-O\text{-}CHF_2$, $-O\text{-}CH_2F$, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, R^{14}, $-O\text{-}R^{14}$, $-(C=O)\text{-}R^8$, $-(C=O)\text{-}R^{14}$, $-(C=O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-(C=O)\text{-}O\text{-}R^{14}$, $-O\text{-}(C=O)\text{-}R^8$, $-O\text{-}(C=O)\text{-}R^{14}$, $-NR^8(C=O)\text{-}R^9$, $-NR^8(C=O)\text{-}R^{14}$, $-(C=O)\text{-}NR^8R^9$, $-(C=O)\text{-}NR^8R^{14}$, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, $-NR^8OR^{14}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1\text{-}C_6)$alkyl, $-S(O)_jR^{14}$, $-NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, and $-NR^8\text{-}S(O)_kR^{14}$.

In another sub-embodiment, R^{11} is $C_1\text{-}C_6)$alkoxy.

In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is unsubstituted -$(CR^5R^6)_v$(3-10)-membered cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, -(CH_3CH)-cyclohexyl, -(CH_2)-cyclohexyl, cyclohexyl, or indanyl, preferably cyclohexyl.

In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is -$(CR^5R^6)_v$(3-10)-membered cycloalkyl substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, -CF_3, -CHF_2, -CH_2F, trifluoromethoxy, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, R^{9a}, -$(CR^8R^9)_q$-$(C=O)$-R^8, -$(CR^8R^9)_q$-$(C=O)$-R^{9a}, -$(CR^8R^9)_q$-$(C=O)$-O-$(C_1$-$C_6)$alkyl, -$(CR^8R^9)_q$-$(C=O)$-O-R^{9a}, -O-$(C=O)$-R^8, -O-$(C=O)$-R^{9a}, -NR^8-$(CR^8R^9)_q(C=O)$-R^9, -NR^8-$(CR^8R^9)_q(C=O)R^{9a}$, -NR^8-$(CR^8R^9)_q$(C=O)-O$(C_1$-$C_6)$alkyl, -NR^8-$(CR^8R^9)_q(C=O)$-OR^9, -NR^8-$(C=O)NR^9$, -NR^8-$(C=O)NR^{9a}$, -NR^8-$(CR^8R^9)_q(C=O)OR^{9a}$, -$(C=O)$-NR^8R^9, -$(C=O)NR^8R^{9a}$, -NR^8R^9, -NR^8R^{9a}, -NR^8OR^9, -NR^8OR^{9a}, -$S(O)_kNR^8R^9$, -$S(O)_k$ NR^8R^{9a}, -$S(O)_j(C_1$-$C_6)$alkyl, -$S(O)_jR^{9a}$, -NR^8-$S(O)_k(C_1$-$C_6)$alkyl, -NR^8-$S(O)_kR^{9a}$, -NR^8-$S(O)_kNR^{9a}$, and -$(CR^8R^9)_qS(O)_jR^{9a}$.

In another sub-embodiment R^{10} is hydroxy, $(C_1$-$C_6)$alkyl, R^{9a}, -NR^8-$(CR^8R^9)_q(C=O)$-R^9, -NR^8-$(CR^8R^9)_q(C=O)R^{9a}$, - -NR^8-$(C=O)NR^{9a}$, -NR^8R^9, -NR^8R^{9a}, -NR^8-$S(O)_k(C_1$-$C_6)$alkyl, and -NR^8-$S(O)_kR^{9a}$.

Within the foregoing embodiment and sub-embodiment, any carbon atoms of each of the foregoing R^{10} $(C_1$-$C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6$-C_{10}aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, -CF_3, -O-CF_3, -O-CHF_2, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, R^{14}, and -$(C=O)$-R^8.

In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is unsubstituted -$(CR^5R^6)_v(C_6$-$C_{10})$aryl, such as phenyl, naphthyl, -(CH_2CH_2)-phenyl, or -(CH_2)-phenyl.

In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is -$(CR^5R^6)_v(C_6$-$C_{10})$aryl substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, -CF_3, -CHF_2, -CH_2F, trifluoromethoxy, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, R^{9a}, -$(CR^8R^9)_q$-$(C=O)$-R^8, -$(CR^8R^9)_q$-$(C=O)$-R^{9a}, -$(CR^8R^9)_q$-$(C=O)$-O-$(C_1$-$C_6)$alkyl, -$(CR^8R^9)_q$-$(C=O)$-O-R^{9a}, -O-$(C=O)$-R^8, -O-$(C=O)$-R^{9a}, -NR^8-$(CR^8R^9)_q(C=O)$-R^9, -NR^8-$(CR^8R^9)_q(C=O)R^{9a}$, -NR^8-$(CR^8R^9)_q$(C=O)-O$(C_1$-$C_6)$alkyl, -NR^8-$(CR^8R^9)_q(C=O)$-OR^9, -NR^8-$(C=O)NR^9$, -NR^8-$(C=O)NR^{9a}$, -NR^8-$(CR^8R^9)_q(C=O)OR^{9a}$, -$(C=O)$-NR^8R^9, -$(C=O)NR^8R^{9a}$, -NR^8R^9, -NR^8R^{9a}, -NR^8OR^9, -NR^8OR^{9a}, -$S(O)_kNR^8R^9$, -$S(O)_k$ NR^8R^{9a}, -$S(O)_j(C_1$-$C_6)$alkyl, -$S(O)_jR^{9a}$, -NR^8-$S(O)_k(C_1$-$C_6)$alkyl, -NR^8-$S(O)_kR^{9a}$, -NR^8-$S(O)_kNR^{9a}$, and -$(CR^8R^9)_qS(O)_jR^{9a}$.

In another sub-embodiment, R^{10} is halo, -CF_3, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, or R^{9a}.

Within the foregoing embodiment and sub-embodiment, any carbon atoms of each of the foregoing R^{10} $(C_1$-$C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6$-C_{10}aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from R^{14}, and -NR^8R^9.

In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is unsubstituted -$(CR^5R^6)_v$(4-12)-membered heterocyclyl, such as dihydrobenzopyranyl,

-(CH_2)-imidazo[12-a]pyrimidinyl, -(CH_2)-morpholinonyl, -(CH_2CH_2)-morpholinyl, -($CH_2C(CH_3)_2$)-morpholinyl -(CH_2)-oxa-azaspiro[4.5]decyl, piperidinyl, pyridinyl, -(CH_2)-pyridinyl, pyrazolidinyl, -(CH_3CHCH_2)-pyrazolyl, pyrrolidinonyl,: -($CH_2C(CH_3)_2$)-pyrrolidinyl, -($CH_2CH_2CH_2$)-piperazinyl, quinolinyl, -(CH_2)-quinolinyl, sulfonylcyclopentyl, -($CH_2CH_2CH_2$)-triazolyl, tetrahydropyranyl, tetrahydrofuranyl, -(CH_2)-tetrahydropyranyl, -(CH_2CH_2)-tetrahydropyranyl, or -(CH_2)-tetrahydroisoquinolinyl.

In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is -$(CR^5R^6)_v$(4-12)-membered heterocyclyl substituted on any carbon atoms with 1 to 3 R^{10} substituents each independently selected from halo, cyano, -CF_3, -CHF_2, -CH_2F, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, -$(CR^8R^9)_q$-(C=O)-R^8, -$(CR^8R^9)_q$-(C=O)-R^{9a}, -$(CR^8R^9)_q$-(C=O)-O-(C_1-C_6)alkyl, -$(CR^8R^9)_q$-(C=O)-O-R^{9a}, -O-(C=O)-R^8, -O-(C=O)-R^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)-R^9, -NR^8-$(CR^8R^9)_q$(C=O)R^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)-O(C_1-C_6)alkyl, -NR^8-$(CR^8R^9)_q$(C=O)-OR^9, -NR^8-(C=O)NR^9, -NR^8-(C=O)NR^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)OR^{9a}, -(C=O)-NR^8R^9, -(C=O)NR^8R^{9a}, -NR^8R^9, -NR^8R^{9a}, -NR^8OR^9, -NR^8OR^{9a}, -$S(O)_kNR^8R^9$, -$S(O)_k$ NR^8R^{9a}, -$S(O)_j$(C_1-C_6)alkyl, -$S(O)_jR^{9a}$, -NR^8-$S(O)_k$(C_1-C_6)alkyl, -NR^8-$S(O)_kR^{9a}$, -NR^8-$S(O)_kNR^{9a}$, and -$(CR^8R^9)_qS(O)_jR^{9a}$.

In another sub-embodiment, R^{10} is halo, cyano, -CF_3, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, or -(C=O)NR^8R^{9a}.

Within the foregoing embodiment and sub-embodiment, any carbon atoms of each of the foregoing R^{10} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, (C_6-C_{10}aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from hydroxy, (C_1-C_6)alkoxy, and (C_1-C_6)alkyl.

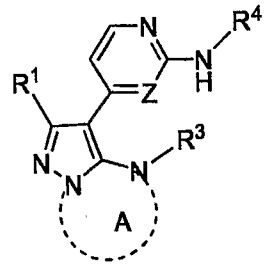
In another embodiment, the invention relates to compounds of the formula (Ia), wherein R^4 is -$(CR^5R^6)_v$(4-12)-membered heterocyclyl substituted on any nitrogen atoms with 1 to 3 R^{12} substituents each independently selected from (C_1-C_6)alkyl, -(C=O)-R^8, -(C=O)-R^{14a}, -(C=O)-O-(C_1-C_6)alkyl, -(C=O)-NR^8R^9, -(C=O)-NR^8R^{14a}, R^{14a}, -$(CR^8R^9)_q$(C=O)R^{14a}, and -$(CR^8R^9)_qS(O)_jR^{14a}$.

In another sub-embodiment, R^{12} is (C_1-C_6)alkyl, -(C=O)-R^8, -(C=O)-O-(C_1-C_6)alkyl, -(C=O)-NR^8R^9, -$(CR^8R^9)_p$(C_6-C_{10}aryl), -$(CR^8R^9)_p$(4-12)-membered heterocyclyl, -$(CR^8R^9)_qS(O)_j$(C_1-C_6)alkyl, -$(CR^8R^9)_qS(O)_j(CR^8R^9)_p$($C_6$-$C_{10}$)aryl, and -$(CR^8R^9)_qS(O)_j(CR^8R^9)_p$(4-12)-membered heterocyclyl.

Within the foregoing embodiment and sub-embodiment, any carbon atoms of each of the foregoing R^{12} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, (C_6-C_{10}aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, -CF_3, -CHF_2, -CH_2F, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, -$(CR^8R^9)_p$(3-10)-membered cycloalkyl, -$(CR^8R^9)_p$(C_6-C_{10}aryl), -$(CR^8R^9)_p$(4-12)-membered heterocyclyl, -(C=O)-R^8, -(C=O)-O-(C_1-C_6)alkyl, -O-(C=O)-R^8, -NR^8(C=O)-R^9, -(C=O)-NR^8R^9, -NR^8R^9, -NR^8OR^9, -$S(O)_kNR^8R^9$, -$S(O)_j$(C_1-C_6)alkyl, and -NR^8-$S(O)_k$(C_1-C_6)alkyl.

In another sub-embodiment, R^{13} is cyano, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, or -$(CR^8R^9)_p$(C_6-C_{10}aryl).

In another embodiment, the invention relates to compounds of the formula (Ib):



(Ib);

wherein ring A is a (5-8)-membered heterocyclyl;

-Z- is -C- or -N-;

R^1 is H or halo,

R^3 is H, (C_1-C_6)alkyl, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, (C_1-C_6)alkoxy, (C_1-C_6)amino$(CR^5R^6)_v$, $-(C=O)-O-R^5$, $-(C=O)-NR^5R^6$, $-S(O)_kNR^5R^6$, $-S(O)_j(C_1-C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10}$aryl), $-(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_q(C=O)(C_1-C_6)$alkyl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v(C_6-C_{10})$aryl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_qS(O)_j(C_1-C_6)$alkyl, $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v$(4-12)-membered heterocyclyl;

Or R^3 may be absent;

R^4 is (C_1-C_6)alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

each of R^5 and R^6 are independently selected from H, (C_1-C_6)alkyl, $-(CR^9R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6-C_{10})$aryl, and $-(CR^8R^9)_p$(4-12)-membered heterocyclyl;

any carbon atoms of said ring A and the (C_1-C_6)alkyl, the (3-10)-membered cycloalkyl, the (C_6-C_{10})aryl and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^3, R^4, R^5, and R^6 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, $-(CR^8R^9)_q-(C=O)-R^8$, $-(CR^8R^9)_q-(C=O)-R^{9a}$, $-(CR^8R^9)_q-(C=O)-O-(C_1-C_6)$alkyl, $-(CR^8R^9)_q-(C=O)-O-R^{9a}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-R^9$, $-NR^8-(CR^8R^9)_q(C=O)R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-O(C_1-C_6)$alkyl, $-NR^8-(CR^8R^9)_q(C=O)-OR^9$, $-NR^8-(C=O)NR^8R^9$, $-NR^8-(C=O)NR^8R^{9a}$, $-NR^8-(C=O)-(C=O)-NR^8R^9$, $-NR^8-(C=O)-(C=O)-NR^8R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)-NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_k$ NR^8R^{9a}, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8-S(O)_k(C_1-C_6)$alkyl, $-NR^8-S(O)_kR^{9a}$, $-NR^8-S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any carbon atoms of each of the foregoing R^{10} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O-CF_3$, $-O-CHF_2$, $-O-CH_2F$, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{14}, $-O-R^{14}$, $-(C=O)-R^8$, $-(C=O)-R^{14}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-O-R^{14}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{14}$, $-NR^8(C=O)-R^9$, $-NR^8(C=O)-R^{14}$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, -

NR^8OR^{14}, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1\text{-}C_6)$alkyl, $-S(O)_jR^{14}$, $NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, $NR^{14}\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, and $-NR^8\text{-}S(O)_kR^{14}$;

any nitrogen atoms of said ring A and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^3, R^4, R^5, R^6, R^{9a}, R^{10}, R^{11} and R^{14} are optionally substituted with R^{12} substituents each independently selected from $(C_1\text{-}C_6)$alkyl, $-(C=O)\text{-}R^8$, $-(C=O)\text{-}R^{14a}$, $-(C=O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-(C=O)\text{-}NR^8R^9$, $-(C=O)\text{-}NR^8R^{14a}$, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14a}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} $(C_1\text{-}C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6\text{-}C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6\text{-}C_{10}$aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(C=O)\text{-}R^8$, $-(C=O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-O\text{-}(C=O)\text{-}R^8$, $-NR^8(C=O)\text{-}R^9$, $-(C=O)\text{-}NR^8R^9$, $-(C=O)\text{-}NR^8R^{14}$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1\text{-}C_6)$alkyl, and $-NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl;

each R^8 and R^9 are independently H or $(C_1\text{-}C_6)$alkyl;

each R^{9a}, R^{14}, and R^{14a} are independently $-(CR^8R^9)_v$(3-10)-membered cycloalkyl, $-(CR^8R^9)_v(C_6\text{-}C_{10})$aryl, or $-(CR^8R^9)_v$(4-12)-membered heterocyclyl;

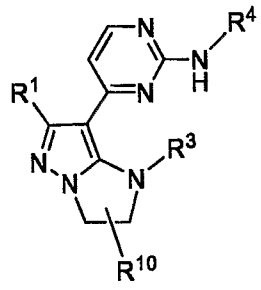
p, q, and v are each independently 0, 1, 2, 3, 4, or 5;

n and j are each independently 0, 1, or 2;

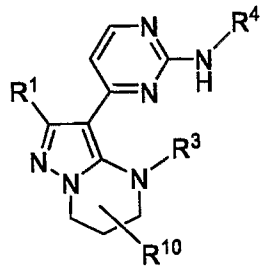
w is 0, 1, 2, or 3, and

k is 1 or 2.

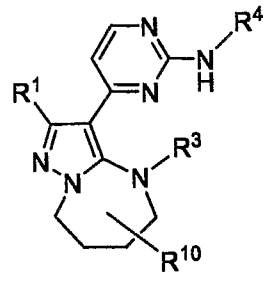
In another embodiment, the invention relates to compounds of the formula (Ib) selected from the group consisting of:



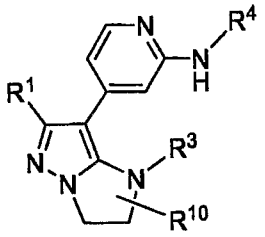
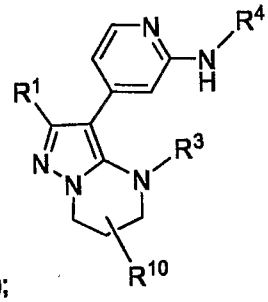
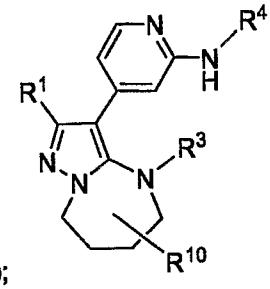
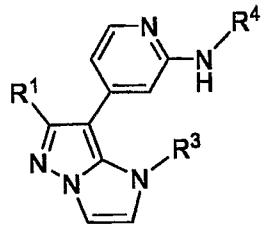
(Ib1);



(Ib2);



(Ib3);


(Ib4);

(Ib5);

(Ib6); and

(Ib7).

In another embodiment, the invention relates to compounds of the formula (Ib) selected from the group consisting of: (Ib1), (Ib2), (Ib3), and (Ib7), as described above.

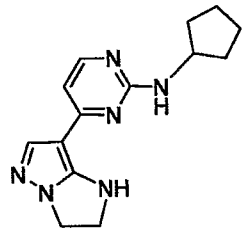
In another embodiment, the invention relates to compounds of the formula (Ib), wherein R^4 is (C_1-C_6)alkyl, such as isopropyl.

In another embodiment, the invention relates to compounds of the formula (Ib), wherein R^4 is -$(CR^5R^6)_v$(3-10)-membered cycloalkyl, such as cyclohexyl, optionally substituted on any carbon atoms by R^{10}, such as hydroxy, –NR^8-SO_2-(C_1-C_6)alkyl, or -NR^8-$(CR^8R^9)_q(C=O)R^{9a}$.

In another embodiment, the invention relates to compounds of the formula (Ib), wherein R^4 is -$(CR^5R^6)_v$(C_6-C_{10})aryl, such as phenyl or naphtyl.

In another embodiment, the invention relates to compounds of the formula (Ib), wherein R^4 is -$(CR^5R^6)_v$(4-12)-membered heterocyclyl, such as pyridinyl.

Specific embodiments of compounds of the formula (Ib) are selected from the group consisting of: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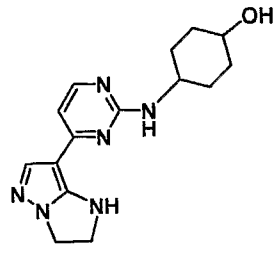
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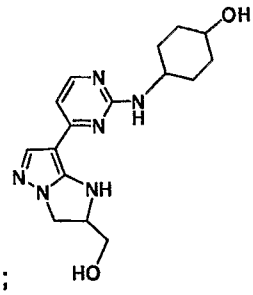
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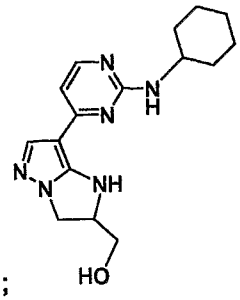
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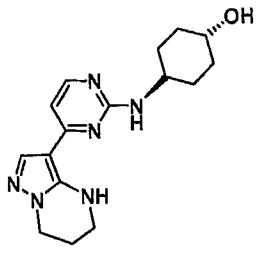
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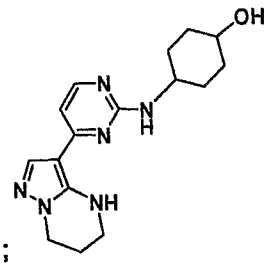
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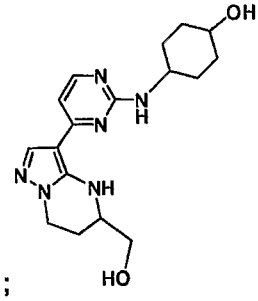
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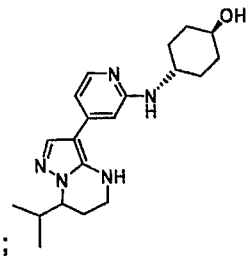
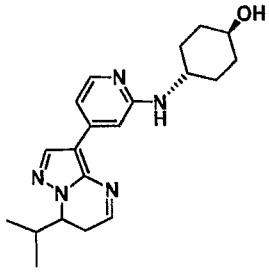
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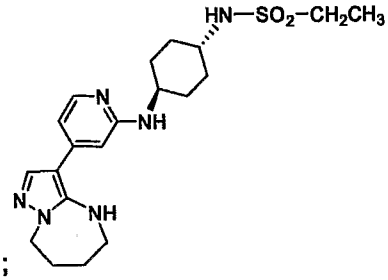
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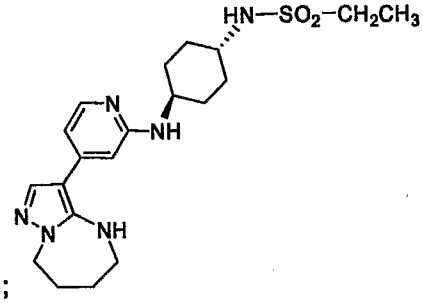
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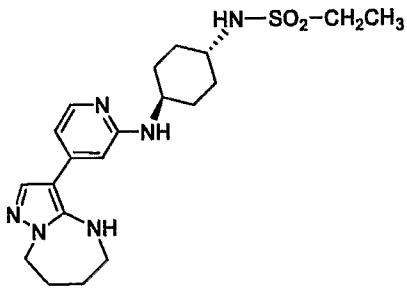
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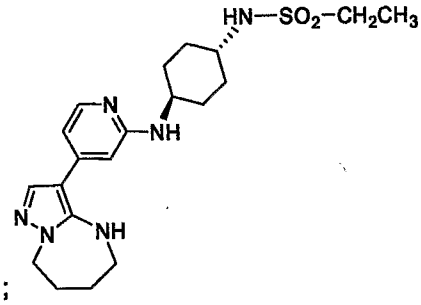
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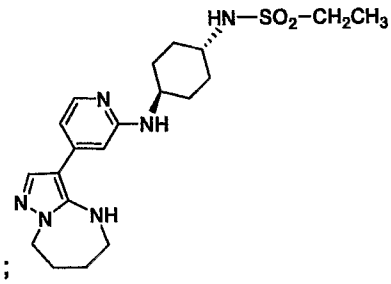
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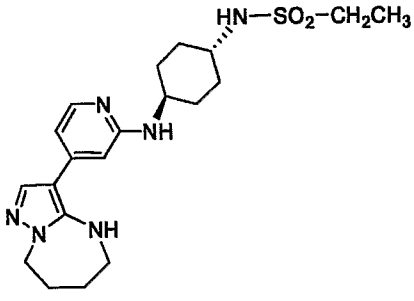
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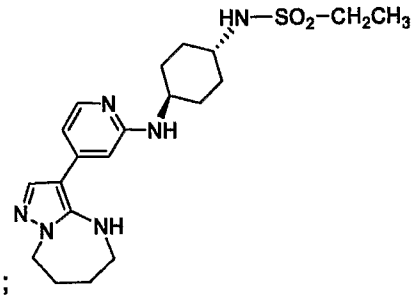
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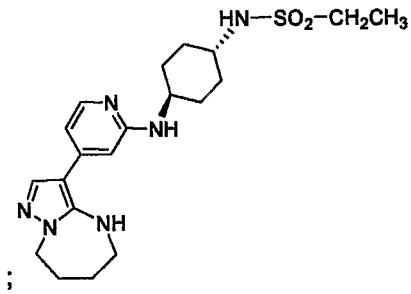
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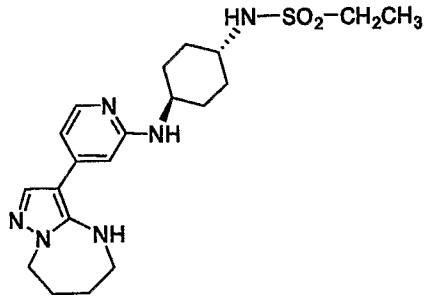
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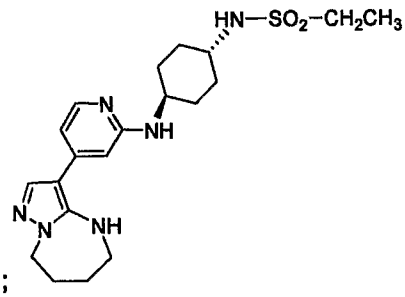
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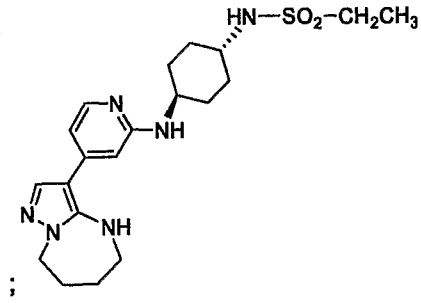

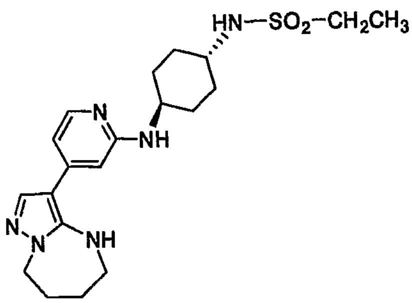
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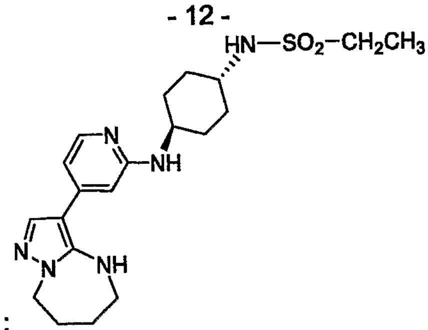
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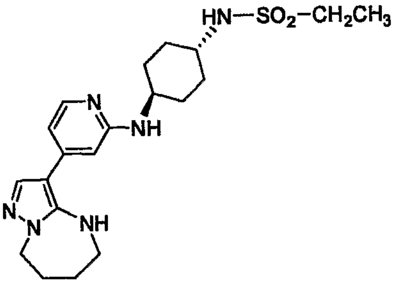
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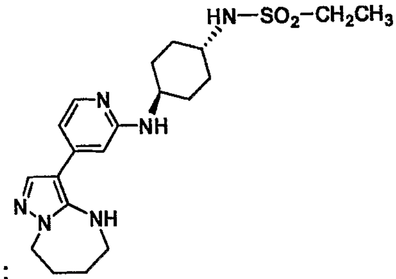
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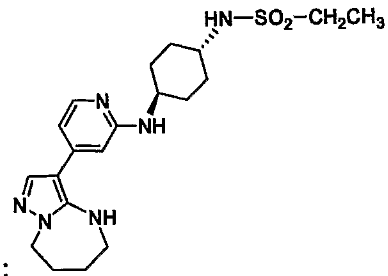
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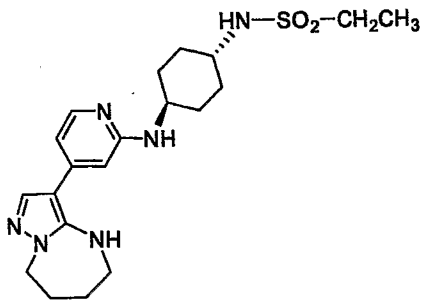
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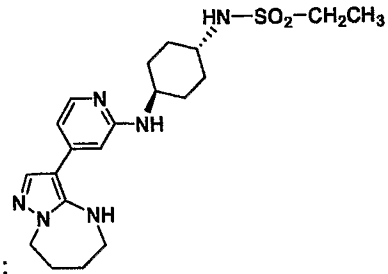
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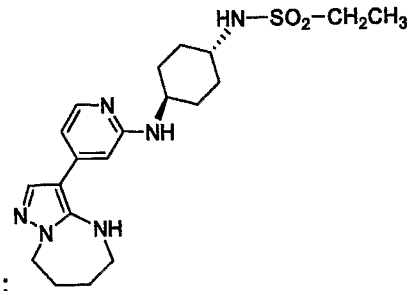
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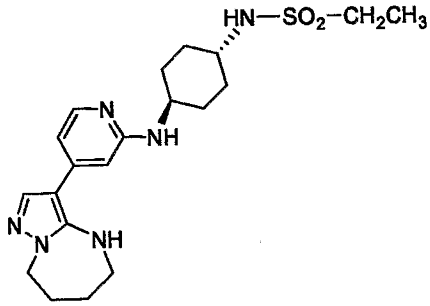
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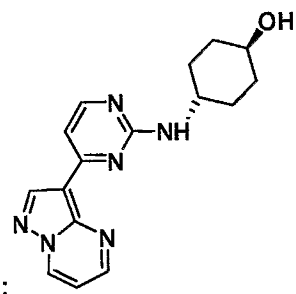
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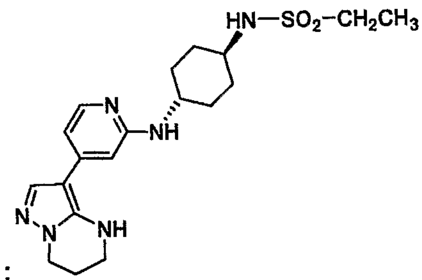
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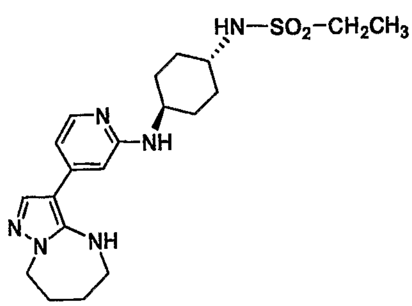
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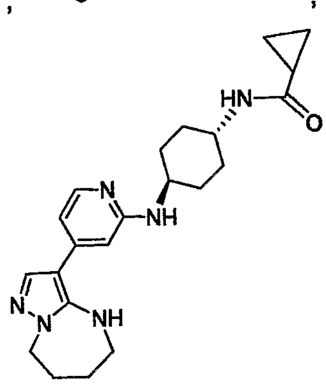
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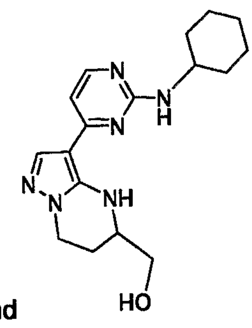
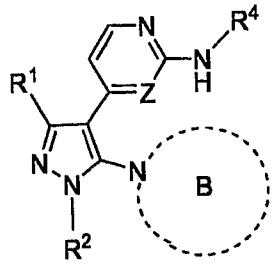

; or

a pharmaceutically acceptable salt thereof.

In another embodiment, the invention relates to compounds of the formula (Ic):



(Ic);

wherein ring B is a (3-8)-membered heterocyclyl;

-Z- is -C- or -N-;

R^1 is H or halo;

R^2 is H, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, (C_1-C_6)alkoxy, (C_1-C_6)amino$(CR^5R^6)_v$, (C_1-C_6)alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

R^4 is (C_1-C_6)alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

each of R^5 and R^6 are independently selected from H, (C_1-C_6)alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6-C_{10})$aryl, and $-(CR^8R^9)_p$(4-12)-membered heterocyclyl;

any carbon atoms of said ring B, and the (C_1-C_6)alkyl, the (3-10)-membered cycloalkyl, the (C_6-C_{10})aryl and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^4, R^5, and R^6 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, $-(CR^8R^9)_q-(C=O)-R^8$, $-(CR^8R^9)_q-(C=O)-R^{9a}$, $-(CR^8R^9)_q-(C=O)-O-(C_1-C_6)$alkyl, $-(CR^8R^9)_q-(C=O)-O-R^{9a}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-R^9$, $-NR^8-(CR^8R^9)_q(C=O)R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-O(C_1-C_6)$alkyl, $-NR^8-(CR^8R^9)_q(C=O)-OR^9$, $-NR^8-(C=O)NR^8R^9$, $-NR^8-(C=O)NR^8R^{9a}$, $-NR^8-(C=O)-(C=O)-NR^8R^9$, $-NR^8-(C=O)-(C=O)-NR^8R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)-NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_k$ NR^8R^{9a}, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8-S(O)_k(C_1-C_6)$alkyl, $-NR^8-S(O)_kR^{9a}$, $-NR^8-S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any carbon atoms of each of the foregoing R^{10} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O-CF_3$, $-O-CHF_2$, $-O-CH_2F$, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{14}, $-O-R^{14}$, $-(C=O)-R^8$, $-(C=O)-R^{14}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-O-R^{14}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{14}$, $-NR^8(C=O)-R^9$, $-NR^8(C=O)-R^{14}$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, $-NR^8OR^{14}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{14}$, $NR^8-S(O)_k(C_1-C_6)$alkyl, $NR^{14}-S(O)_k(C_1-C_6)$alkyl, and $-NR^8-S(O)_kR^{14}$;

any nitrogen atoms of said ring B, and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^4, R^5, R^6, R^{9a}, R^{10}, R^{11} and R^{14} are optionally substituted with R^{12} substituents each independently selected from (C_1-C_6)alkyl,

$-(C=O)-R^8$, $-(C=O)-R^{14a}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14a}$, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14a}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6-C_{10}$aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(C=O)-R^8$, $-(C=O)-O-(C_1-C_6)$alkyl, $-O-(C=O)-R^8$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, and $-NR^8-S(O)_k(C_1-C_6)$alkyl;

each R^8 and R^9 are independently H or (C_1-C_6)alkyl;

each R^{9a}, R^{14}, and R^{14a} are independently $-(CR^8R^9)_v$(3-10)-membered cycloalkyl, $-(CR^8R^9)_v(C_6-C_{10})$aryl, or $-(CR^8R^9)_v$(4-12)-membered heterocyclyl;

p, q, and v are each independently 0, 1, 2, 3, 4, or 5;

n and j are each independently 0, 1, or 2;

w is 0, 1, 2, or 3, and

k is 1 or 2.

In another embodiment, the invention relates to compounds of the formula (Ic), wherein Ring B is a (3-8)-membered heterocyclyl selected from the group consisting of morpholinyl, piperidinyl, piperazinyl, and pyrrolidinyl.

In another embodiment, the invention relates to compounds of the formula (Ic), wherein any carbon atoms of said ring B are optionally substituted with 1 to 3 R^{10} substituents each independently selected from $-NR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, and $-NR^8-S(O)_k(C_1-C_6)$alkyl.

In another embodiment, the invention relates to compounds of the formula (Ic), wherein any nitrogen atoms of said ring B are optionally substituted with R^{12} substituents each independently selected from (C_1-C_6)alkyl, $-(C=O)-R^8$, $-(C=O)-R^{14a}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14a}$, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14a}$.

In another sub-embodiment, R^{12} is-$(CR^8R^9)_qS(O)_j(C_1-C_6)$alkyl.

or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention relates to compounds of the formula (I), wherein –Z- is –N-.

In another embodiment, the invention relates to compounds of the formula (I), wherein R^1 is H.

In another embodiment, the invention relates to compounds of the formula (I), wherein R^2 is R^2 is H, (C_1-C_6)alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl.

In another embodiment, the invention relates to compounds of the formula (I), wherein R^2 is R^2 is H, (C_1-C_6)alkyl, benzyl, or phenyl, wherein any carbon atoms of the said benzyl or phenyl are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, $-(C=O)-R^8$, $-(C=O)-O-(C_1-C_6)$alkyl, $-O-(C=O)-R^8$, $-(C=O)-NR^8R^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, and $-NR^8-S(O)_k(C_1-C_6)$alkyl.

In another embodiment, the invention relates to compounds of the formula (I), wherein R^3 is H, $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10}$aryl), $-(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_q(C{=}O)(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_qS(O)_j(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v$(4-12)-membered heterocyclyl.

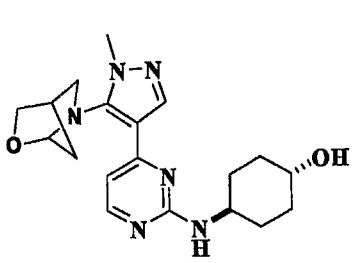
In another embodiment, the invention relates to compounds of the formula (I), wherein R^3 is H, $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10}$aryl), $-(CR^5R^6)_q(C{=}O)(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v$(4-12)-membered heterocyclyl, or $-(CR^5R^6)_qS(O)_j(C_1\text{-}C_6)$alkyl.

In another embodiment, the invention relates to compounds of the formula (I), wherein any carbon atoms of said R^3 $(C_1\text{-}C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6\text{-}C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, $-(C{=}O)\text{-}R^8$, $-(C{=}O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-O\text{-}(C{=}O)\text{-}R^8$, $-NR^8(C{=}O)\text{-}R^9$, $-(C{=}O)\text{-}NR^8R^9$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6\text{-}C_{10}$aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(CR^8R^9)_q(C{=}O)(CR^8R^9)_p(C_6\text{-}C_{10})$aryl, $-(CR^8R^9)_q(C{=}O)(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(CR^8R^9)_qO(CR^8R^9)_p(C_6\text{-}C_{10})$aryl, $-(CR^8R^9)_qO(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(CR^8R^9)_qS(O)_j(CR^8R^9)_p(C_6\text{-}C_{10})$aryl, and $-(CR^8R^9)_qS(O)_j(CR^8R^9)_p$(4-12)-membered heterocyclyl.

In another embodiment, the invention relates to compounds of the formula (I), wherein R^4 is $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl; wherein any carbon atoms of said R^4 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, R^{9a}, $-(CR^8R^9)_q\text{-}(C{=}O)\text{-}R^8$, $-(CR^8R^9)_q\text{-}(C{=}O)\text{-}R^{9a}$, $-(CR^8R^9)_q\text{-}(C{=}O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_q\text{-}(C{=}O)\text{-}O\text{-}R^{9a}$, $-O\text{-}(C{=}O)\text{-}R^8$, $-O\text{-}(C{=}O)\text{-}R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C{=}O)\text{-}R^9$, $-NR^8\text{-}(CR^8R^9)_q(C{=}O)R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C{=}O)\text{-}O(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}(CR^8R^9)_q(C{=}O)\text{-}OR^9$, $-NR^8\text{-}(C{=}O)NR^9$, $-NR^8\text{-}(C{=}O)NR^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C{=}O)OR^{9a}$, $-(C{=}O)\text{-}NR^8R^9$, $-(C{=}O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{9a}$, $-NR^8\text{-}S(O)_k(C_1\text{-}C_6)$alkyl, $-NR^8\text{-}S(O)_kR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$.

In another embodiment, the invention relates to compounds of the formula (I), wherein R^7 is H or methyl.

In another specific embodiment, the invention relates to compounds of the formula (I), selected from the group consisting of: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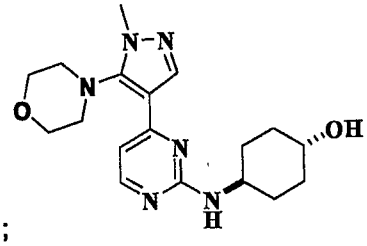
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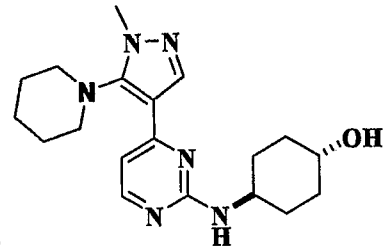
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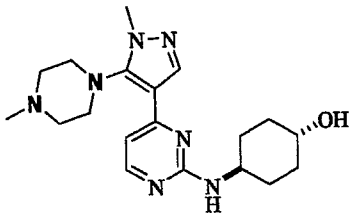
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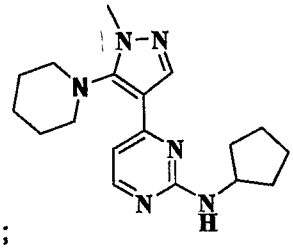
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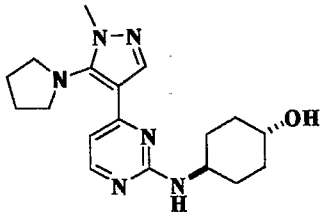
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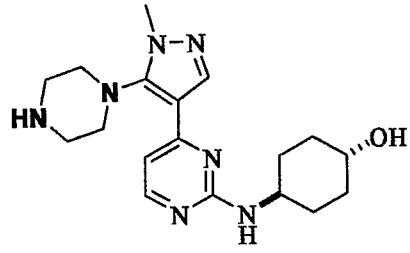

; or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition comprising an effective amount of compounds of the formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating a condition that is mediated by the modulation of JNK, the method comprising administering to a mammal an effective amount of compounds of the formula (I), or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method of treating diabetes, metabolic syndrome, insulin resistance syndrome, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, atherosclerosis, dementia, depression, virus diseases, inflammatory disorders, or diseases in which the liver is a target organ, the method comprising administering to a mammal an effective amount of compounds of the formula (I), or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method of treating chronic or acute cardiac failure, cardiac hypertrophy, dilated, hypertrophic or restrictive cardiomyopathy, acute myocardial infarction, post-myocardial infarction, acute or chronic myocarditis, diastolic dysfunction of the left ventricle, systolic dysfunction of the left ventricle, hypertension and nephropathy and nephritis as complications thereof, endothelial dysfunction, arteriosclerosis or post-angioplasty restenosis, which comprises administering an effective amount of compounds of the formula (I), to a mammal in need thereof.

The present invention also relates to a method of treating chronic rheumatoid arthritis, osteoarthritis, gout, chronic obstructive pulmonary disease, asthma, bronchitis, cystic fibrosis, inflammatory bowel disease, irritable colon syndrome, mucous colitis, ulcerative colitis, Crohn's disease, gastritis, esophagitis, multiple sclerosis, eczema, dermatitis, hepatitis, glomerulonephritis, diabetes,

ophthalmic diseases, diabetic retinopathy, diabetic macular edema, diabetic nephropathy, diabetic neuropathy, obesity, psoriasis or cancer, which comprises administering an effective amount of compounds of the formula (I), to a mammal in need thereof.

The present invention also relates to a method of treating Alzheimer's disease, Huntington's chorea, Parkinson's syndrome, epilepsy, amyotrophic lateral sclerosis, peripheral neuropathy, neurodegenerative disease or spinal injury, which comprises administering an effective amount of compounds of the formula (I), to a mammal in need thereof.

The present invention also relates to a method of treating cerebral apoplexy, cerebrovascular disorder, an ischemic disorder of an organ selected from the heart, kidney, liver and brain, ischemia-reperfusion injury, organ failure, endotoxin shock or rejection in transplantation, which comprises administering an effective amount of compounds of the formula (I), to a mammal in need thereof.

Definitions

For purposes of the present invention, as described and claimed herein, the following terms are defined as follows:

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

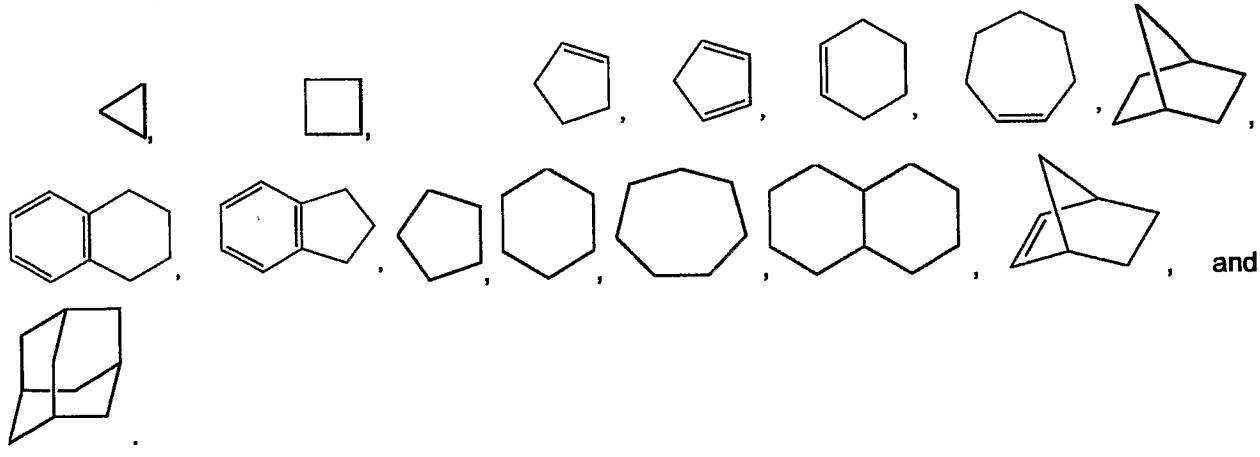
The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated, partially unsaturated, or unsaturated hydrocarbon radicals having straight or branched moieties. The term "alkyl", as used herein, includes alkenyl, which includes alkyl moieties having at least one carbon-carbon double bond and including E and Z isomers of said alkenyl moiety. The term "alkyl", as used herein, includes alkynyl, which includes alkyl moieties having at least one carbon-carbon triple bond.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

The term "Me" means methyl, "Et" means ethyl, and "Ac" means acetyl.

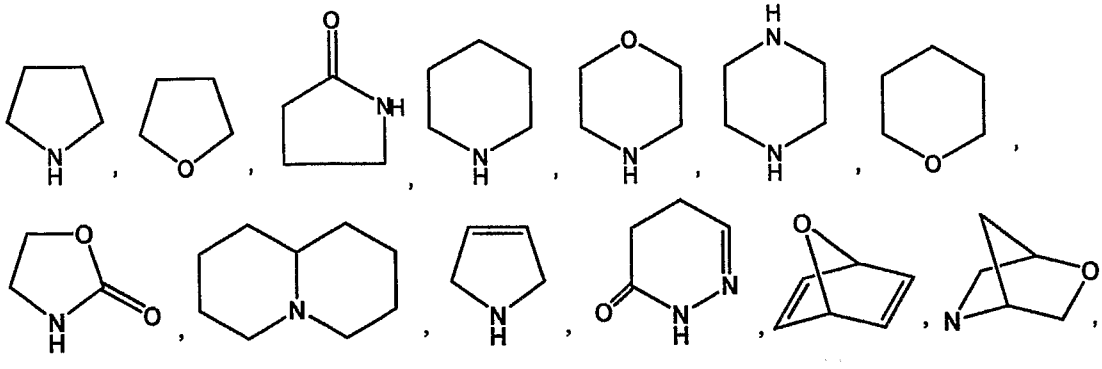
The term "cycloalkyl", as used herein, unless otherwise indicated refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon referred to herein containing a total of from 3 to 10 carbon atoms, preferably 5-8 ring carbon atoms. Exemplary cycloalkyls include monocyclic rings having from 3-10 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantyl. Illustrative examples of cycloalkyl are derived from, but not limited to, the following:

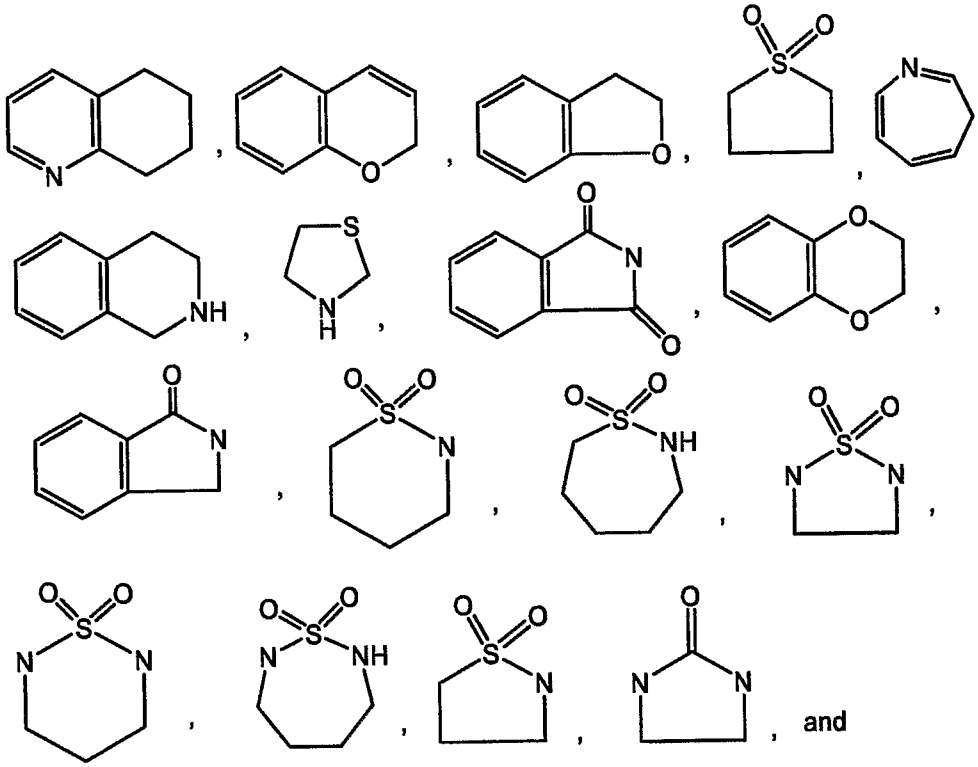


and

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "(4-12)-membered heterocyclyl", "(4-10)-membered heterocyclyl", "(4-7)-membered heterocyclyl", "(5-8)-membered heterocyclyl", or "(3-8)-membered heterocyclyl"as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3 membered heterocyclic group is aziridine, an example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl, an example of a 7 membered ring is azepinyl, and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). The 4-12 membered heterocyclic may be optionally substituted on any ring carbon, sulfur, or nitrogen atom(s) by one to two oxo, per ring. An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo moieties is 1,1-dioxo-thiomorpholinyl. Other Illustrative examples of 4-12 membered heterocyclic are derived from, but not limited to, the following:





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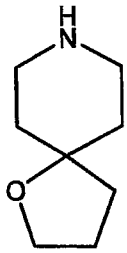


Unless otherwise indicated, the term "oxo" refers to =O.

A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO (dimethylsulfoxide), ethyl acetate, acetic acid, or ethanolamine.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula (I). The compounds of formula (I) that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formula (I) are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edislyate, estolate, esylate, ethylsuccinate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate,

phospate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The term "diseases in which the liver is a target organ", as used herein, unless otherwise indicated means diabetes, hepatitis, liver cancer, liver fibrosis, and malaria.

The term "Metabolic syndrome", as used herein, unless otherwise indicated means psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases, galactosemia, maple syrup urine disease, phenylketonuria, hypersarcosinemia, thymine uraciluria, sulfinuria, isovaleric acidemia, saccharopinuria, 4-hydroxybutyric aciduria, glucose-6-phosphate dehydrogenase deficiency, and pyruvate dehydrogenase deficiency.

In the compounds of formula (I), where terms such as $(CR^5R^6)_v$ or $(CR^8R^9)_p$ are used, R^5, R^6, $R^8$and R^9 may vary with each iteration of v or p. For instance, where v or p is 2 the terms $(CR^5R^6)_v$ or $(CR^8R^9)_p$ may equal $-CH_2CH_2-$, or $-CH(CH_3)C(CH_2CH_3)(CH_2CH_2CH_3)-$, or any number of similar moieties falling within the scope of the definitions of R^5, R^6, $R^8$and R^9.

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

The term "modulate" or "modulating", as used herein, refers to the ability of a modulator for a member of the steroid/thyroid superfamily to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of ligand from a precursor) induce expression of gene(s) maintained under hormone expression control, or to repress expression of gene(s) maintained under such control.

The term "obesity" or "obese", as used herein, refers generally to individuals who are at least about 20-30% over the average weight for his/her age, sex and height. Technically, "obese" is defined, for males, as individuals whose body mass index is greater than 27.8 kg/ m^2, and for females, as individuals whose body mass index is greater than 27.3 kg/m^2. Those of skill in the art readily recognize that the invention method is not limited to those who fall within the above criteria. Indeed, the method of the invention can also be advantageously practiced by individuals who fall outside of these traditional criteria, for example, by those who may be prone to obesity.

The term "inflammatory disorders", as used herein, refers to disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, chondrocalcinosis, gout, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibromyalgia, and cachexia.

The phrase "therapeutically effective amount", as used herein, refers to that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

The phrase "amount . . . effective to lower blood glucose levels", as used herein, refers to levels of compound sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10 nM up to 2 μM; with concentrations in the range of about 100 nM up to 500 nM being preferred. As noted previously, since the activity of different

compounds which fall within the definition of Formula (I) as set forth above may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

The phrase "insulin resistance", as used herein, refers to the reduced sensitivity to the actions of insulin in the whole body or individual tissues, such as skeletal muscle tissue, myocardial tissue, fat tissue or liver tissue. Insulin resistance occurs in many individuals with or without diabetes mellitus.

The phrase "insulin resistance syndrome", as used herein, refers to the cluster of manifestations that include insulin resistance, hyperinsulinemia, non insulin dependent diabetes mellitus (NIDDM), arterial hypertension, central (visceral) obesity, and dyslipidemia.

Certain compounds of formula (I) may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula (I), and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of formula (I), the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. The compounds of formula (I) may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are not limited to moieties described in Patini et al., Chem. Rev, 1996, 96, 3147-3176 and references cited therein.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention and pharmaceutically acceptable salts s of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula (I) of this invention thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

Other aspects, advantages, and features of the invention will become apparent from the detailed description below.

Detailed Description and Embodiments of the invention

The compounds of the present invention may have asymmetric carbon atoms. Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomeric mixtures and pure enantiomers are considered as part of the invention.

The compounds of formulas (I) that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formula (I) from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of formula (I) that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula (I). Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compounds of the present invention may also be useful in the treatment of other metabolic disorders associated with impaired glucose utilization and insulin resistance include major late-stage complications of NIDDM, such as diabetic angiopathy, atherosclerosis, diabetic nephropathy, diabetic neuropathy, and diabetic ocular complications such as retinopathy, cataract formation and glaucoma, and many other conditions linked to NIDDM, including dyslipidemia glucocorticoid induced insulin resistance, dyslipidemia, polycysitic ovarian syndrome, obesity, hyperglycemia, hyperlipidemia, hypercholesteremia,

hypertriglyceridemia, hyperinsulinemia, and hypertension. Brief definitions of these conditions are available in any medical dictionary, for instance, Stedman's Medical Dictionary (Xth Ed.).

Pharmaceutical Compositions/Formulations, Dosaging and Modes of Administration

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. In addition, those of ordinary skill in the art are familiar with formulation and administration techniques. Such topics would be discussed, *e.g.* in Goodman and Gilman's The Pharmaceutical Basis of Therapeutics, current edition, Pergamon Press; and Remington's Pharmaceutical Sciences, current edition. Mack Publishing, Co., Easton, Pa. These techniques can be employed in appropriate aspects and embodiments of the methods and compositions described herein. The following examples are provided for illustrative purposes only and are not meant to serve as limitations of the present invention.

The amino heterocyclyl compounds of formula (I) may be provided in suitable topical, oral and parenteral pharmaceutical formulations for use in the treatment of GK mediated diseases. The compounds of the present invention may be administered orally as tablets or capsules, as oily or aqueous suspensions, lozenges, troches, powders, granules, emulsions, syrups or elixirs. The compositions for oral use may include one or more agents for flavoring, sweetening, coloring and preserving in order to produce pharmaceutically elegant and palatable preparations. Tablets may contain pharmaceutically acceptable excipients as an aid in the manufacture of such tablets. As is conventional in the art these tablets may be coated with a pharmaceutically acceptable enteric coating, such as glyceryl monostearate or glyceryl distearate, to delay disintegration and absorption in the gastrointestinal tract to provide a sustained action over a longer period.

Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain active ingredients in admixture with excipients suitable for the manufacture of an aqueous suspension. Such excipients may be a suspending agent, such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; a dispersing or wetting agent that may be a naturally occurring phosphatide such as lecithin, a condensation product of ethylene oxide and a long chain fatty acid, for example polyoxyethylene stearate, a condensation product of ethylene oxide and a long chain aliphatic alcohol such as heptadecaethylenoxycetanol, a condensation product of ethylene oxide and a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate or a fatty acid hexitol anhydrides such as polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to know methods using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be formulated as a suspension in a non toxic perenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and

solvents that may be employed are water, Ringers solution and isotonic sodium chloride solution. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables.

The amino heterocyclyl compounds of formula (I) 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 that is solid at about 25 Celcius but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and other glycerides.

For topical use preparations, for example, creams, ointments, jellies solutions, or suspensions, containing the compounds of the present invention are employed.

The amino heterocyclyl compounds of formula (I) may also be administered in the form of liposome delivery systems such as small unilamellar vesicles, large unilamellar vesicles and multimellar vesicles. Liposomes can be formed from a variety of phospholipides, such as cholesterol, stearylamine or phosphatidylcholines.

Dosage levels of the compounds of the present invention are of the order of about 0.5 mg/kg body weight to about 100 mg/kg body weight. A preferred dosage rate is between about 30 mg/kg body weight to about 100 mg/kg body weight. It will be understood, however, that the specific dose level for any particular patient will depend upon a number of factors including the activity of the particular compound being administered, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. To enhance the therapeutic activity of the present compounds they may be administered concomitantly with other orally active antidiabetic compounds such as the sulfonylureas, for example, tolbutamide and the like.

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

The invention will now be described in reference to the following Examples. These Examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

EXAMPLES

In the examples described below, unless otherwise indicated, all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents may be purchased from commercial suppliers, such as Sigma-Aldrich Chemical Company, Acros Organics, or Lancaster Synthesis Ltd. and may be used without further purification unless otherwise indicated. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), and *N,N*-dimethylformamide (DMF) may be purchased from Aldrich in

Sure-Seal bottles and used as received. All solvents may be purified using standard methods known to those skilled in the art, unless otherwise indicated.

The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed using glass-backed silica gel 60 F 254 precoated plates (Merck Art 5719) and eluted with appropriate solvent ratios (v/v). Reactions were assayed by TLC or LCMS and terminated as judged by the consumption of starting material. Visualization of the TLC plates was done with UV light (254 nM wavelength) or with an appropriate TLC visualizing solvent and activated with heat. Flash column chromatography (Still et al., J. Org. Chem., 1978, 43, 2923) was performed using silica gel 60 (Merck Art 9385) or various MPLC systems, such as Biotage or ISCO purification system.

The compound structures in the examples below were confirmed by one or more of the following methods: proton magnetic resonance spectroscopy, mass spectroscopy, and elemental microanalysis. Proton magnetic resonance (^{1}H NMR) spectra were determined using a Bruker spectrometer operating at a field strength of 300 or 400 megahertz (MHz). Chemical shifts are reported in parts per million (PPM, δ) downfield from an internal tetramethylsilane standard. Alternatively, ^{1}H NMR spectra were referenced to signals from residual protons in deuterated solvents as follows: $CDCl_3$ = 7.25 ppm; DMSO-d_6 = 2.49 ppm; C_6D_6 = 7.16 ppm; CD_3OD = 3.30 ppm. Peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet; br, broadened; m, multiplet. Coupling constants are given in Hertz (Hz). Mass spectra (MS) data were obtained using Agilent mass spectrometer with APCI or ESI ionization. Elemental microanalyses were performed by Atlantic Microlab Inc. and gave results for the elements stated within ±0.4% of the theoretical values.

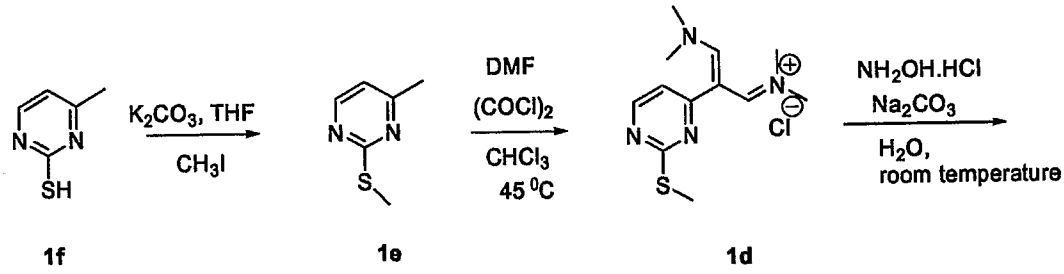
Preferred compounds in accordance with the invention may be prepared in manners analogous to those specifically described below.

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. The skilled artisan will recognize that different acids, amines, alkyl halides, aryl halides, coupling reagents, and heterocycles may be substituted in the following descriptions to suit the preparations of a desired embodiment. The following methods may be scaled upwards or downwards to suit the amount of desired material.

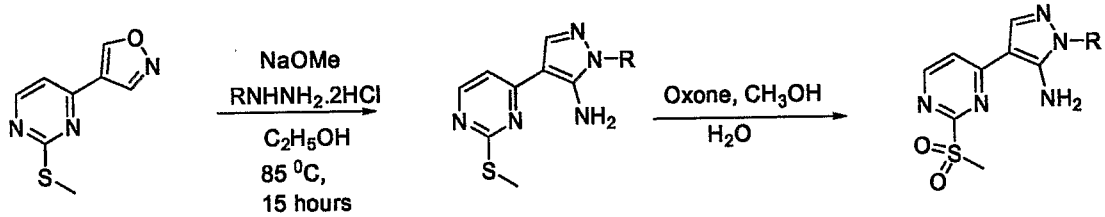
In the examples and specification, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, "ETOAC" or "EtOAc" means ethyl acetate, "THF" means tetrahydrofuran, and "Bu" means butyl. Et_2O refers to diethyl ether. DMF refers to *N,N*-dimethylformamide. DMSO refers to dimethylsulfoxide. MTBE refers to *tert*-butylmethyl ether. Other abbreviations include: CH_3OH or MeOH (methanol), EtOH (ethanol), DME (ethylene glycol dimethyl ether), DCM or CH_2Cl_2 (dichloromethane or methylene chloride), $CHCl_3$ (chloroform), 1,2-DCE (1,2-dichloroethane), Ph (phenyl), TFA (trifluoroacetic acid), DIEA (*N,N*-diisopropylethylamine), TEA or Et_3N (triethylamine), NMM (4-methylmorpholine), HOBt (1-

hydroxybenzotriazole hydrate), HATU [O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate], EDCI [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride], DCC (dicyclohexyl carbodiimide), DMAP (4-dimethylaminopyridine), NaOH (sodium hydroxide), KOH (potassium hydroxide), HCl (hydrogen chloride), $MgSO_4$ (magnesium sulfate), Na_2SO_4 (sodium sulfate), NH_4Cl (ammonium chloride), and $NaHCO_3$ (sodium bicarbonate).

Method A:



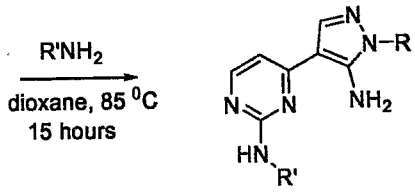
1f **1e** **1d**



1c

1b R = benzyl (Bn)
2b R = phenyl
3b R = methyl
4b R = p-methoxybenzyl (PMB)

1a R = Bn
2a R = Ph
3a R = Me
4a R = PMB



1 R = Benzyl, R' = 4-*trans*-cyclohexanol
2 R = Benzyl, R' = cyclohexyl
3 R = Benzyl, R' = *iso*propyl
4 R = Phenyl, R' = cyclohexyl
5 R = Phenyl, R' = *iso*propyl
6 R = PMB, R' = cyclohexyl
7 R = PMB, R' = *iso*propyl
8 R = Me, R' = 4-*trans*-cyclohexanol
9 R = Me, R' = 4-*trans*-benzyloxycyclohexanyl

Pyrimidine **1e** (4-methyl-2-(methylthio)pyrimidine) was prepared from 4-methylpyrimidine-2-thiol (**1f**) according to the procedure described in *Org. Lett.* **2003**, *4 (6)*, 979.

Preparation of (Z)-N-(3-(Dimethylamino)-2-(2-(methylthio)pyrimidin-4-yl)allylidene)-N-methylmethanaminium (1d)

Oxalyl chloride (33 mL, 375 mmol) was added dropwise via addition funnel to an ice-cooled mixture of DMF (30 mL, 393 mmol) in $CHCl_3$ (218 mL) with vigorous stirring. The mixture was stirred for 5 minutes after the addition was complete, and the solution was then warmed to 45 °C and allowed to stir for 30

minutes. The mixture then re-cooled to 0 °C, and **1e** (25.0 g, 179 mmol) in $CHCl_3$ (10 mL) was added dropwise via an addition funnel. The solution was then warmed to 45 °C, and the mixture was allowed to stir vigorously for 12 hour(s). The mixture was then removed from the heat, and the resulting solid mass was filtered, washed with cold $CHCl_3$, and dried under high vacuum to yield a pale brown solid (44.5 g, 99 %). This crud=e product (**1d**) was used without further purification. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 8.53 (d, 1 H), 8.19 (s, 2 H), 7.14 (d, 1 H), 3.42 (s, 6 H), 2.84 (s, 6 H), 2.52 (s, 3 H). LRMS m/z calculated for $C_{12}H_{20}N_4S$ ($[M+H]^+$): 252. Found: 252.

Preparation of 4-(Isoxazol-4-yl)-2-(methylthio)pyrimidine (1c)

Hydroxylamine hydrochloride (30.0 g, 434 mmol) was dissolved in water (400 mL) at room temperature. Na_2CO_3 (55.3 g, 521 mmol) was added slowly and the mixture stirred rapidly for 10 minutes. Compound **1d** (30.0 g, 119 mmol) was then added portion-wise over 15 minutes, and the resulting mixture was stirred rapidly at room temperature with the aid of a mechanical stirrer. After stirring for an additional 5 hour(s), the solid was filtered off, washed with cold water, and dried under high vacuum. The resulting tan solid (18.7 g) was suspended in CH_3CN / methanol (60 mL of each), and the mixture cooled to 0 °C. TFA (10 mL) was added as a stream over 5 minutes. The mixture was then allowed to warm to room temperature and stirred for 2 hour(s). After re-cooling to 0 °C, the mixture was basified with NH_4OH (concentrated aq), and the solid was filtered off, rinsed with cold water, and dried under high vacuum. The light tan solid (**1c**, 15.2 g, 66 %) was used without further purification. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.13 (s, 1 H), 8.84 (s, 1 H), 8.60 (d, 1 H), 7.21 (d, 1 H), 2.64 (s, 3 H). LRMS m/z calculated for $C_8H_8N_3OS$ ($[M+H]^+$): 194. Found: 194.

Preparation of 1-benzyl-4-[2-(methylthio)pyrimidin-4-yl]-1*H*-pyrazol-5-amine (1b)

Isoxazole **1c** (3.86 g, 20.0 mmol) was dissolved in ethanol (60 mL), and benzylhydrazine dihydrochloride (3.25 g, 16.7 mmol) and sodium methoxide (1.06 g, 33.4 mmol) were added sequentially. The mixture was heated at 85 °C for 15 hour(s), and then was allowed to cool to room temperature. The precipitate thus formed was filtered, washed thoroughly with ether, and dried *in vacuo* to yield pure methylthiopyrimidine **1b** as a pale yellow solid (2.23 g, 40 %). The filtrate was concentrated *in vacuo* to give an orange solid which, upon washing with ether followed by filtration, afforded an orange solid (1.40 g) which consisting of the desired product **1b** and unreacted isoxazole **1c**. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 2.34 (s, 3 H), 5.02 (s, 2 H), 5.39 (s, 2 H), 6.82 (d, 1 H), 7.03 (d, 2 H), 7.12 - 7.21 (m, 3 H), 7.59 (s, 1 H), 8.12 (d, 1 H). LRMS m/z calculated for $C_{15}H_{16}N_5S$ $[M+H]^+$ 298. Found: 298.

Preparation of 1-Methyl-4-(2-methylthio)pyrimidin-4-yl)-1H-pyrazole-5-amine (3b)

Isoxazole **1c** (2.50 g, 12.9 mmol) was dissolved in acetic acid (50 mL) and cooled in an ice bath to 0 °C. The mixture was stirred vigorously while methylhydrazine (10.3 mL, 194 mmol) was added dropwise via syringe at a rate such that the internal temperature remained below 35 °C. After the addition was complete, the mixture was removed from the ice bath, allowed to slowly warm to room temperature over 15 minutes, and then slowly warmed in an oil bath until a temperature of 85 °C was reached. The

reaction was stirred vigorously at 85 °C for 4.5 hour(s), at which time the flask was removed from the oil bath and cooled to 0 °C. The mixture was basified with NH_4OH (concentrated) to a pH of 10. The solid that precipitated out was filtered off, rinsed with a small amount of cold water, and dried under high vacuum. The resultant crude product (**7**, light tan solid, 2.12 g, 74 %) contained a mixture of regioisomers (6:1, methyl-5-aminopyrazole: methyl-3-aminopyrazole) and was used without further purification. ^1H NMR (400 MHz, DMSO-D6) δ ppm 8.30 (d, 1 H), 7.87 (s, 1 H), 7.22 (d, 1 H), 6.64 (s, 2 H), 3.56 (s, 3 H), 2.52 (s, 3 H). LRMS m/z calculated for $C_9H_{12}N_5S$ ([M+H]+): 222. Found: 222.

Preparation of 1-(4-methoxybenzyl)-4-[2-(methylthio)pyrimidin-4-yl]-1*H*-pyrazol-5-amine (4b)

Isoxazole **1c** (1.80 g, 9.32 mmol) was dissolved in ethanol (30 mL), and 4-methoxybenzylbenzylhydrazine hydrochloride (1.76 g, 9.32 mmol) and sodium methoxide (0.504 g, 9.32 mmol) were added sequentially. The mixture was refluxed under N_2 for 15 hour(s), and then was allowed to cool to room temperature. Analysis of an aliquot by LCMS showed incomplete conversion. An additional portion of 4-methoxybenzylbenzylhydrazine hydrochloride (0.352 g, 1.86 mmol) and sodium methoxide (0.100 g, 1.86 mmol) were added, and the mixture was then refluxed for an additional 8 hour(s). The resulting solution was cooled to room temperature and concentrated *in vacuo*, and the resulting solid was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered. The filtrate thus obtained was concentrated *in vacuo* to give reddish paste. Purification by column chromatography (0 –50 % ethyl acetate in hexanes) yielded pyrimidine **4b** (1.52 g, 50 %) as an orange solid. ^1H NMR (400 MHz, CD_2Cl_2) δ ppm 2.34 (s, 3 H), 5.02 (s, 2 H), 5.39 (s, 2 H), 6.82 (d,1 H), 7.03 (d, 2 H), 7.12 - 7.21 (m, 3 H), 7.59 (s, 1 H), 8.12 (d,1 H). LRMS m/z calculated for $C_{16}H_{18}N_5O_2S$ $[M+H]^+$ 344. Found: 344.

Preparation of 1-benzyl-4-[2-(methylsulfonyl)pyrimidin-4-yl]-1H-pyrazol-5-amine (1a)

Methylthiopyrimidine **1b** (2.20 g, 3.40 mmol) was dissolved in methanol/water (10 mL/1.2 mL) and a suspension of oxone (2.93 g, 4.76 mmol) in water (8.5 mL) was added in portions while stirring the methylthiopyrimidine solution at room temperature. An additional 8.5 mL of water was used to complete the addition of oxone. The resulting yellow suspension turned orange in color after stirring 3 hour(s) at room temperature. The suspension was filtered, and the filtrate was extracted several times with 10% methanol in CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product (900 mg). Purification by column chromatography (0 – 70 % ethyl acetate in hexanes) yielded the sulfone **1a** (319 mg, 15 %) as a pale yellow solid. ^1H NMR (400 MHz, CD_3OD) δ ppm 3.35 (s, 3 H), 5.26 (s, 2 H), 7.23 (d, 2 H), 7.27 - 7.71 (m, 5H), 8.03 (s, 1 H), 8.62 (d, 1 H). LRMS m/z calculated for $C_{15}H_{15}N_5O_2S$ $[M+H]^+$ 330. Found: 330.

Compound **2a** was prepared analogous to the method of preparing compound **1a**.

Preparation of 1-Methyl-4-(2-methylsulfonyl)pyrimidin-4-yl)-1H-pyrazole-5-amine (3a)

Compound **3b** (2.00 g, 9.05 mmol) was dissolved in THF (40 mL), cooled in an ice bath to 0 °C, and *m*-CPBA (4.81 g, 27.9 mmol, 77 % tech grade) was added in one portion. The mixture was then allowed to

warm to room temperature slowly, and stirred for 6 hour(s). The mixture was then cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ until a pH of 9 was reached. The aqueous solution was extracted with ethyl acetate (6 x 50 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide a dark orange oil. The crude product was purified by medium pressure liquid chromatography (CH_2Cl_2 to 100 % ethyl acetate / CH_2Cl_2) to afford pure product (**3a**) as a white solid (1.85 g, 81 %). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 8.65 (d, 1 H), 8.01 (s, 1 H), 7.75 (d, 1 H), 6.88 (s, 2 H), 3.59 (s, 3 H), 3.37 (s, 3 H). LRMS m/z calculated for $C_9H_11N_5O_2S$ ([M+H]+): 254. Found: 254.

Preparation of 1-(4-methoxybenzyl)-4-[2-(methylsulfonyl)pyrimidin-4-yl]-1*H*-pyrazol-5-amine (4a)
Methylthiopyrimidine **4b** (2.00 g, 6.12 mmol) was reacted with oxone as described in the synthesis of compound **1a** to yield a mixture of sulfoxide **4a** and the corresponding sulfoxide (total of 1.60 g, 70%, **4a**:sulfoxide in a 2:1 ratio by ^{1}H NMR) as a pale yellow solid. For the mixture of **4a** and sulfoxide: ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 2.73 - 2.80 (m, 2 H), 3.15 - 3.23 (m, 5 H), 3.67 - 3.76 (m, 8 H), 5.05 (s, 5 H), 5.69 (s, 3 H), 5.92 (s, 1 H), 6.76 - 6.87 (m, 5 H), 7.08 (d, *J* = 8.6 Hz, 5 H), 7.17 (d, *J* = 5.6 Hz, 1 H), 7.30 (d, *J* = 5.6 Hz, 2 H), 7.69 - 7.77 (m, 2 H), 8.46 (d, *J* = 5.6 Hz, 2 H). Sulfone **4a**: LRMS m/z calculated for $C_{16}H_{18}N_5O_3S$ $[M+H]^+$ 360. Found: 360.; Sulfoxide: LRMS m/z calculated for $C_{16}H_{18}N_5O_2S$ $[M+H]^+$ 344. Found: 344.

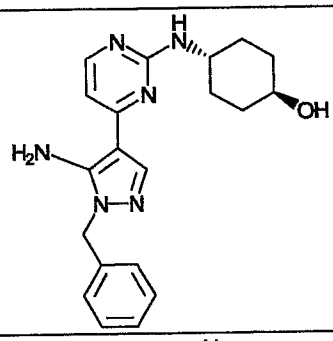
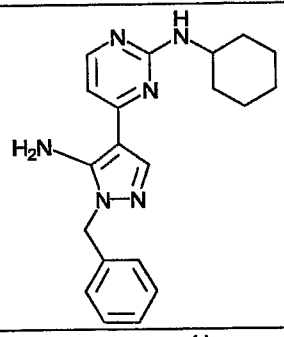
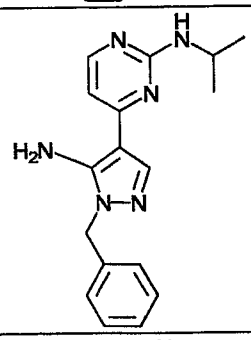
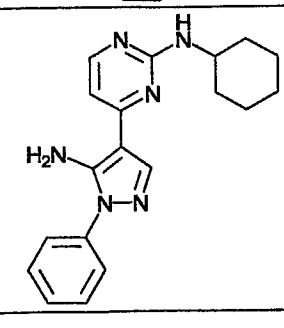
Preparation of *trans*-4-{[4-(5-amino-1-benzyl-1*H*-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol (1)
Methylsulfonylpyrimidine **1a** (315 mg, 0.96 mmol) was suspended in 1,4-dioxane (2 mL) and *trans*-aminocyclohexanol (553 mg, 4.80 mmol) was added at room temperature. The resulting suspension was stirred at 85 °C for 2.5 days under an inert atmosphere in a sealed tube. The solution was cooled to room temperature, and the resulting slurry was dissolved in CH_2Cl_2 with the aid of a small amount of methanol. The solution thus obtained was concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0 – 7% methanol in CH_2Cl_2) to yield *trans*-pyrimidine **1** (197 mg, 59%) as a pale yellow solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.29 - 1.42 (m, 5 H), 1.94 - 2.03 (m, 2 H), 2.15 (dd, 2 H), 3.63 - 3.75 (m, 2 H), 5.00 (s, 1 H), 5.22 (s, 2 H), 5.59 (s, 2 H), 6.64 (d, 1 H), 7.21 - 7.29 (m, 2 H), 7.32 - 7.43 (m, 3 H), 7.74 (s, 1 H), 8.12 (d, 1 H). LRMS m/z calculated for $C_{20}H_{25}N_6O$ $[M+H]^+$ 365. Found: 365.

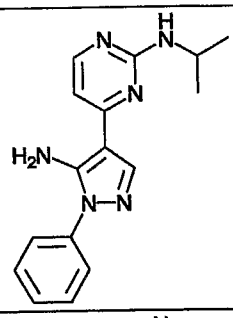
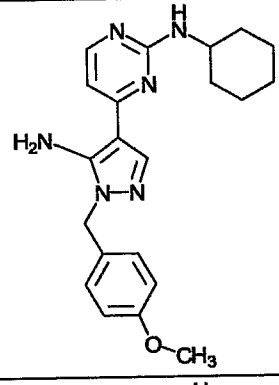
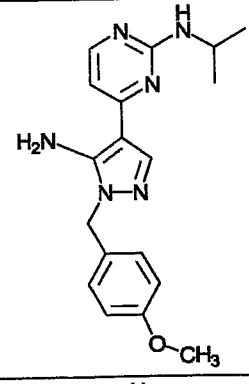
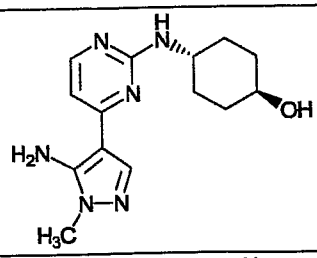
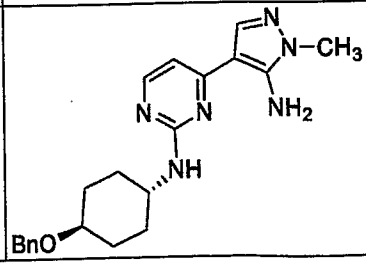
Preparation of 4-[5-amino-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]-*N*-isopropylpyrimidin-2-amine (7)
A mixture of sulfone **4a** and the corresponding sulfoxide (1.50 g, 4.23 mmol) were reacted as described for the synthesis of compound **1**, except that aminocyclohexanol was replaced with isopropyl amine, to afford compound **7** (1.28 g, 89%) as an off-white solid. See tabulated data.

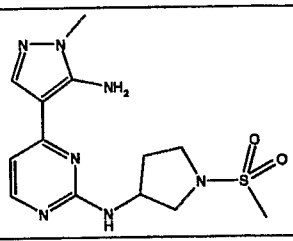
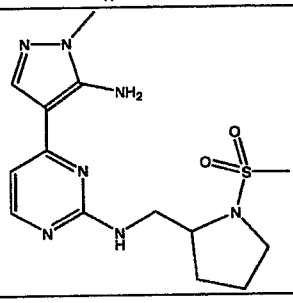
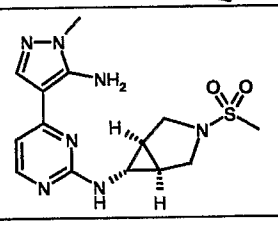
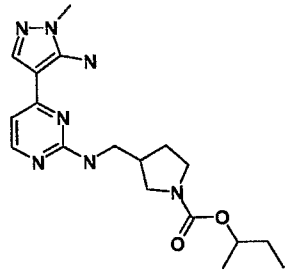
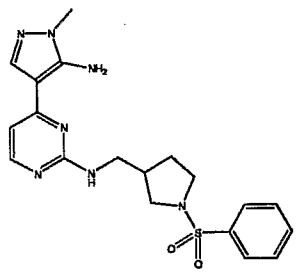
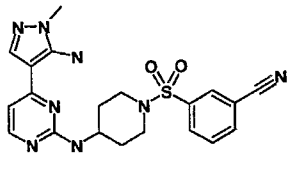
Preparation of 4-(5-Amino-1-methyl-1H-pyrazol-4-yl)-N-((1R,4R)-4-(benzyloxy)cyclohexyl)pyrimidin-2-amine (9)
Compound **3a** (0.30 g, 1.18 mmol) was dissolved in dioxane (12 mL) in a sealed tube, and trans-4-benzyloxy-cyclohexylamine (2.40 g, 11.7 mmol) was added in one portion. The mixture was warmed to

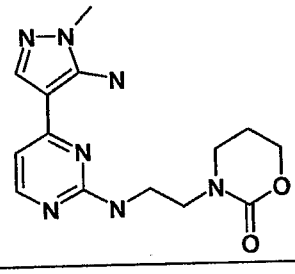
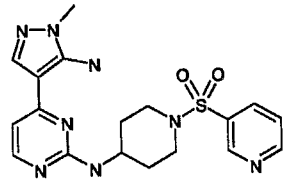
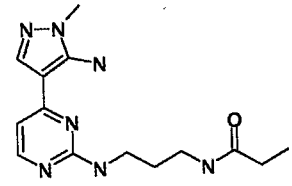
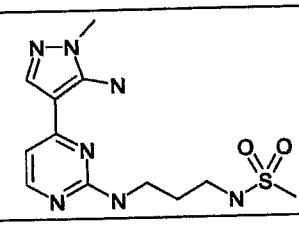
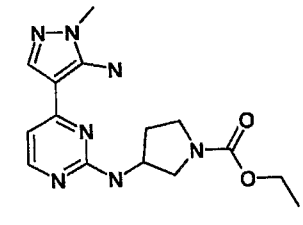
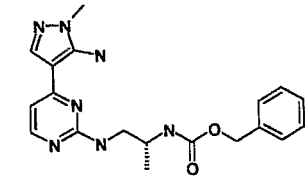
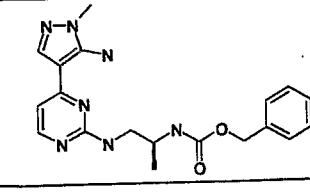
125 °C and stirred for 24 hour(s). The mixture was then removed from the oil bath and concentrated *in vacuo* to afford a reddish oil. The crude product was purified by medium pressure liquid chromatography (hexanes to ethyl acetate) to afford pure product (**9**) as a white solid (0.29 g, 65 %). ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.07 (d, 1 H), 7.61 (s, 1 H), 7.22 - 7.37 (m, 5 H), 6.57 (d, 1 H), 5.59 (br s, 2 H), 4.84 - 5.02 (m, 1 H), 4.54 (s, 2 H), 3.69 - 3.83 (m, 1 H), 3.62 (s, 3 H), 3.35 - 3.48 (m, 1 H), 2.06 - 2.25 (m, 4 H), 1.39 - 1.53 (m, 2 H), 1.22 - 1.38 (m, 2 H). LRMS m/z calculated for $C_{21}H_{27}N_6O$ ([M+H]+): 379. Found: 379.

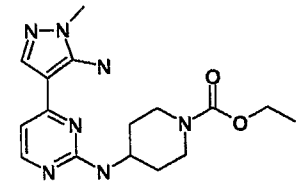
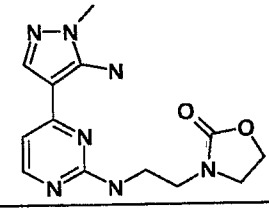
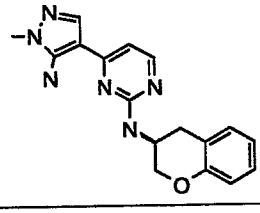
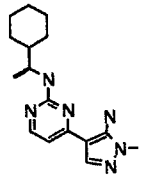
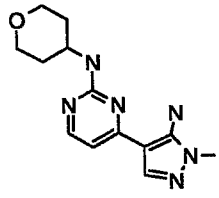
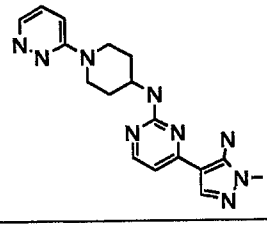
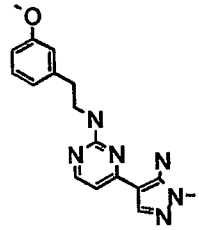
Table 1. Compounds 1-109 were prepared according to the method A as described above.

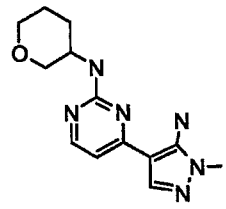
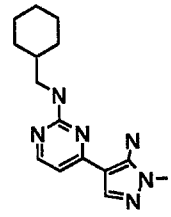
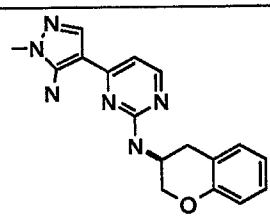
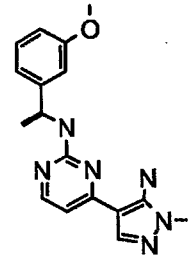
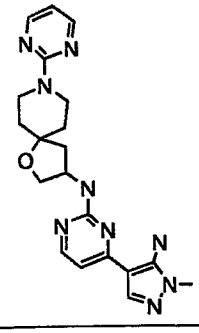
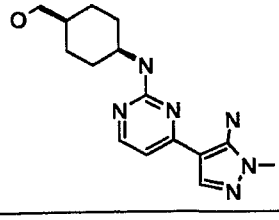
#	Structure	Compound Name	LRMS	^{1}H NMR
1		trans-4-{[4-(5-amino-1-benzyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	364	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 1.16 - 1.28 (m, 4 H), 1.84 - 1.95 (m, 3 H), 2.02 -2.05 (m, 2H), 3.51 - 3.62 (m, 2 H), 4.81 - 4.93 (m, 1 H), 5.10 (s, 2 H), 5.46 (s, 2 H), 6.52 (d, 1 H), 7.09 - 7.16 (m, 2 H), 7.20 - 7.31 (m, 3 H), 7.63 (s, 1 H), 8.00 (d, 1 H)
2		4-(5-amino-1-benzyl-1H-pyrazol-4-yl)-N-cyclohexylpyrimidin-2-amine	349	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 1.09 - 1.20 (m, 3 H), 1.21 - 1.33 (m, 2 H), 1.65 - 1.71 (m, 2 H), 1.93 - 1.96 (m, 2 H), 3.61 (m, 1 H), 4.91 (s, 1 H), 5.10 (s, 2 H), 5.47 (s, 2 H), 6.50 (d, 1 H), 7.11 (m, 2 H), 7.20 - 7.30 (m, 3 H), 7.60 - 7.65 (m, 1 H), 8.00 (d, 1 H)
3		4-(5-amino-1-benzyl-1H-pyrazol-4-yl)-N-isopropylpyrimidin-2-amine	309	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 1.13 (d, 6 H), 3.92 - 3.98 (m, 1 H), 4.82 (s, 1 H), 5.10 (s, 2 H), 5.45 (s, 2 H), 6.52 (d, 1 H), 7.11 (d, 2 H), 7.20 - 7.31 (m, 3 H), 7.62 (s, 1 H), 8.01 (d, 1 H)
4		4-(5-amino-1-phenyl-1H-pyrazol-4-yl)-N-cyclohexylpyrimidin-2-amine	335	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 8.11 (d, *J*=5.3 Hz, 1 H), 7.83 (s, 1 H), 7.47 - 7.64 (m, 4 H), 7.36 - 7.45 (m, 1 H), 6.64 (d, *J*=5.6 Hz, 1 H), 5.99 (br s, 2 H), 4.93 - 5.03 (m, 1 H), 3.67 - 3.80 (m, 1 H), 2.02 - 2.12 (m, 2 H), 1.71 - 1.83 (m, 2 H), 1.58 - 1.69 (m, 1 H), 1.19 - 1.44 (m, 5 H)

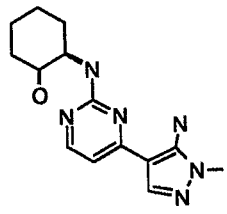
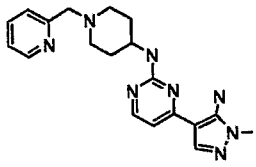
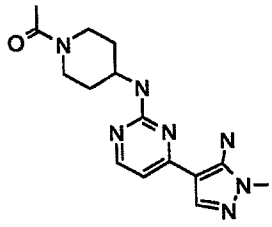
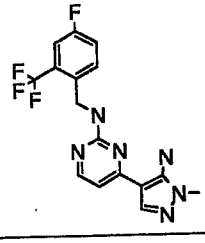
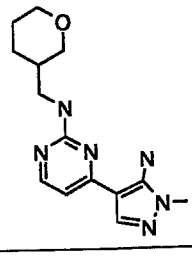
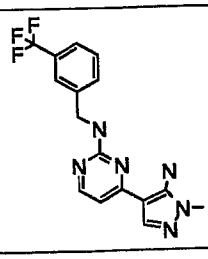
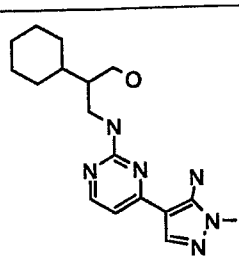
#	Structure	Compound Name	LRMS	^{1}H NMR
5		4-(5-amino-1-phenyl-1H-pyrazol-4-yl)-N-isopropylpyrimidin-2-amine	295	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 8.12 (d, *J*=5.3 Hz, 1 H), 7.83 (s, 1 H), 7.48 - 7.64 (m, 4 H), 7.36 - 7.48 (m, 1 H), 6.65 (d, *J*=5.3 Hz, 1 H), 5.99 (bs, 2 H), 4.85 - 4.97 (m, 1 H), 4.00 - 4.13 (m, 1 H), 1.21 - 1.29 (m, 6 H)
6		4-[5-amino-1-(4-methoxybenzyl)-1H-pyrazol-4-yl]-N-cyclohexylpyrimidin-2-amine	378	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 1.26 – 1.30 (m, 3 H), 1.35-1.41 (m, 2 H), 1.78 – 1.82 (m, 3 H), 2.06 – 2.10 (m, 2 H), 3.71 – 3.75 (m, 1 H), 3.81 (s, 3 H) 4.98 (s, 1 H), 5.14 (s, 2 H), 5.56 (s, 2 H), 6.61 (d, 1 H), 6.89 - 7.00 (m, 2 H), 7.17 – 7.19 (m, 2 H), 7.72 (s, 1 H), 8.10 (d, 1 H)
7		4-[5-amino-1-(4-methoxybenzyl)-1H-pyrazol-4-yl]-N-isopropylpyrimidin-2-amine	338	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 1.14 (d, 6 H), 3.69 (s, 3 H), 3.92 – 3.96 (m, 1 H), 4.82 (s, 1 H), 5.03 (s, 2 H), 5.44 (s, 2 H), 6.50 (d, 1 H), 6.77 - 6.86 (m, 2 H), 7.06 (d, 2 H), 7.60 (s, 1 H), 8.00 (d, 1 H)
8		4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	289	1H NMR (400 MHz, CD_3OD) δ ppm 7.98 (d, 1 H), 7.72 (s, 1 H), 6.66 (d, 1 H), 3.55 - 3.69 (m, 5 H), 2.05 - 2.16 (m, 2 H), 1.95 - 2.04 (m, 2 H), 1.27 - 1.51 (m, 4 H)
9		4-(5-Amino-1-methyl-1H-pyrazol-4-yl)-N-((1R,4R)-4-(benzyloxy)cyclohexyl)pyrimidin-2-amine	379	^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.07 (d, 1 H), 7.61 (s, 1 H), 7.22 - 7.37 (m, 5 H), 6.57 (d, 1 H), 5.59 (br s, 2 H), 4.84 - 5.02 (m, 1 H), 4.54 (s, 2 H), 3.69 - 3.83 (m, 1 H), 3.62 (s, 3 H), 3.35 - 3.48 (m, 1 H), 2.06 - 2.25 (m, 4 H), 1.39 - 1.53 (m, 2 H), 1.22 - 1.38 (m, 2 H).

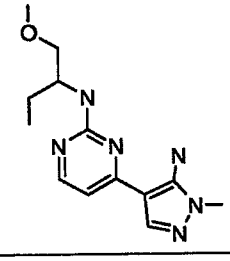
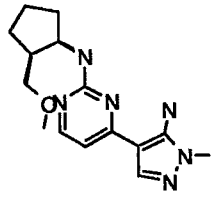
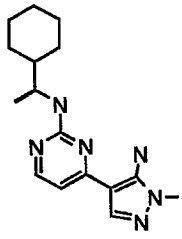
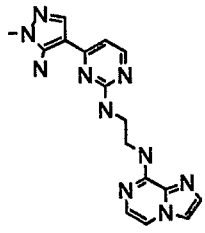
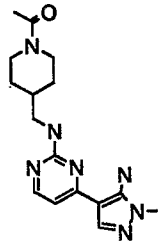
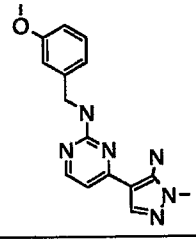
#	Structure	Compound Name	LRMS	^{1}H NMR
10		4-(5-Amino-1-methyl-1H-pyrazol-4-yl)-N-(1-(methylsulfonyl)pyrrolidin-3-yl)pyrimidin-2-amine	338	1H NMR (400 MHz, DMSO-d6) δ ppm 1.95 - 2.07 (m, 1 H) 2.23 - 2.37 (m, 3 H) 3.20 - 3.30 (m, 1 H) 3.33 - 3.49 (m, 2 H) 3.58 (s, 3 H) 7.04 (d, J = 7.1 Hz, 1 H) 7.90 - 7.97 (m, 1 H) 8.00 (s, 1 H)
11		4-(5-Amino-1-methyl-1H-pyrazol-4-yl)-N-((1-(methylsulfonyl)pyrrolidin-2-yl)methyl)pyrimidin-2-amine	352	1H NMR (400 MHz, DMSO-d6) δ ppm 1.67 - 2.08 (m, 5 H) 2.93 (s, 3 H) 3.25 – 3.40 (m, 2 H) 3.43 - 3.55 (m, 1 H) 3.59 (s, 3 H) 3.81 - 3.95 (m, 1 H) 6.91 - 7.12 (m, 1 H) 7.90 - 8.10 (m, 2 H)
12		(1S,5R,6S)-N-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-3-(methylsulfonyl)-3-aza-bicyclo[3.1.0]hexan-6-amine	350	1H NMR (400 MHz, DMSO-d6) δ ppm 2.48 - 2.51 (m, 3 H) 2.71 - 2.74 (m, 1 H) 2.92 (s, 3 H) 3.37 (d, J = 9.1 Hz, 1 H) 3.57 (s, 3 H) 3.68 (d, J = 9.3 Hz, 1 H) 7.06 (d, J = 7.1 Hz, 1 H) 7.97 (d, J = 6.8 Hz, 1 H) 8.01 (s, 1 H)
13		sec-butyl 3-({[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}methyl)pyrrolidine-1-carboxylate	374	1H NMR (400 MHz, DMSO-d6) δ ppm 0.88 (m, 6 H) 1.65 (m, 1 H) 1.84 (m, 1 H) 1.96 (m, 1 H) 3.07 (m, 1 H) 3.20 - 3.70 (m, 6 H) 3.56 (s, 3 H) 3.75 (d, J = 6.3 Hz, 2 H) 6.65 (d, J = 5.5 Hz, 1 H) 6.69 (br s, 2 H) 7.22 (t, J = 5.8 Hz, 1 H) 7.72 (s, 1 H) 8.02 (d, J = 5.3 Hz, 1 H)
14		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-{[1-(phenylsulfonyl)pyrrolidin-3-yl]methyl}pyrimidin-2-amine	414	1H NMR (400 MHz, DMSO-d6) δ ppm 1.42 - 1.53 (m, 1 H) 1.78 - 1.88 (m, 1 H) 2.26 - 2.39 (m, 1 H) 2.97 (dd, J = 10.1, 6.8 Hz, 1 H) 3.06 - 3.13 (m, 1 H) 3.13 (t, J = 7.6 Hz, 1 H) 3.23 - 3.28 (m, 1 H) 3.31 (dd, J = 9.8, 7.3 Hz, 2 H) 3.56 (s, 3 H) 6.64 (d, J = 5.5 Hz, 1 H) 6.64 (br s, 2 H) 7.13 (t, J = 5.5 Hz, 1 H) 7.61 (t, J = 7.3 Hz, 2 H) 7.68 (t, J = 7.3 Hz, 1 H) 7.71 (s, 1 H) 7.80 (d, J = 8.6 Hz, 1 H) 7.79 (s, 1 H) 7.99 (d, J = 5.4 Hz, 1 H)
15		3-[(4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}piperidin-1-yl)sulfonyl]benzonitrile	439	1H NMR (400 MHz, DMSO-d6) δ ppm 1.48 - 1.52 (m, 2 H) 1.93 - 2.02 (m, 2 H) 2.61 (t, J = 10.7 Hz, 1 H) 3.61 (s, 3 H) 3.65 - 3.74 (m, 1 H) 6.64 (br. s., 2 H) 6.63 (d, J = 5.3 Hz, 1 H) 7.03 (d, J = 7.6 Hz, 1 H) 7.70 (s, 1 H) 7.87 (t, J = 7.8 Hz, 1 H) 7.98 (d, J = 5.5 Hz, 1 H) 8.09 (dt, J = 8.1, 1.4 Hz, 1 H) 8.22 (d, J = 7.8 Hz, 1 H) 8.24 - 8.25 (m, 1 H)

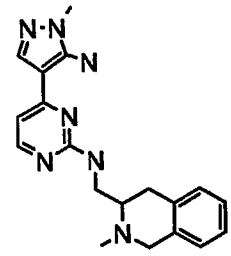
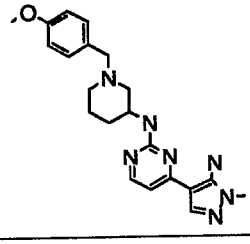
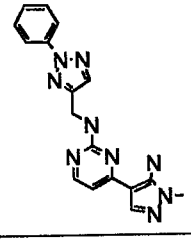
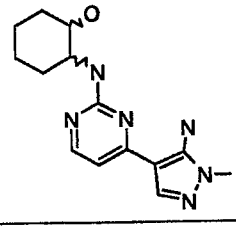
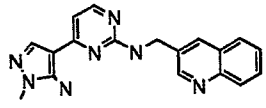
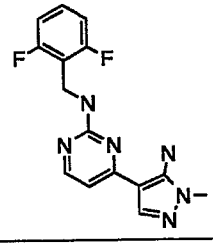
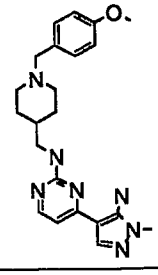
#	Structure	Compound Name	LRMS	^{1}H NMR
16		3-(2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}ethyl)-1,3-oxazinan-2-one	318	1H NMR (400 MHz, DMSO-d6) δ ppm 1.90 (m, 2 H) 3.33 (t, J = 6.0 Hz, 2 H) 3.37 (t, J = 6.8 Hz, 2 H) 3.46 (q, J = 6.0 Hz, 2 H) 3.56 (s, 3 H) 4.13 (t, 2 H) 6.66 (d, J = 5.3 Hz, 1 H) 6.66 (br s, 2 H) 7.19 (br s, 1 H) 7.72 (s, 1 H) 8.04 (d, J = 5.5 Hz, 1 H)
17		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[1-(pyridin-3-ylsulfonyl)piperidin-4-yl]pyrimidin-2-amine	415	1H NMR (400 MHz, DMSO-d6) δ ppm 1.46 - 1.70 (m, 2 H) 2.02 (d, J = 12.8 Hz, 2 H) 2.41 - 2.54 (m, 1 H) 3.53 - 3.65 (m, 2 H) 3.57 (s, 3 H) 3.66 - 3.79 (m, 2 H) 6.99 (d, J = 7.1 Hz, 1 H) 7.73 (s, 1 H) 7.85 - 7.93 (m, 1 H) 7.99 (br s, 1 H) 8.18 - 8.25 (m, 1 H) 8.91 (dd, J = 4.8, 1.5 Hz, 1 H) 8.93 - 8.98 (m, 1 H)
18		N-(3-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}propyl)propanamide	304	1H NMR (400 MHz, DMSO-d6) δ ppm 0.99 (t, J = 7.7 Hz, 3 H) 1.67 (m, 2 H) 2.07 (q, J = 7.6 Hz, 2 H) 3.12 (q, J = 6.8 Hz, 2 H) 3.26 (q, J = 6.5 Hz, 2 H) 3.57 (s, 3 H) 6.70 (d, J = 5.5 Hz, 1 H) 6.76 (br s, 2 H) 7.31 (br s, 1 H) 7.77 (s, 1 H) 7.78 (t, J = 5.3 Hz, 1 H) 8.02 (d, J = 5.5 Hz, 1 H)
19		N-(3-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}propyl)methanesulfonamide	326	1H NMR (400 MHz, DMSO-d6) δ ppm 1.74 (m, 2 H) 2.89 (s, 3 H) 3.02 (q, J = 6.8 Hz, 2 H) 3.31 (q, J = 6.8 Hz, 2 H) 3.56 (s, 3 H) 6.69 (d, J = 5.5 Hz, 1 H) 6.75 (br s., 2 H) 7.02 (t, J=5.8 Hz, 1 H) 7.29 (br.s, 1 H) 7.76 (s, 1 H) 8.02 (d, J = 5.5 Hz, 1 H)
20		ethyl 3-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}pyrrolidine-1-carboxylate	332	1H NMR (400 MHz, DMSO-d6) δ ppm 1.11 - 1.21 (m, 3 H) 1.81 - 1.95 (m, 1 H) 2.04 - 2.18 (m, 1 H) 3.18 - 3.27 (m, 1 H) 3.31 - 3.40 (m, 1 H) 3.40 - 3.50 (m, 1 H) 3.51 - 3.63 (m, 1 H) 3.55 (s, 3 H) 3.95 - 4.08 (m, 2 H) 4.25 - 4.37 (m, 1 H) 6.66 (br s, 2 H) 6.68 (d, J = 5.3 Hz, 1 H) 7.29 (t, J = 6.0 Hz, 1 H) 7.72 (s, 1 H) 8.04 (d, J = 5.3 Hz, 1 H)
21		benzyl [(1R)-2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}-1-methylethyl]carbamate	382	1H NMR (400 MHz, DMSO-d6) δ ppm 1.06 (d, J = 6.55 Hz, 3 H) 3.27 (t, J = 6.04 Hz, 2 H) 3.54 (s, 3 H) 3.68 - 3.81 (m, 1 H) 4.98 (s, 2 H) 6.54 - 6.73 (m, J = 5.54 Hz, 3 H) 7.18 (d, J = 7.55 Hz, 1 H) 7.23 - 7.38 (m, 6 H) 7.70 (s, 1 H) 8.00 (d, J = 5.29 Hz, 1 H)
22		benzyl [(1S)-2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}-1-methylethyl]carbamate	382	1H NMR (400 MHz, DMSO-d6) δ ppm 1.08 (d, J = 6.55 Hz, 3 H) 3.25 - 3.32 (m, 2 H) 3.56 (s, 3 H) 3.70 - 3.82 (m, 1 H) 5.00 (s, 2 H) 6.66 (d, J = 5.29 Hz, 2 H) 7.25 - 7.39 (m, 4 H) 7.72 (s, 1 H) 8.02 (d, J = 5.29 Hz, 1 H)

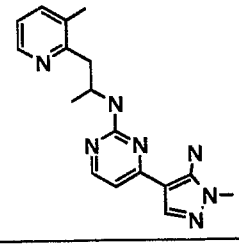
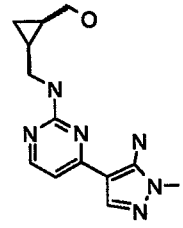
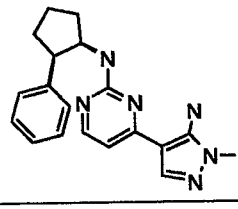
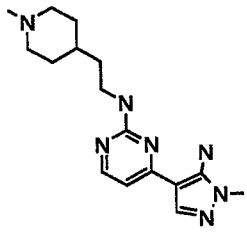
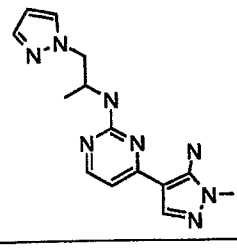
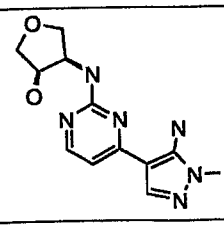
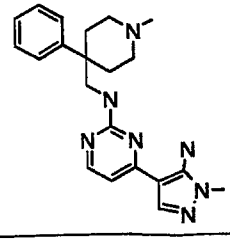
#	Structure	Compound Name	LRMS	^{1}H NMR
23		ethyl 4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate	346	1H NMR (400 MHz, DMSO-d6) δ ppm 1.19 (t, J = 7.18 Hz, 3 H) 1.27 - 1.41 (m, J = 6.29 Hz, 2 H) 1.91 (dd, J = 12.72, 2.64 Hz, 2 H) 2.82 - 3.03 (m, 2 H) 3.33 (s, 1 H) 3.56 (s, 3 H) 3.94 (d, J = 13.09 Hz, 2 H) 4.04 (q, J = 7.05 Hz, 2 H) 6.64 (d, J = 5.54 Hz, 1 H) 6.67 (s, 2 H) 6.97 - 7.06 (m, J = 7.55 Hz, 1 H) 7.71 (s, 1 H) 8.02 (d, J = 5.29 Hz, 1 H)
24		3-{2-[4-(5-Amino-1-methyl-1H-pyrazol-4-yl)-pyrimidin-2-ylamino]-ethyl}-oxazolidin-2-one	304	1H NMR (400 MHz, DMSO-d6) δ ppm 8.03 (d, J = 5.5, 1H), 7.77 (br s, 1H), 6.78-6.68 (m, 3H), 4.23 (t, J = 7.8, 2H), 3.61 (t, J = 8.1, 2H), 3.57 (s, 3H), 3.46 (dd, J = 12.3, 6.3, 2H), 3.37-3.31 (m, 2H)
25		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(3S)-34-dihydro-2H-chromen-3-yl]pyrimidin-2-amine	323	
26		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(1R)-1-cyclohexylethyl]pyrimidin-2-amine	301	
27		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-2-amine	275	
28		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(1-pyridazin-3-ylpiperidin-4-yl)pyrimidin-2-amine	352	
29		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[2-(3-methoxyphenyl)ethyl]pyrimidin-2-amine	325	

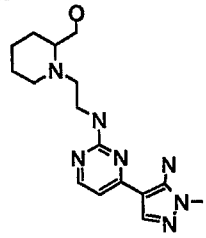
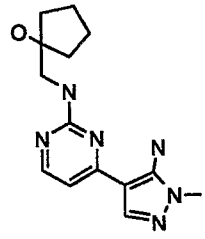
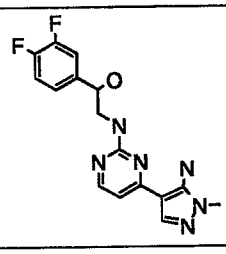
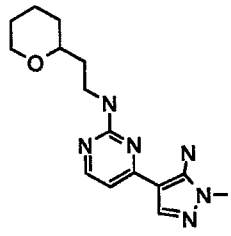
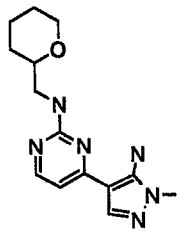
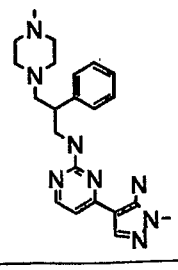
#	Structure	Compound Name	LRMS	^{1}H NMR
30		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(tetrahydro-2H-pyran-3-yl)pyrimidin-2-amine	275	
31		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(cyclohexylmethyl)pyrimidin-2-amine	287	
32		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(3R)-34-dihydro-2H-chromen-3-yl]pyrimidin-2-amine	323	
33		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(1R)-1-(3-methoxyphenyl)ethyl]pyrimidin-2-amine	325	
34		N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-8-pyrimidin-2-yl-1-oxa-8-azaspiro[4.5]decan-3-amine	408	
35		(cis-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)methanol	303	

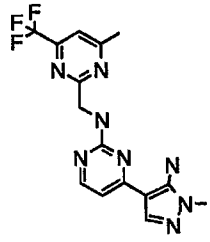
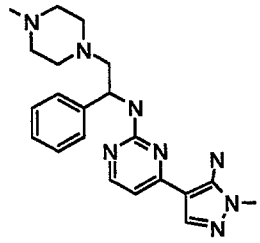
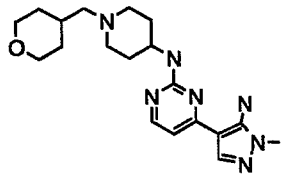
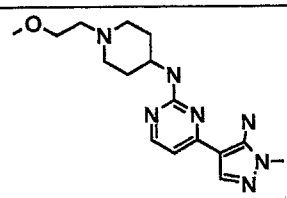
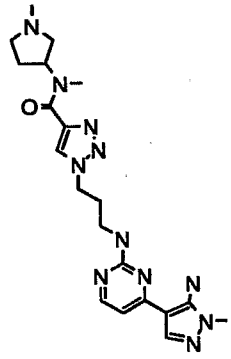
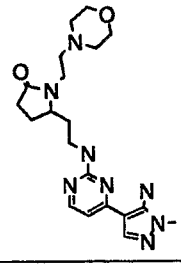
#	Structure	Compound Name	LRMS	^{1}H NMR
36		(1S2S)-2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	289	
37		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[1-(pyridin-2-ylmethyl)piperidin-4-yl]pyrimidin-2-amine	365	
38		N-(1-acetylpiperidin-4-yl)-4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine	316	
39		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[4-fluoro-2-(trifluoromethyl)benzyl]pyrimidin-2-amine	367	
40		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(tetrahydro-2H-pyran-3-ylmethyl)pyrimidin-2-amine	289	
41		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[3-(trifluoromethyl)benzyl]pyrimidin-2-amine	349	
42		3-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}-2-cyclohexylpropan-1-ol	331	

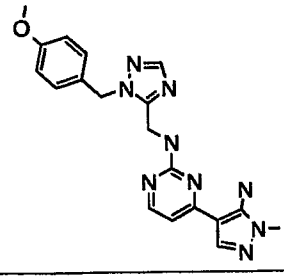
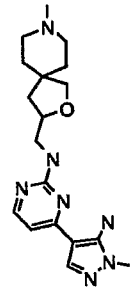
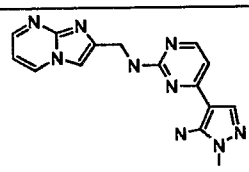
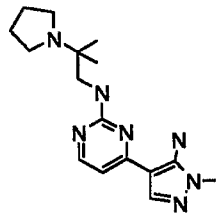
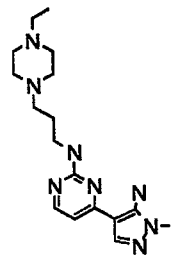
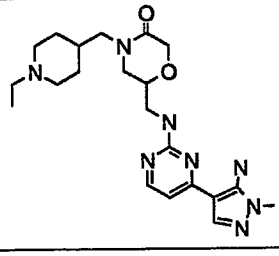
#	Structure	Compound Name	LRMS	^{1}H NMR
43		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[1-(methoxymethyl)propyl]pyrimidin-2-amine	277	
44		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(1R2S)-2-(methoxymethyl)cyclopentyl]pyrimidin-2-amine	303	
45		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(1S)-1-cyclohexylethyl]pyrimidin-2-amine	301	
46		N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-imidazo[12-a]pyrazin-8-ylethane-12-diamine	351	
47		N-[(1-acetylpiperidin-4-yl)methyl]-4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine	330	
48		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(3-methoxybenzyl)pyrimidin-2-amine	311	

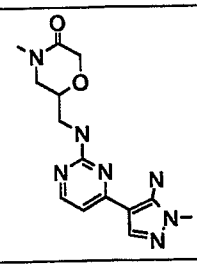
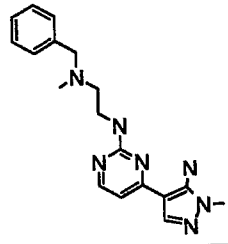
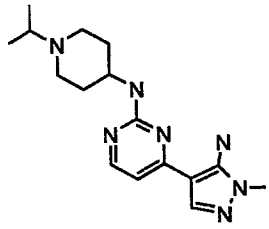
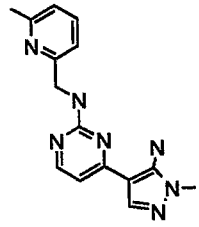
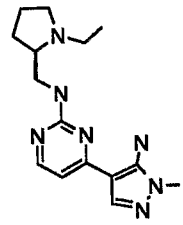
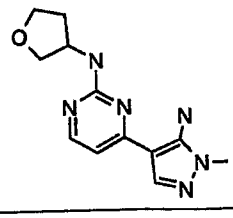
#	Structure	Compound Name	LRMS	^{1}H NMR
49		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(2-methyl-1234-tetrahydroisoquinolin-3-yl)methyl]pyrimidin-2-amine	350	
50		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[1-(4-methoxybenzyl)piperidin-3-yl]pyrimidin-2-amine	394	
51		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(2-phenyl-2H-123-triazol-4-yl)methyl]pyrimidin-2-amine	348	
52		2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	289	
53		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(quinolin-3-ylmethyl)pyrimidin-2-amine	332	
54		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(26-difluorobenzyl)pyrimidin-2-amine	317	
55		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-{[1-(4-methoxybenzyl)piperidin-4-yl]methyl}pyrimidin-2-amine	409	

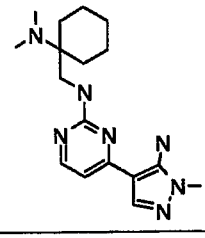
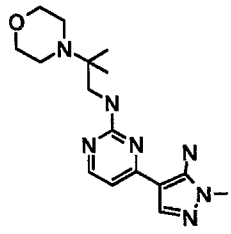
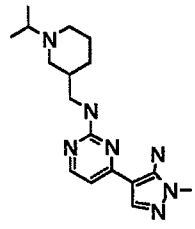
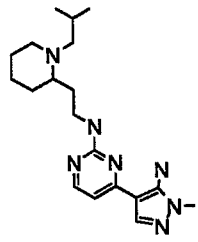
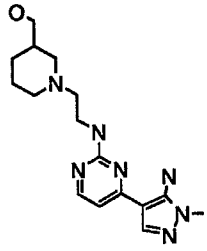
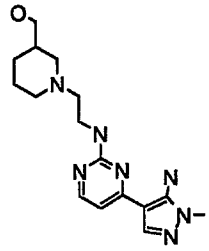
#	Structure	Compound Name	LRMS	^{1}H NMR
56		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[1-methyl-2-(3-methylpyridin-2-yl)ethyl]pyrimidin-2-amine	324	
57		[(1S2S)-2-({[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}methyl)cyclopropyl]methanol	275	
58		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(1R2R)-2-phenylcyclopentyl]pyrimidin-2-amine	335	
59		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[2-(1-methylpiperidin-4-yl)ethyl]pyrimidin-2-amine	316	
60		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[1-methyl-2-(1H-pyrazol-1-yl)ethyl]pyrimidin-2-amine	299	
61		(3S4R)-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}tetrahydrofuran-3-ol	277	
62		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(1-methyl-4-phenylpiperidin-4-yl)methyl]pyrimidin-2-amine	378	

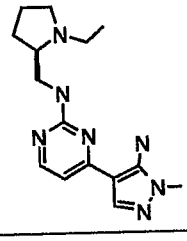
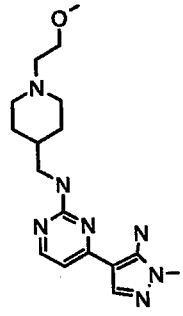
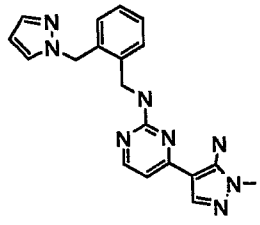
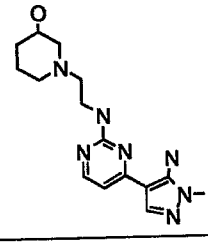
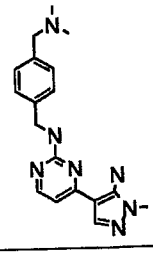
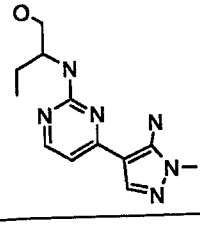
#	Structure	Compound Name	LRMS	^{1}H NMR
63		[1-(2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}ethyl)piperidin-2-yl]methanol	332	
64		1-({[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}methyl)cyclopentanol	289	
65		2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}-1-(34-difluorophenyl)ethanol	347	
66		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[2-(tetrahydro-2H-pyran-2-yl)ethyl]pyrimidin-2-amine	303	
67		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-2-amine	289	
68		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[3-(4-methylpiperazin-1-yl)-2-phenylpropyl]pyrimidin-2-amine	408	

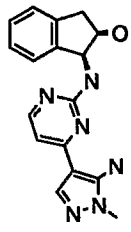
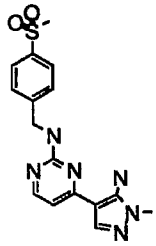
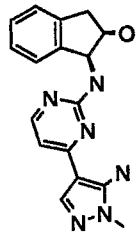
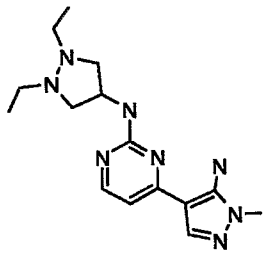
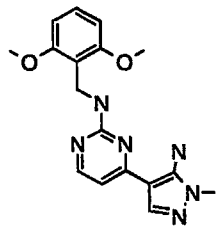
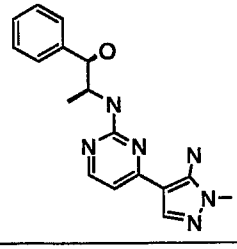
#	Structure	Compound Name	LRMS	^{1}H NMR
69		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]methyl}pyrimidin-2-amine	365	
70		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[2-(4-methylpiperazin-1-yl)-1-phenylethyl]pyrimidin-2-amine	394	
71		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[1-(tetrahydro-2H-pyran-4-ylmethyl)piperidin-4-yl]pyrimidin-2-amine	372	
72		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[1-(2-methoxyethyl)piperidin-4-yl]pyrimidin-2-amine	332	
73		1-(3-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}propyl)-N-methyl-N-(1-methylpyrrolidin-3-yl)-1H-123-triazole-4-carboxamide	441	
74		5-(2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}ethyl)-1-(2-morpholin-4-ylethyl)pyrrolidin-2-one	416	

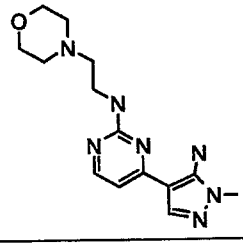
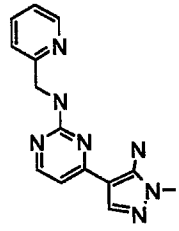
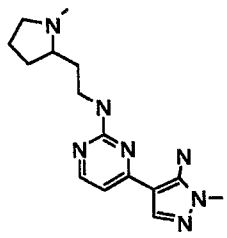
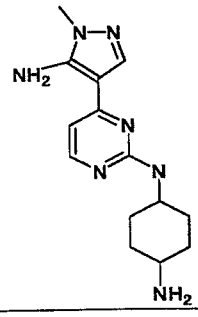
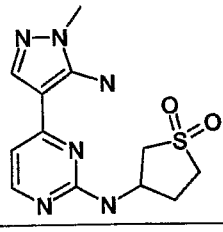
#	Structure	Compound Name	LRMS	^{1}H NMR
75		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-{[1-(4-methoxybenzyl)-1H-124-triazol-5-yl]methyl}pyrimidin-2-amine	392	
76		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(8-methyl-2-oxa-8-azaspiro[4.5]dec-3-yl)methyl]pyrimidin-2-amine	358	
77		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(imidazo[12-a]pyrimidin-2-ylmethyl)pyrimidin-2-amine	322	
78		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(2-methyl-2-pyrrolidin-1-ylpropyl)pyrimidin-2-amine	316	
79		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[3-(4-ethylpiperazin-1-yl)propyl]pyrimidin-2-amine	345	
80		6-({[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}methyl)-4-[(1-ethylpiperidin-4-yl)methyl]morpholin-3-one	430	

#	Structure	Compound Name	LRMS	^{1}H NMR
81		6-({[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}methyl)-4-methylmorpholin-3-one	318	
82		N'-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N-benzyl-N-methylethane-12-diamine	338	
83		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(1-isopropylpiperidin-4-yl)pyrimidin-2-amine	316	
84		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(6-methylpyridin-2-yl)methyl]pyrimidin-2-amine	296	
85		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-{[(2R)-1-ethylpyrrolidin-2-yl]methyl}pyrimidin-2-amine	302	
86		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(tetrahydrofuran-3-yl)pyrimidin-2-amine	261	

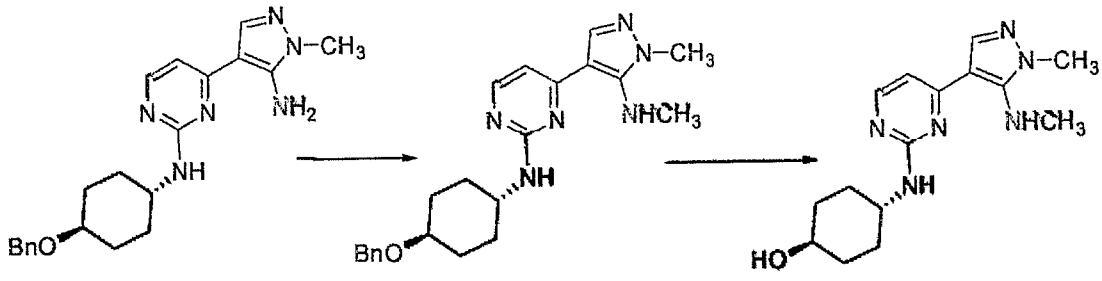
#	Structure	Compound Name	LRMS	^{1}H NMR
87		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-{[1-(dimethylamino)cyclohexyl]methyl}pyrimidin-2-amine	330	
88		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(2-methyl-2-morpholin-4-ylpropyl)pyrimidin-2-amine	332	
89		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(1-isopropylpiperidin-3-yl)methyl]pyrimidin-2-amine	330	
90		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[2-(1-isobutylpiperidin-2-yl)ethyl]pyrimidin-2-amine	358	
91		[1-(2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}ethyl)piperidin-3-yl]methanol	332	
92		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[(3-ethylisoxazol-5-yl)methyl]pyrimidin-2-amine	300	

#	Structure	Compound Name	LRMS	^{1}H NMR
93		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-{[(2S)-1-ethylpyrrolidin-2-yl]methyl}pyrimidin-2-amine	302	
94		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}pyrimidin-2-amine	346	
95		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[2-(1H-pyrazol-1-ylmethyl)benzyl]pyrimidin-2-amine	361	
96		1-(2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}ethyl)piperidin-3-ol	318	
97		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-{4-[(dimethylamino)methyl]benzyl}pyrimidin-2-amine	338	
98		2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}butan-1-ol	263	

#	Structure	Compound Name	LRMS	^{1}H NMR
99		(1R2S)-1-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}indan-2-ol	323	
100		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[4-(methylsulfonyl)benzyl]pyrimidin-2-amine	359	
101		(1S2R)-1-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}indan-2-ol	323	
102		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(12-diethylpyrazolidin-4-yl)pyrimidin-2-amine	317	
103		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(26-dimethoxybenzyl)pyrimidin-2-amine	341	
104		(1R2S)-2-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}-1-phenylpropan-1-ol	325	

#	Structure	Compound Name	LRMS	^{1}H NMR
105		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(2-morpholin-4-ylethyl)pyrimidin-2-amine	304	
106		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-ylmethyl)pyrimidin-2-amine	282	
107		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyrimidin-2-amine	302	
108		N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]cyclohexane-1,4-diamine	288	1H NMR (400 MHz, DMSO-d6) δ ppm 1.48 - 1.66 (m, 4 H) 1.70 - 1.79 (m, 4 H) 2.83 - 2.99 (m, 1 H) 3.56 (s, 3 H) 3.63 - 3.78 (m, 1 H) 6.62 (d, J = 5.6 Hz, 1 H) 6.68 (br s, 2 H) 6.96 (br s, 1 H) 7.70 (s, 1 H) 8.01 (d, J = 5.3 Hz, 1 H)
109		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(1,1-dioxidotetrahydro-3-thienyl)pyrimidin-2-amine	309	1H NMR (400 MHz, DMSO-d6) δ ppm 1.45 - 1.70 (m, 1 H) 2.12 (d, J = 13.6 Hz, 1 H) 2.93 (dd, J = 13.0, 7.5 Hz, 1 H) 3.07 - 3.21 (m, 1 H) 3.44 - 3.66 (m, 5 H) 4.30 - 4.68 (m, 1 H) 6.67 (s, 1 H) 6.71 (d, J = 5.6 Hz, 1 H) 7.4 (d, J = 6.8 Hz, 1 H) 7.71 (s, 1 H) 8.04 (d, J = 5.31 Hz, 1 H)

Method B:



9 110a 110

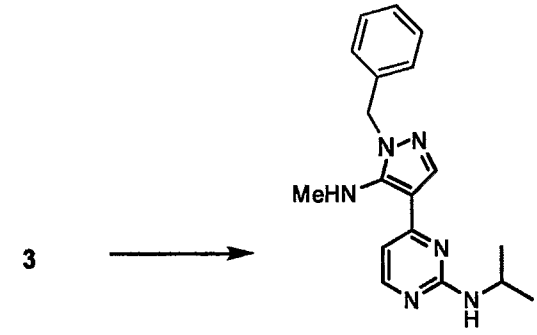
Preparation of N-((1R,4R)-4-(Benzyloxy)cyclohexyl)-4-(1-methyl-5-(methylamino)-1H-pyrazol-4-yl)pyrimidin-2-amine (110a)

Compound **9** (0.10 g, 0.27 mmol) was suspended in triethylorthoformate (1 mL) and pTsOH (0.03 g, 0.13 mmol) was added. The mixture was heated to 145 °C while being stirred vigorously. After stirring for 10 minutes, the mixture was removed from the oil bath, cooled to 0 °C, and basified to pH of 9 using Na_2CO_3 (saturated aqueous solution). The aqueous mixture was extracted with ethyl acetate (3 x 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield an orange oil. This crude product was dissolved in methanol (3 mL), cooled to 0 °C, and $NaBH_4$ (0.26 g, 5.30 mmol) was added in one portion. The mixture was allowed to warm to room temperature and stirred for 72 hour(s), after which the reaction was quenched with 0.5 M Rochelle's salt solution. The resulting aqueous solution was diluted with ethyl acetate and stirred for 3 hour(s). The layers were separated, the aqueous phase was further extracted with ethyl acetate (2 x 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a brown oil. The crude material was purified by medium pressure liquid chromatography (hexanes to ethyl acetate) to afford pure product (**110a**) as a colorless oil (0.07 g, 67 %). ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.01 - 8.11 (d, 1 H), 7.68 (s, 1 H), 7.23 - 7.41 (m, 5 H), 7.12 - 7.22 (m, 1 H), 6.53 - 6.63 (d, 1 H), 4.87 - 5.03 (m, 1 H), 4.55 (s, 2 H), 3.80 (s, 3 H), 3.67 - 3.76 (m, 1 H), 3.37 - 3.46 (m, 1 H), 3.00 (d, 3 H), 2.09 - 2.25 (m, 4 H), 1.39 - 1.51 (m, 2 H), 1.24 - 1.37 (m, 2 H). LRMS m/z calculated for $C_{22}H_{29}N_6O$ ([M+H]+): 393. Found: 393.

Preparation of (1R,4R)-4-(4-(1-Methyl-5-(methylamino)-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol (110)

Compound **110a** (60 mg, 0.15 mmol) was dissolved in methanol (1 mL) and added slowly via syringe to a flask containing 10% Pd/C (30 mg) under argon. HCl (conc, 0.04 mL, 0.46 mmol) was added, then the reaction flask was evacuated, and H_2 gas was introduced via a balloon. The mixture was stirred at room temperature for 4 hour(s), after which time the H_2 balloon was removed. Amberlite IRA-410 ion-exchange resin (0.50 g) was then added and the mixture was stirred at room temperature for 10 minutes. The resin was filtered off, and the filtrate was concentrated to an oil. The crude product was purified by medium pressure liquid chromatography (CH_2Cl_2 to 10 % methanol / CH_2Cl_2) to afford pure product **B2** as a white solid (0.03 g, 67 %). ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.06 (d, 1 H), 7.62 (s, 1 H), 7.10 - 7.26 (m, 1 H), 6.57 (d, 1 H), 4.84 - 4.99 (m, 1 H), 3.80 (s, 3 H), 3.57 - 3.77 (m, 2 H), 2.95 (d, 3 H), 2.10 - 2.22 (m, 2 H),

1.95 - 2.10 (m, 2 H), 1.23 - 1.49 (m, 4 H). LRMS m/z calculated for $C_{15}H_{23}N_6O$ ([M+H]$^+$): 303. Found: 303.

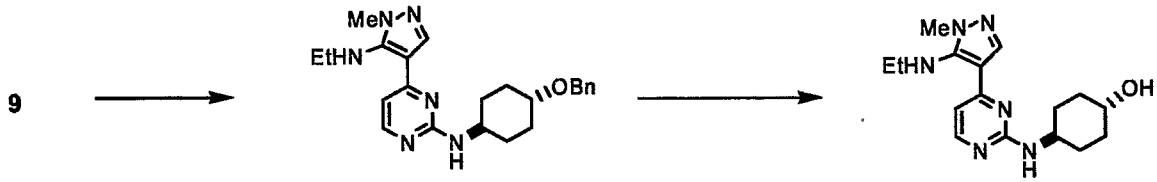


111

Preparation of 4-(5-Amino-1-benzyl-1H-pyrazol-4-yl)-N-isopropylpyrimidin-2-amine (111)

The above compound was prepared according to the method described for compound **110a**, except that compound **3** was used as the starting material. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.13 (d, 6 H), 3.92 - 3.98 (m, 1 H), 4.82 (s, 1 H), 5.10 (s, 2 H), 5.45 (s, 2 H), 6.52 (d, 1 H), 7.11 (d, 2 H), 7.20 - 7.31 (m, 3 H), 7.62 (s, 1 H), 8.01 (d, 1 H). LRMS m/z calculated for $C_{18}H_{22}N_6$ ([M+H]$^+$): 323. Found: 323.

Method C:



112a 112

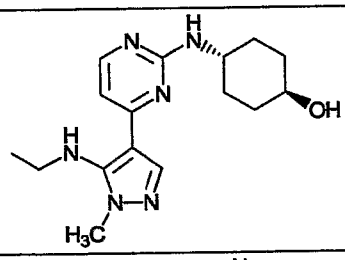
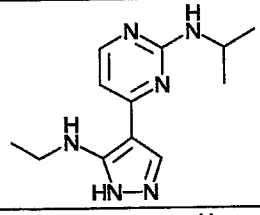
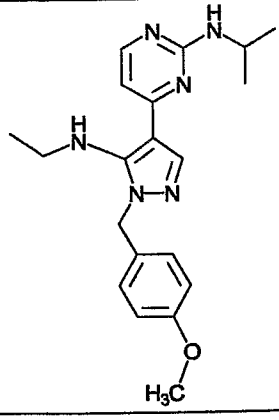
Preparation of N-((1R,4R)-4-(benzyloxy)cyclohexyl)-4-(5-ethylamino)-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (112a)

Compound **9** (0.10 g, 0.27 mmol) was dissolved in THF (2 mL) and NaH (0.01 g, 0.27 mmol, 60 % dispersion in oil) was added in one portion. The mixture was stirred at room temperature for 10 minutes, followed by cooling to 0 °C. Ethyl iodide (0.03 mL, 0.38 mmol) was added dropwise, and then the mixture was slowly allowed to warm to room temperature. After stirring for 5 hour(s), the temperature was warmed to 100 °C and the mixture was stirred for 24 hour(s). After cooling to room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a yellow oil. The crude material was purified by column chromatography (CH_2Cl_2 to 100 % ethyl acetate) to afford pure product (**111a**) as a colorless oil (50 mg, 47 %). ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.07 (d, 1 H), 7.63 (s, 1 H), 7.23 - 7.38 (m, 5 H), 6.90 - 7.03 (m, 1 H), 6.58 (d, 1 H), 4.83 - 4.96 (m, 1 H), 4.54 (s, 2 H), 3.76 (s, 3 H), 3.37 - 3.46 (m, 2 H), 3.24 - 3.34 (m, 2 H), 2.07 - 2.24 (m, 4 H), 1.38 - 1.50 (m, 2 H), 1.19 - 1.37 (m, 5 H). LRMS m/z calculated for $C_{23}H_{31}N_6O$ ([M+H]+): 407. Found: 407.

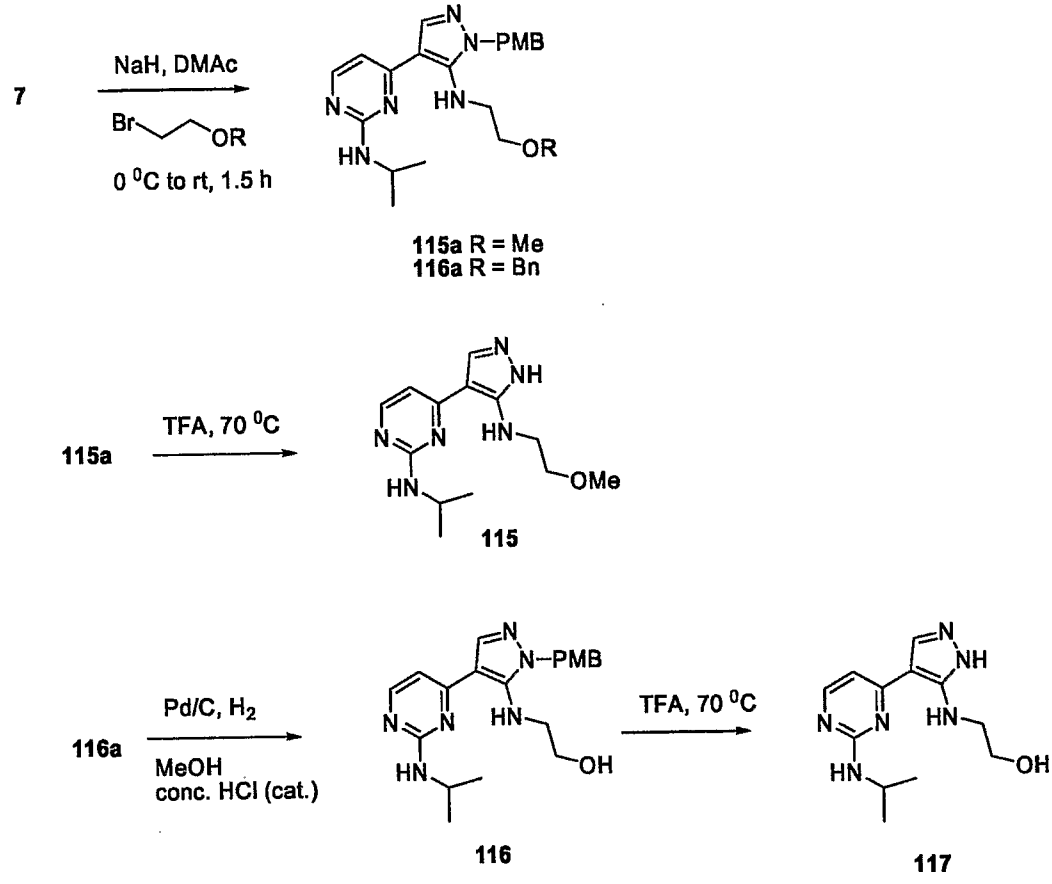
Preparation of (1R,4R)-4-(4-(5-ethylamino)-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol (112)

Compound **112a** was prepared from compound **9** as described in Method B. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.06 (d, 1 H), 7.62 (s, 1 H), 6.90 - 6.99 (m, 1 H), 6.57 (d, 1 H), 4.82 - 4.93 (m, 1 H), 3.58 - 3.79 (m, 5 H), 3.23 - 3.33 (m, 2 H), 2.06 - 2.20 (m, 4 H), 1.35 - 1.47 (m, 2 H), 0.98 - 1.19 (m, 5 H). LRMS m/z calculated for $C_{16}H_{25}N_6O$ ($[M+H]^+$): 317. Found: 317.

Table 2. Compounds 112-114 were prepared according to the method C as described above.

#	Structure	Compound Name	LRMS	^{1}H NMR
112		4-({4-[5-(ethylamino)-1-methyl-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	317	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 8.06 (d, 1 H), 7.62 (s, 1 H), 6.89 - 7.02 (m, 1 H), 6.57 (d, 1 H), 4.80 - 4.96 (m, 1 H), 3.58 - 3.80 (m, 5 H), 3.21 - 3.34 (m, 2 H), 2.06 - 2.17 (m, 2 H), 1.94 - 2.05 (m, 2 H), 0.99 - 1.43 (m, 7 H)
113		4-[5-(ethylamino)-1H-pyrazol-4-yl]-N-isopropylpyrimidin-2-amine	247	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 7.95 - 8.11 (m, 1 H), 7.76 (s, 1 H), 6.88 - 7.09 (m, 1 H), 6.57 (d, *J*=5.6 Hz, 1 H), 5.25 - 5.45 (m, 2 H), 3.98 - 4.17 (m, 1 H), 3.24 - 3.41 (m, 2 H), 1.16 - 1.38 (m, 9 H)
114		4-[5-(ethylamino)-1-(4-methoxybenzyl)-1H-pyrazol-4-yl]-N-isopropylpyrimidin-2-amine	367	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 8.08 (d, 1 H), 7.73 (s, 1 H), 7.04 - 7.16 (m, 3 H), 6.81 - 6.91 (m, 2 H), 6.60 (d, 1 H), 5.19 - 5.22 (m, 2 H), 4.81 - 4.95 (m, 1 H), 3.98 - 4.13 (m, 1 H), 3.77 (s, 3 H), 3.12 - 3.27 (m, 2 H), 1.20 - 1.33 (m, 6 H), 1.16 (t, 3 H)

Method D:



Alkylation of an aminopyrazole with a primary alkyl bromide

General Procedure:

To a stirred solution of aminopyrazole **7** in DMAC (3 mL/mmol) at room temperature was added 60% NaH in mineral oil (2.2 equivalent). The resulting suspension was stirred for 20 minutes before it was cooled to 0-5 °C, and the alkyl bromide (1.3 equiv.) was added to the yellowish suspension. After stirring the resulting reaction mixture at 0-5 °C for an additional 1.5 hour(s), cold water was added. The solution was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated *in vacuo*. The residue thus obtained was purified by column chromatography using 0-50 % ethyl acetate in hexanes as the eluent.

Preparation of *N*-isopropyl-4-{1-(4-methoxybenzyl)-5-[(2-methoxyethyl)amino]-1*H*-pyrazol-4-yl}pyrimidin-2-amine (115a)

The above compound was prepared according to the general procedure using aminopyrazole **7** (50 mg, 0.15 mmol) and 2-bromoethylmethyl ether to give the product (34 mg, 57%) as a white solid. ^{1}H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 1.14 (t, *J* = 6.3 Hz, 7 H), 3.14 - 3.20 (m, 2 H), 3.22 (s, 3 H), 3.34 - 3.41 (m, 2 H), 3.69 (s, 3 H), 3.99 - 4.10 (m, 1 H), 4.84 (s, 1 H), 5.15 (s, 2 H), 6.51 (d, *J* = 5.3 Hz, 1 H), 6.75 - 6.83 (m, 2 H), 7.03 (d, *J* = 8.6 Hz, 2 H), 7.31 (s, 1 H), 7.65 (s, 1 H), 8.02 (d, *J* = 5.3 Hz, 1 H). LRMS m/z calculated for $C_{21}H_{29}N_6O_2$ $[M+H]^+$ 397. Found: 397.

Preparation of 4-[5-{[2-(benzyloxy)ethyl]amino}-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]-*N*-isopropylpyrimidin-2-amine (116a)

The above compound was prepared according to the general procedure using aminopyrazole **7** (100 mg, 0.30 mmol) and benzyl-2-bromoethyl ether to give crude material (64 mg) containing the title compound **116a**. The crude material was subjected to debenzylation conditions as described below. LRMS m/z calculated for $C_{27}H_{33}N_6O_2$ $[M+H]^+$ 473. Found: 473.

Preparation of *N*-isopropyl-4-{5-[(2-methoxyethyl)amino]-1*H*-pyrazol-4-yl}pyrimidin-2-amine (115)

A solution of pyrazole **115a** (34 mg, 0.09 mmol) in TFA (0.5 mL) was heated at 70 °C for 4 hour(s) while stirring under N_2. The reaction mixture was cooled, diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (0-5% methanol in CH_2Cl_2) to afford methoxyethylaminopyrazole **115** (17 mg, 68%) as an off white solid. See Table 3.

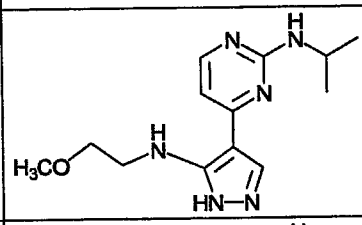
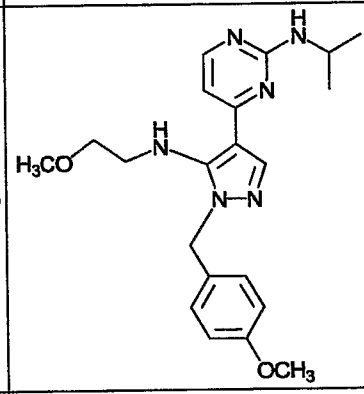
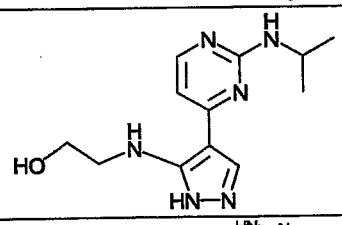
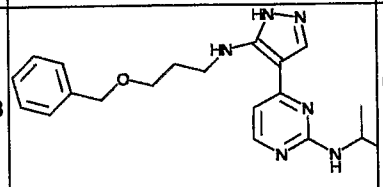
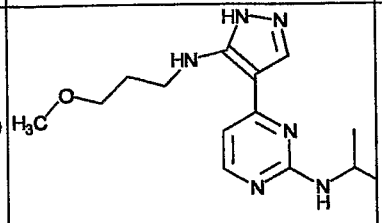
Preparation of 2-{[4-[2-(isopropylamino)pyrimidin-4-yl]-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl]amino}ethanol (116)

The crude material (64 mg) containing compound **116a** was dissolved in methanol (3 mL) and the resulting solution was purged with N_2 for 15 minutes. Pd on carbon (10 %, 13 mg, 20 wt.%) followed by concentrated HCl (3 drops) were added to the solution. The suspension was hydrogenated at atmospheric pressure and room temperature for 3 hour(s). The solids were filtered off, and the residue was washed thoroughly with methanol. The filtrate was concentrated *in vacuo*, and the resulting oil was taken up in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0-5% methanol in CH_2Cl_2) to afford alcohol **116** (17 mg, 15 % for the 2 steps from **7**) as an off-white solid. See Table 3.

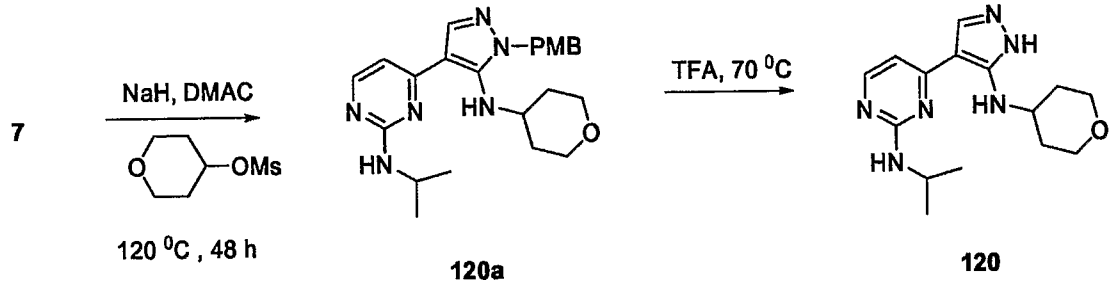
Preparation of 2-({4-[2-(isopropylamino)pyrimidin-4-yl]-1*H*-pyrazol-5-yl}amino)ethanol (D5)

A solution of pyrazole **D4** (10 mg, 0.03 mmol) in TFA (0.5 mL) was heated at 70 °C for 15 hour(s) while stirring under N_2. The reaction mixture was cooled, diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by preparative TLC using 3 % 7 N NH_3/methanol in CH_2Cl_2 as the eluant to afford aminopyrazole **D5** (3 mg, 38 %) as an off white solid. See Table 3.

Table 3. Compounds 115-119 were prepared according to the method D as described above.

#	Structure	Compound Name	LRMS	^{1}H NMR
115		N-isopropyl-4-{5-[(2-methoxyethyl)amino]-1H-pyrazol-4-yl}pyrimidin-2-amine	277	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 1.17 (d, 6 H), 3.34 - 3.44 (m, 5 H), 3.52 - 3.59 (m, 3 H), 3.99 - 4.01 (m, 1 H), 4.82 (br s, 1 H), 6.49 (d, 1 H), 7.34 (br s, 1 H), 7.64 (s, 1 H), 7.98 (d, 1 H)
116		2-({4-[2-(isopropylamino)pyrimidin-4-yl]-1-(4-methoxybenzyl)-1H-pyrazol-5-yl}amino)ethanol	383	1H NMR (400 MHz, MeOD) δ ppm 1.13 (m, 6 H), 3.11 (t, 2 H), 3.51 (t, 2 H), 3.68 (s, 3 H), 3.96 - 4.07 (m, 1 H), 5.20 (s, 2 H), 6.65 (d, 1 H), 6.79 (ddd, 2 H), 7.01 (d, 2 H), 7.80 (s, 1 H), 7.94 (d, 1 H)
117		2-({4-[2-(isopropylamino)pyrimidin-4-yl]-1H-pyrazol-3-yl}amino)ethanol	263	1H NMR (400 MHz, MeOD) δ ppm 1.16 (d, 6 H), 3.33 (t, 2 H), 3.67 (t, 2 H), 3.97 - 4.08 (m, 1 H), 6.61 (d, 1 H), 7.84 (s, 1 H), 7.88 (d, 1 H)
118		4-(5-{[3-(benzyloxy)propyl]amino}-1H-pyrazol-4-yl)-N-isopropylpyrimidin-2-amine	367	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 8.04 (d, 1 H), 7.73 (s, 1 H), 7.22 - 7.44 (m, 6 H), 6.56 (d, 1 H), 4.54 (s, 2 H), 4.91 – 5.04 (m, 1 H), 3.97 - 4.13 (m, 1 H), 3.57 - 3.68 (m, 2 H), 3.43 (q, 2 H), 1.89 - 2.01 (m, 2 H), 1.19 - 1.29 (m, 6 H)
119		N-isopropyl-4-{5-[(3-methoxypropyl)amino]-1H-pyrazol-4-yl}pyrimidin-2-amine	291	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 8.04 (d, 1 H), 7.73 (s, 1 H), 7.10 - 7.43 (m, 1 H), 6.48 - 6.63 (m, 1 H), 4.96 - 5.24 (m, 1 H), 3.97 - 4.15 (m, 1 H), 3.51 (t, 2 H), 3.32 - 3.46 (m, 5 H), 1.83 - 2.03 (m, 2 H), 1.16 - 1.40 (m, 6 H)

Method E:



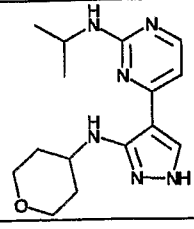
Preparation of *N*-isopropyl-4-[1-(4-methoxybenzyl)-5-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-amine (120a) and *N*-isopropyl-4-[5-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-amine (120)

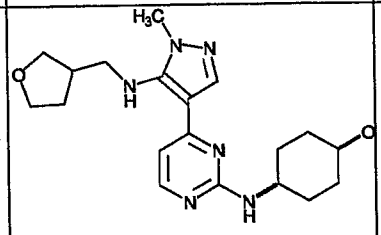
To a stirred solution of aminopyrazole **7** (100 mg, 0.30 mmol) in DMAC (2 mL) at room temperature was added NaH in mineral oil (60 %, 79 mg, 2.0 mmol). The resulting suspension was stirred for 20 minutes, and then tetrahydropyran-4-mesylate (1.2 g, 6.6 mmol) was added to the yellowish suspension at room temperature. The resulting reaction mixture was stirred under N_2 at 120 °C for 48 hour(s). Although analysis of an aliquot by LCMS showed only about 50% conversion to the desired product, cold water was added to quench the reaction. The solution was extracted with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue thus obtained containing compound **120a** was subjected to PMB deprotection as described for compound **116** above followed by chromatographic purification (0-5% methanol in CH_2Cl_2) to afford 4-terahydropyranylaminopyrazole **120** (10 mg, 11 % for the 2 steps from **7**) as a off-white solid. LRMS m/z calculated for $C_{23}H_{31}N_6O_2$ $[M+H]^+$ 423. Found: 423.

Preparation of (4-[(4-{1-methyl-5-[(tetrahydrofuran-3-ylmethyl)amino]-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]cyclohexanol) (121)

The above compound **121** was prepared in a similar manner, starting from aminopyrazole **8**. See Table 4.

Table 4. Compounds 120-121 were prepared according to the method E as described above.

#	Structure	Compound Name	LRMS	^{1}H NMR
120		N-isopropyl-4-[3-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazol-4-yl]pyrimidin-2-amine	423	1H NMR (400 MHz, MeOD) δ ppm 1.19 (d, 6H), 1.47 (d, 4 H), 1.91 - 2.02 (m, 4 H), 3.44 (td, 4 H), 3.57 (br s, 2 H), 3.87 - 3.98 (m, 5 H), 6.62 (d, 2 H), 7.86 (s, 1 H), 7.89 (d, 2 H)

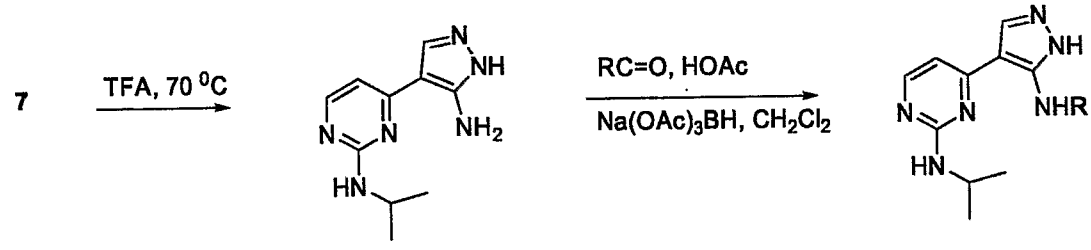
#	Structure	Compound Name	LRMS	^{1}H NMR
121		4-[(4-{1-methyl-5-[(tetrahydrofuran-3-ylmethyl)amino]-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]cyclohexanol	373	1H NMR (400 MHz, CH_2Cl_2-D2) δ ppm 10.68 (s, 1 H), 8.23 (d, 1 H), 7.87 (s, 1 H), 6.80 (d, 1 H), 4.93 - 5.16 (m, 1 H), 3.53 - 3.99 (m, 8 H), 3.35 - 3.50 (m, 1 H), 3.15 - 3.34 (m, 2 H), 1.89 - 2.18 (m, 4 H), 1.18 - 1.75 (m, 7 H)

Method F:

Amino deprotection followed by Reductive amination of an aminopyrazole with cyclic ketones

General Procedure:

A suspension of aminopyrazole, a ketone (5 eq) and $Na(OAc)_3BH$ (2 eq) in dichloroethane (0.15 M) was stirred under N_2 at room temperature as glacial acetic acid (1.1 eq) was added at once. Stirring was continued for 15 hour(s) at room temperature, and then the reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0-5% methanol in CH_2Cl_2) to afford the desired product.



122a

122 R = *c*-butyl
123 R = 3-THF

Preparation of 4-(5-amino-1*H*-pyrazol-4-yl)-*N*-isopropylpyrimidin-2-amine (122a)

Pyrazole **7** (150 mg, 0.450 mmol) was deprotected according to the procedure described for the preparation of **D5**, using TFA (2 mL) at 70 °C for 48 hour(s). Purification by column chromatography (0-5% methanol in CH_2Cl_2) afforded aminopyrazole **122a** (69 mg, 70 %) as a pale yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.11 - 1.20 (m, 6 H), 3.88 - 3.98 (m, 1 H), 4.72 (s, 1 H), 6.61 (d, *J* = 5.6 Hz, 1 H), 7.76 (s, 1 H), 7.86 - 7.94 (m, 1 H). LRMS m/z calculated for $C_{10}H_{115}N_6$ $[M+H]^+$ 219. Found: 219.

Preparation of (4-(5-amino-1H-pyrazol-4-yl)-N-cyclohexylpyrimidin-2-amine) (124)

The above compound was prepared in a similar manner, starting from compound **6**. See Table 5.

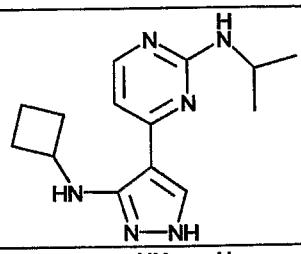
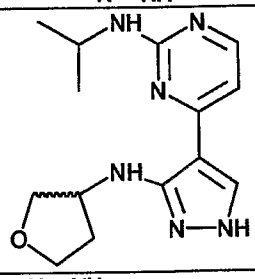
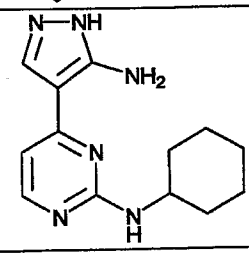
Preparation of 4-[5-(cyclobutylamino)-1*H*-pyrazol-4-yl]-*N*-isopropylpyrimidin-2-amine (122)

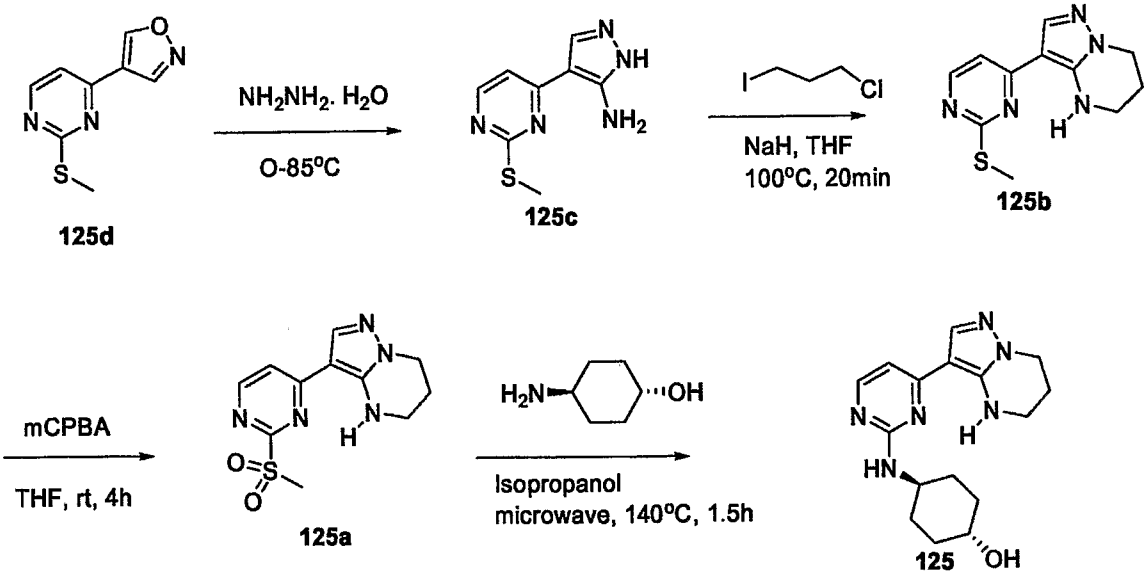
Compound **122** was prepared as a white solid following the general procedure described above. Aminopyrazole **122a** (50 mg, 0.23 mmol), cyclobutanone (81 mg, 1.1 mmol), $Na(OAc)_3BH$ (98 mg, 0.46 mmol) and glacial acetic acid (0.015 mL) were reacted in dichloroethane (1.5 mL) to afford the title compound **122** (6 mg, 10 %). See Table 5.

Preparation of *N*-isopropyl-4-[5-(tetrahydrofuran-3-ylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-amine (123)

Compound **123** was prepared as an off-white solid following the general procedure described above. Aminopyrazole **122a** (50 mg, 0.23 mmol), tetrahydrofuran-3-one (97 mg, 1.1 mmol), $Na(OAc)_3BH$ (98 mg, 0.46 mmol), and glacial acetic acid (0.015 mL) were reacted in dichloroethane (1.5 mL) to afford the title compound **123** (12 mg, 18 %). See Table 5.

Table 5. Compounds 122-127 were prepared according to the method F as described above.

#	Structure	Compound Name	LRMS	^{1}H NMR
122		4-[3-(cyclobutylamino)-1H-pyrazol-4-yl]-N-isopropylpyrimidin-2-amine	273	1H NMR (400 MHz, MeOD) δ ppm 1.32 (d, 6H), 1.76 - 1.87 (m, 2 H), 2.01 - 2.06 (m, 2 H), 2.49 (d, 2 H), 4.06 - 4.17 (m, 2 H), 6.72 (d, 2 H), 7.89 (s, 1 H), 8.00 (d, 2 H)
123		N-isopropyl-4-[3-(tetrahydrofuran-3-ylamino)-1H-pyrazol-4-yl]pyrimidin-2-amine	289	1H NMR (400 MHz, MeOD) δ ppm 1.17 (d, 6 H), 1.82 - 1.92 (m, 1 H), 2.21 (dd, 1 H), 3.68 (dd, 1 H), 3.72 - 3.79 (m, 1 H), 3.81 - 3.84 (m, 1 H), 3.85 - 3.91 (m, 1 H), 3.92 - 4.00 (m, 1 H), 4.19 (d, 1 H), 6.63 (s, 1 H), 7.87 - 7.98 (m, 2 H)
124		4-(5-amino-1H-pyrazol-4-yl)-N-cyclohexylpyrimidin-2-amine	259	1H NMR (400 MHz, DMSO-d6) δ ppm 1.07 - 1.48 (m, 5 H), 1.50 - 1.64 (m, 1 H) ,1.66 - 1.81 (m, 2 H), 1.83 - 2.02 (m, 2 H), 3.54 - 3.81 (m, 1 H), 5.96 - 6.53 (m, 1 H), 6.57 - 6.75 (m, 1 H), 6.79 - 7.03 (m, 1 H), 7.68 - 7.95 (m, 1 H), 7.95 - 8.18 (m, 2 H), 11.46 - 12.19 (m, 1 H)



125d 125c 125b 125a 125

Preparation of (1R.4R)-4-(4,5,6,7-tetrahydropyrazolo [1,5-a]pyrimidin-2-ylamino)cyclohexanol (125)

A solution of compound 3-(2-(methylsulfonyl)pyrimidine-4-yl)-4,5,6,7-tetrahydropyazolo [1,5-a]pyrimidine **125a** (287mg, crude), (1R,2R)-4-aminocyclohexanol (500 mg, 4.35 mmol) in isopropanol (6 mL) was heated to 140°C for 1.5h by microwave. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (2 X 50 mL), dried over $MgSO_4$ filtered, and concentrated *in vacuo.* The resulting crude residue was purified HPLC to yield *trans*-cyclohexanol pyrimidine **125** (20 mg) as a pale yellow solid. 1H NMR (400 MHz, CD_3CN) δ ppm 1.12 - 1.41 (m, 6 H) 1.99 - 2.18 (m, 4 H) 2.69 - 2.75 (m, 1 H) 3.35 - 3.46 (m, 2 H) 3.48 - 3.59 (m, 1 H) 3.66 (dd, *J* = 7.1, 3.3 Hz, 1 H) 4.01 (t, *J* = 6.1 Hz, 2 H) 5.70 (s, 1 H) 6.55 (d, *J* = 5.6 Hz, 1 H) 6.91 (s, 1 H) 7.59 (s, 1 H) 7.88 - 8.02 (m, 1 H). LRMS m/z calcd. for $C_{16}H_{23}N_6O$ $[M+H]^+$ 315. Found: 315.

Preparation of 3-(2-(methylsulfonyl)pyrimidine-4-yl)-4,5,6,7-tetrahydropyazolo [1,5-a]pyrimidine (125a)

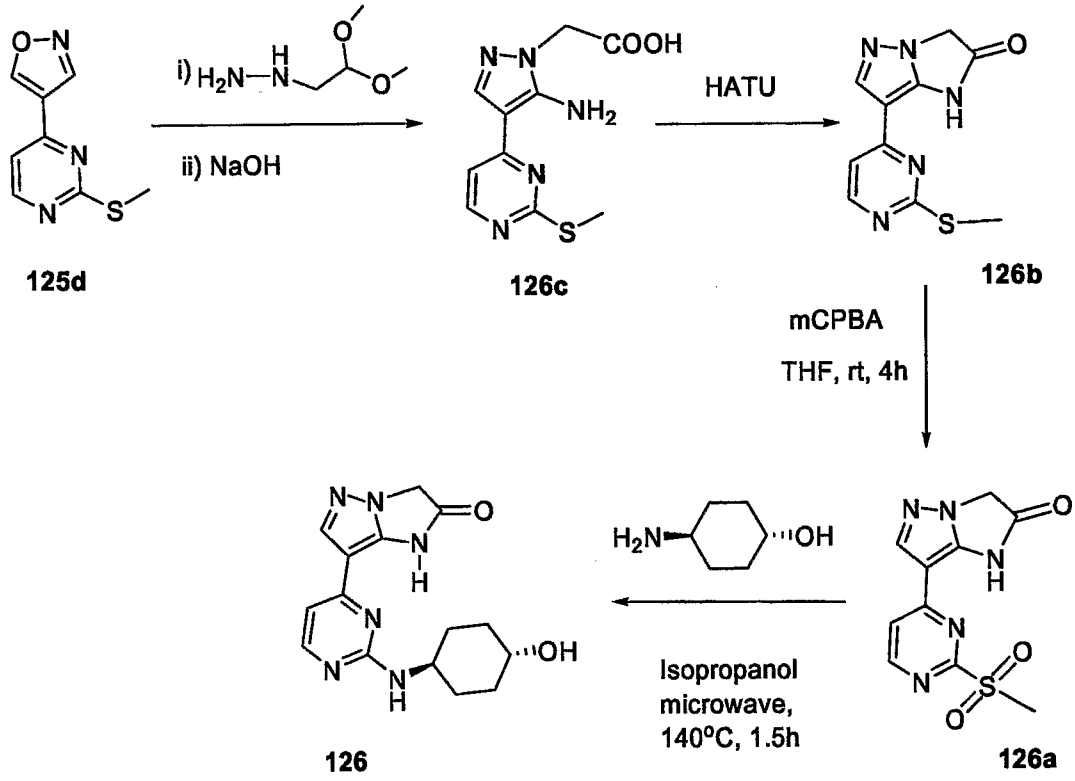
The crude product 3-(2-(methylthio)pyrimidine-4-yl)-4,5,6,7-tetrahydropyazolo [1,5-a]pyrimidine **125b** (310mg) was dissolved in THF (8 mL). To the solution was added 3-chloroperoxybenzoic acide (mCPBA) (810 mg, 3.63 mmol, 77 % tech grade) at 0°C. The mixture was then allowed to warm to room temperature slowly, and stirred for 4 hours. The mixture was then quenched with $NaHCO_3$ (saturated, aqueous) until a pH of 9 was reached. The aqueous solution was extracted with ethyl acetate (3 x 50 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide a orange oil (287mg, crude).

Preparation of 3-(2-(methylthio)pyrimidine-4-yl)-4,5,6,7-tetrahydropyrazolo [1,5-a]pyrimidine (125b)

4-(2-(methylthio)pyrimidine-4-yl)-1*H*-pyrazole-5-amine (B) (300mg, 1.45 mmol) was dissolved in THF (5 mL). To the solution was added 60%NaH (182mg, 4.35 mmol) slowly. The suspension was stirred at room temperature for 5 minutes followed by addition of 1-chloro-3-iodopropane (295mg, 1.45 mmol). The solution was heated to 100°C by microwave for 20 minutes, cooled to room temperature, extracted with ethyl acetate (3 X 50mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 312 mg of orange solid crude product.

Preparation of 4-(2-(methylthio)pyrimidine-4-yl)-1*H*-pyrazole-5-amine (125c):

To a suspension of 4-(isoxazol-4-yl)-2-(methylthio)pyrimidine **125d** (3.9 g, 20.2 mmol) in acetic acid (50mL) was added hydrazine (3.0 mL, 61.8 mmol) dropwise over 5 min at 0 °C. After the reaction mixture was stirred for 10 min the ice bath was removed. The suspension was stirred at room temperature for 1hour and slowly heated to 85°C for 5hours. The crude mixture was cooled to room temperature, basified with NH_4OH to pH ~9, filtered, and dried *in vacuo*. The resulting crude residue was purified by column chromatography (0 – 10% MeOH in CH_2Cl_2) to yield pure methylthiopyrimidine **125c** as a pale yellow solid (3.12 g, 75 %). 1H NMR (400 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 5.35 (m, 2H), 6.91 (d, *J* = 5.3 Hz, 1 H), 7.77 (s, 1 H), 8.29 (d, *J* = 5.3 Hz, 1 H). LRMS m/z calcd. for $C_8H_{10}N_5S$ $[M+H]^+$ 208. Found: 208.



Preparation 7-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-imidazo[1,2-*b*]pyrazol-2-one (126)

Compound **126** was prepared in a similar manner described for preparation of **125** starting from compound **126a**. 1H NMR (400 MHz, DMSO-d6) δ ppm 11.22 (s, 1 H) 8.17 (d, J = 5.3 Hz, 1 H) 7.96 (s, 1 H) 6.74 (d, J = 5.3 Hz, 1 H) 6.74 (d, J = 5.3 Hz, 1 H) 6.64 (d, J = 6.6 Hz, 1 H) 6.64 (d, J = 6.6 Hz, 1 H) 4.77 (s, 2 H) 4.55 (d, J = 4.3 Hz, 1 H) 3.55 - 3.76 (m, 1 H) 3.37 - 3.49 (m, 1 H) 1.90 - 2.03 (m, 2 H) 1.79 - 1.88 (m, 2 H) 1.18 - 1.30 (m, 4 H). LRMS m/z calcd. for $C_{15}H_{19}N_6O_2$ $[M+H]^+$ 315. Found: 315.

Preparation of 7-(2-Methanesulfonyl-pyrimidin-4-yl)-1*H*-imidazo[1,2-*b*]pyrazol-2-one (126a)

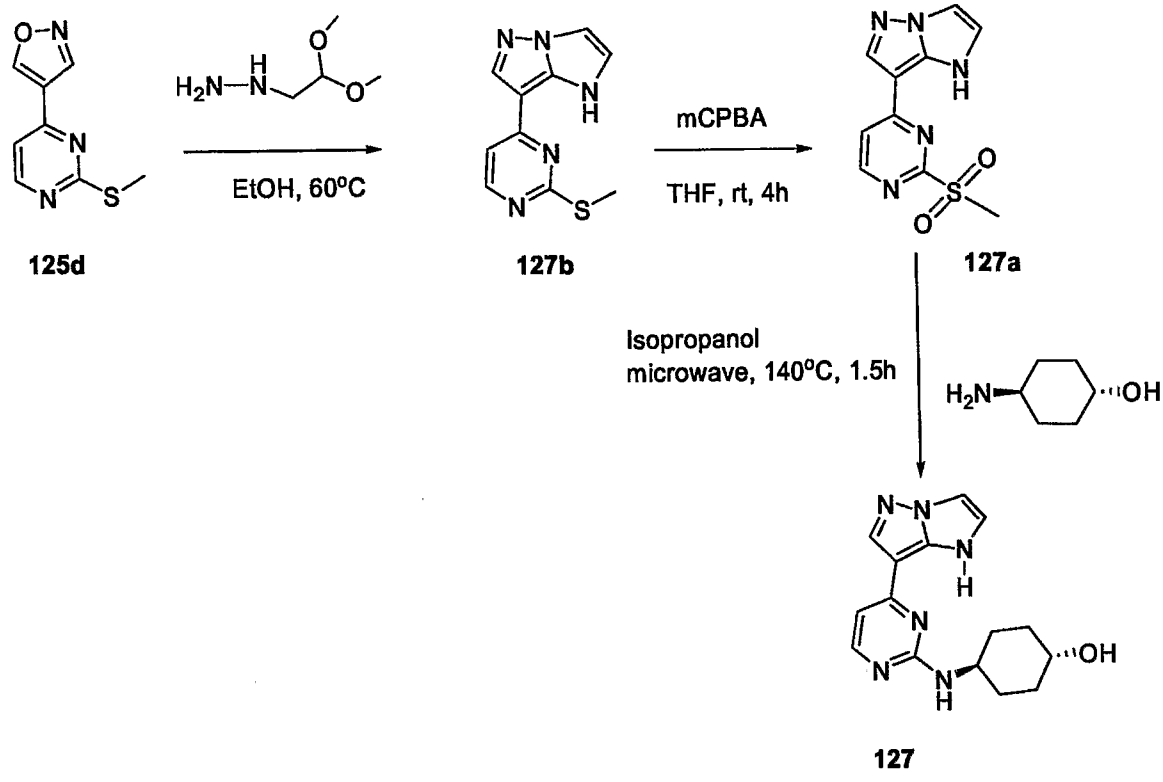
Compound **126a** was prepared in a similar manner described for preparation of **125a.** 1H NMR (400 MHz, DMSO-d6) δ ppm 12.01 (s, 1 H) 8.89 (d, J = 5.3 Hz, 1 H) 8.23 (s, 1 H) 7.89 (d, J = 5.5 Hz, 1 H) 4.83 (s, 2 H) 3.50 (s, 3 H). LRMS m/z calcd. for $C_{10}H_{10}N_5O_3S$ $[M+H]^+$ 280. Found: 280.

Preparation of 7-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-imidazo[1,2-*b*]pyrazol-2-one (126b):

HATU (6.56 g, 17.2 mmol) was added to a stirring mixture of **1** (3.52 g, 13.3 mmol), DIEA (3.00 mL, 17.2 mmol) in DMF (78 mL) at 45°C. The resulting mixture was stirred at 60 °C for 2 hours. DMF was evaporated under reduced pressure; the residue was washed with water (250 mL). The yellow solid crude product was collected by filtration and then stirred in ethyl acetate (50 mL) for 16 hours. The yellow solid product was filtered off and air dried to gain 2.05 g, 62 % yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 11.81 (s, 1 H), 8.48 (d, J = 5.3 Hz, 1 H), 8.08 (s, 1 H), 7.33 (d, J = 5.5 Hz, 1 H), 4.79 (s, 2 H), 2.53 (s, 3 H). LRMS m/z calcd. for $C_{10}H_{10}N_5OS$ $[M+H]^+$ 248. Found: 248.

Preparation of [5-Amino-4-(2-methylsulfanyl-pyrimidin-4-yl)-pyrazol-1-yl]-acetic acid (126c):

Ethyl hydrazinoacetate HCl (Aldrich) (2.10 g, 13.6 mmol) was added to a mixture of **125d** (2.5 g, 12.9 mmol) in Ethanol (20 mL). The reaction was completed after the above mixture was stirred at 95°C for 3 hours. The pyrazole ethyl ester product was detected by LCMS [M=H] = 294. The reaction mixture was diluted with ethanol (60 mL) and treated with a mixture of NaOH (1.29 g, 32.3 mmol) in H2O (6 mL) at 50°C while stirring. The acid product was precipitated immediately after the addition was completed. The pH of the mixture was adjusted to 7- 6 with 1N HCl aq. solution, and the resulting mixture was concentrated down to the volume of 30 m L. The light yellow solid crude product (3.9 g) was collected by filtration and dried under reduced pressure. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.29 (d, J = 5.5 Hz, 1 H) 7.81 (s, 1 H) 7.21 (d, J = 5.5 Hz, 1 H) 6.61 (s, 2 H) 4.34 (s, 2 H) 3.16 (s, 3 H). LRMS m/z calcd. for $C_{10}H_{12}N_5O_2S$ $[M+H]^+$ 266. Found: 266.



125d 127b 127a

127

Preparation 4-[4-(1*H*-Imidazo[1,2-*b*]pyrazol-7-yl)-pyrimidin-2-ylamino]-cyclohexanol (127)

Compound **127** was prepared in a similar manner described for preparation of **125** starting from compound **127a** instead of **125a**. 1H NMR (400 MHz, DMSO-d6) δ ppm 11.45 (s, 1 H) 8.12 (s, 1 H), 8.08 (d, J = 5.0 Hz, 1 H), 7.69 (s, 1 H), 7.38 (s, 1 H), 6.72 (d, J = 5.3 Hz, 1 H), 6.33 (s, 1 H), 3.57 - 3.79 (m, 1 H), 3.39 - 3.55 (m, 2 H), 1.91 - 2.05 (m, 2 H), 1.78 - 1.90 (m, 2 H), 1.21 - 1.34 (m, 2 H). LRMS m/z calcd. for $C_{15}H_{19}N_6O$ $[M+H]^+$ 299. Found: 299.

Preparation of 7-(2-Methanesulfonyl-pyrimidin-4-yl)-1*H*-imidazo[1,2-*b*]pyrazole (127a)

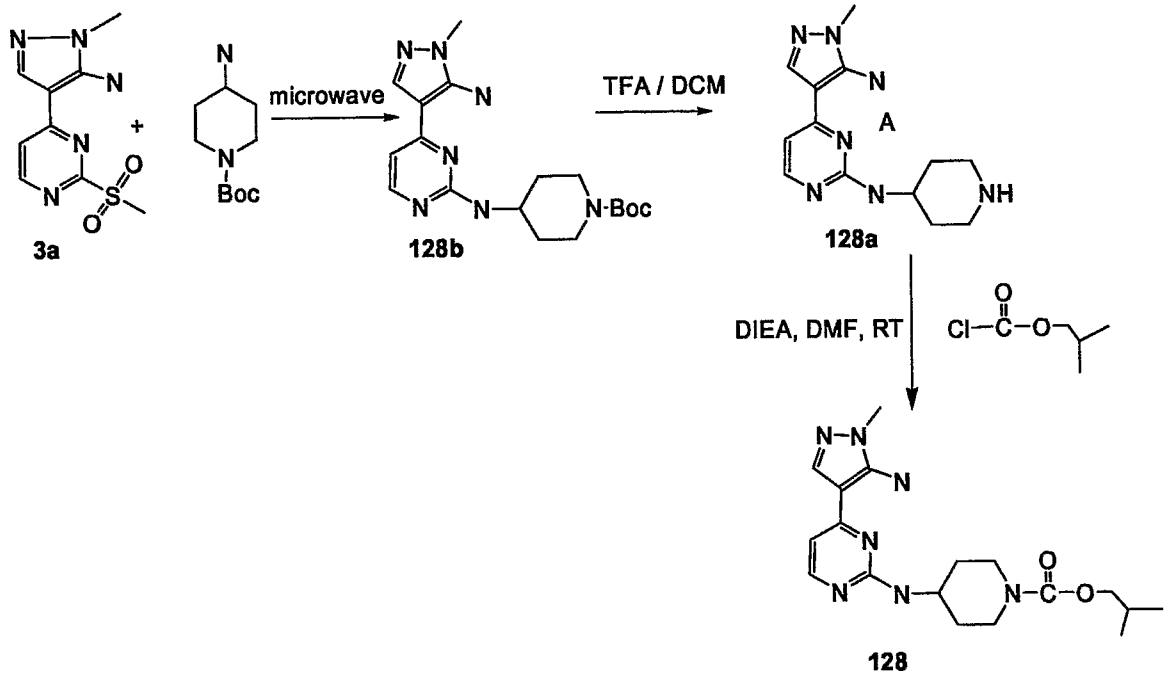
Compound **127a** was prepared in a similar manner described for preparation of **125a** starting from compound **127b** instead of **125b**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 10.13 (s, 1 H) 8.53 (d, J=5.5 Hz, 1 H) 8.14 (d, J=1.0 Hz, 1 H) 7.41 - 7.46 (m, 2 H) 7.07 - 7.11 (m, 1 H) 3.36 (s, 3 H). LRMS m/z calcd. for $C_{10}H_{10}N_5O_2S$ $[M+H]^+$ 264. Found: 264.

Preparation of 7-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-imidazo[1,2-*b*]pyrazole(127b):

1-(2-2-dimethoxyethyl) hydrazine (0.93 g, 7.7 mmol) (see US 005334595A) was added to a suspension of compound **125d** (1.5 g, 7.7 mmol) in absolute ethanol (15 mL) at room temperature. The red solution resulting mixture was stirred at 60 °C for 16 hours. After cooling to room temperature, 20% v/v H_2SO_4 aqueous solution (15 mL) was added and the resulting mixture was stirred at 95 °C further 1hour. After cooling to room temperature the mixture was poured into crushed ice and the pH was brought to 8 by adding solid $NaHCO_3$. The mixture was extracted into DCM (2x70 mL), washed with brine, dried over MgSO4, and concentrated to gain 1.5 g of dark semi solid crude product. The crude product was triturated with ethyl acetate. The tan color solid desired product (800 mg) was filtrated and air dried. The dark red filtrate was concentrated down to the volume of 15 mL and diluted with Hexanes. The resulting dark red

solution was stirred at room temperature 16 hours. The red solid product was filtered to gain 250 mg product **127b**. The total amount of isolated product was 1.05 g (58%). 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.93 (s, 1 H), 8.34 (d, J = 5.3 Hz, 1 H), 8.09 (s, 1 H), 7.42 (d, J = 2.3 Hz, 1 H), 7.06 (dd, J=2.3, 1.3 Hz, 1 H), 7.03 (d, J=5.3 Hz, 1 H) 2.62 (s, 3 H). LRMS m/z calcd. for $C_{10}H_{10}N_5S$ $[M+H]^+$ 232. Found: 232.

Method G



Preparation of 4-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid isobutyl ester (128)

Iso-butyl chloroformate (36 mg, 0.26 mmol) was added to a mixture of **128a** (65 mg, 0.24 mmol) and DIEA (34 mg, 0.26 mmol) in DMF (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature under nitrogen atmosphere for 1 h. The mixture was diluted with ethyl acetate (25 mL) and washed with water, dried MgSO4, concentrated to dryness. The crude product was purified by ISCO silica gel column chromatography, eluting with CHCl3: MeOH (9:1) to gain 52 mg (58%) of off white solid product **G3**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (d, J = 5.5 Hz, 1 H), 7.67 (s, 1 H), 6.6 (d, J = 5.5 Hz, 1 H), 5.58 (s, 2 H), 5.20 (s, 1 H), 4.05 - 4.25 (m, 2 H), 3.88 (d, J = 6.6 Hz, 2 H) 3.67 (s, 3 H) 3.02 (t, J = 11.6 Hz, 2 H), 2.09 (dd, J = 12.8, 3.0 Hz, 2 H), 1.76 - 2.02 (m, 2 H) 1.47 (q, J = 9.8 Hz, 2 H), 0.94 (d, J = 6.8 Hz, 6 H).. LRMS m/z calcd. for $C_{18}H_{28}N_7O_2$ $[M+H]^+$ 374. Found: 374.

Preparation of [4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-piperidin-4-yl-amine (128a)

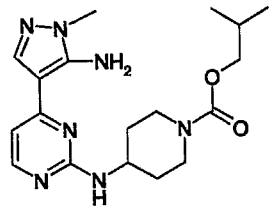
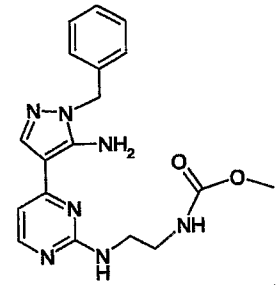
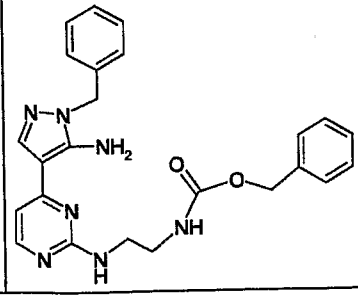
A mixture of **128b** (0.9 g, 2.4 mmol) in 4 mL of DCM: TFA (1:1) was stirred at room temperature for 10 min. Solvent and TFA were removed under reduced pressure. The residue was taken to $CHCl_3$: IPA (4:1) (50 mL) and treated with 10% KOH aqueous solution (5 mL). The organic layer was separated, concentrated to dryness to gain a light yellow solid. The crude product was washed with ethyl acetate to gain 0.63 g colorless solid product **128a**. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.69 (d, J = 4.3 Hz, 1 H),

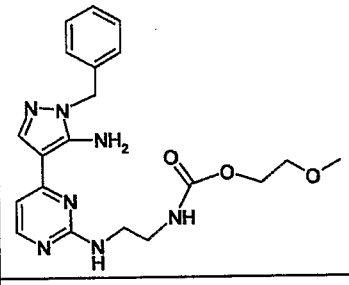
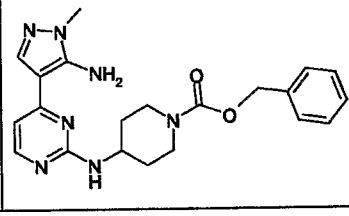
8.58 (s, 1 H), 8.05 (d, J = 6.3 Hz, 1 H), 7.94 (s, 1 H), 7.04 (s, 1 H), 6.92 (s, 2 H), 3.84 - 4.04 (m, 1 H), 3.59 (s, 3 H), 3.37 (d, J = 12.1 Hz, 2 H), 2.88 - 3.06 (m, 2 H), 2.10 (d, J = 13.4 Hz, 2 H), 1.63 - 1.75 (m, 2 H). LRMS m/z calcd. for $C_{13}H_{20}N_7S$ $[M+H]^+$ 274. Found: 274.

Preparation of 4-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (128b)

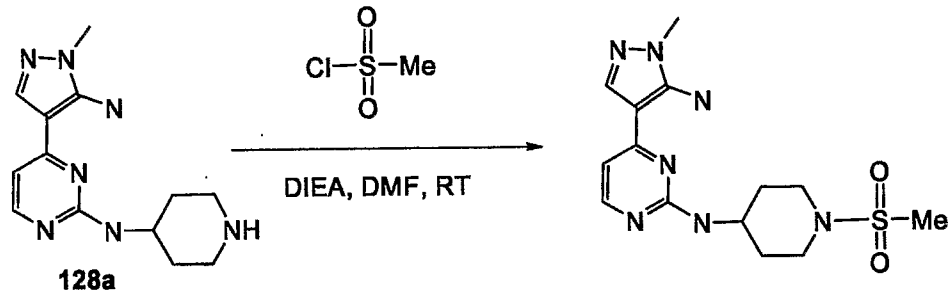
Compound **(128b)** was prepared according to method A, starting with compound **3a** and 4-amino-1-boc-piperidine 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (d, J = 5.3 Hz, 1 H), 7.67 (s, 1 H), 6.62 (d, J = 5.5 Hz, 1 H), 5.55 (s, 2 H), 5.05 (s, 1 H), 3.97 - 4.10 (m, 2 H), 3.93 (s, 1 H), 3.67 (s, 3 H), 2.96 (t, J = 12.0 Hz, 2 H), 2.06 - 2.12 (m, 2 H), 1.48 (s, 9 H), 1.40 - 1.47 (m, 2 H). LRMS m/z calcd. for $C_{18}H_{28}N_7O_2$ $[M+H]^+$ 374. Found: 374.

Table 6. Compounds 128-132 were prepared according to the method G as described above.

#	Structure	Compound name	LRMS m/z	1H NMR
128		4-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid isobutyl ester	374	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (d, J = 5.5 Hz, 1 H), 7.67 (s, 1 H), 6.63 (d, J=5.5 Hz, 1 H), 5.58 (s, 2 H), 5.20 (s, 1 H) 4.05 - 4.25 (m, 2 H) 3.88 (d, J=6.6 Hz, 2 H), 3.67 (s, 3 H), 3.02 (t, J=11.6 Hz, 2 H), 2.09 (dd, J=12.8, 3.02 Hz, 2 H), 1.76 - 2.02 (m, 2 H), 1.47 (q, J=9.8 Hz, 2 H) 0.94 (d, J=6.8 Hz, 6 H).
129		{2-[4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-ethyl}-carbamic acid methyl ester	368	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, J=5.0 Hz, 1 H), 7.8 (s, 1 H), 7.36 (d, J = 7.6 Hz, 2 H) 7.30 - 7.41 (m, 1 H) 7.22 (d, J = 7.6 Hz, 2 H), 6.67 (d, J=5.0 Hz, 1 H), 5.46 (s, 2 H), 5.22 (s, 2 H), 5.07 - 5.20 (m, 2 H), 3.62 (s, 3 H), 3.50 - 3.57 (m, 2 H), 3.34 - 3.46 (m, 2 H)
130		{2-[4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-ethyl}-carbamic acid benzyl ester	444	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (d, J = 5.3 Hz, 1 H), 7.75 (s, 1 H), 7.28 - 7.40 (m, 8 H), 7.21 (d, J = 6.8 Hz, 2 H), 6.65 (d, J=5.3 Hz, 1 H), 5.45 (s, 2 H), 5.27 (s, 1 H), 5.25 (s, 1 H), 5.20 (s, 2 H), 5.05 (s, 2 H), 3.54 (q, J = 5.6 Hz, 2 H), 3.41 (q, J = 5.9 Hz, 2 H)

#	Structure	Compound name	LRMS m/z	1H NMR
131		{2-[4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-ethyl}-carbamic acid 2-methoxy-ethyl ester	412	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (d, J = 5.3 Hz, 1 H), 7.74 (s, 1 H), 7.28 - 7.40 (m, 3 H), 7.21 (d, J=7.30 Hz, 2 H), 6.64 (d, J = 5.3 Hz, 1 H), 5.50 (s, 2 H), 5.31 (s, 2 H), 5.20 (s, 2 H), 4.12 - 4.19 (m, 2 H), 3.46 - 3.57 (m, 4 H), 3.36 - 3.44 (m, 2 H), 3.35 (s, 3 H)
132		4-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid benzyl ester	408	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, J = 5.3 Hz, 1 H), 7.67 (s, 1 H), 7.30 - 7.43 (m, 5 H), 6.63 (d, J=5.5 Hz, 1 H), 5.52 (s, 2 H), 5.15 (s, 2 H), 4.87 (d, J=6.3 Hz, 1 H), 4.15 (dd, J = 11.0, 6.9 Hz, 2 H), 3.81 - 4.08 (m, 1 H), 3.67 (s, 3 H), 3.05 (t, J = 11.2 Hz, 2 H), 2.11 (d, J = 12.8 Hz, 2 H) 1.39 - 1.53 (m, 2 H)

Method H

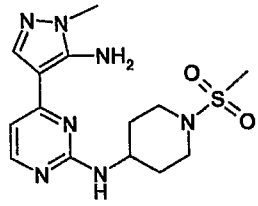
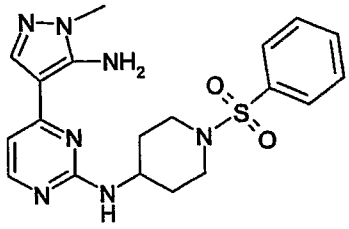
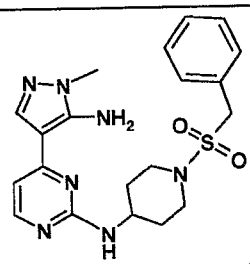
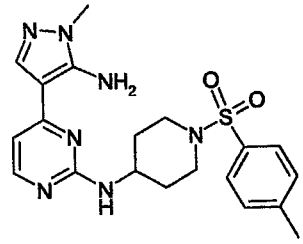
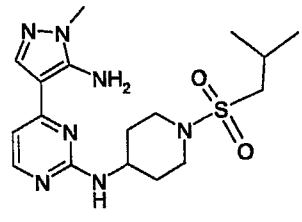
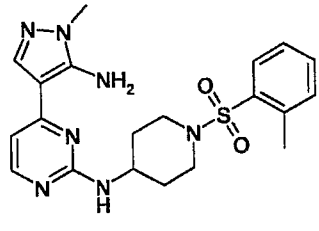


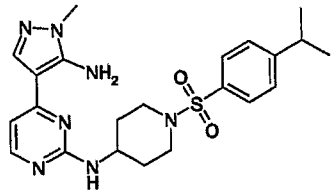
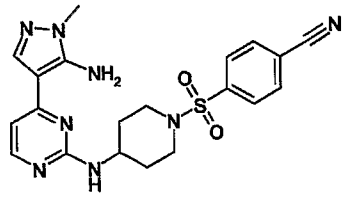
128a **133**

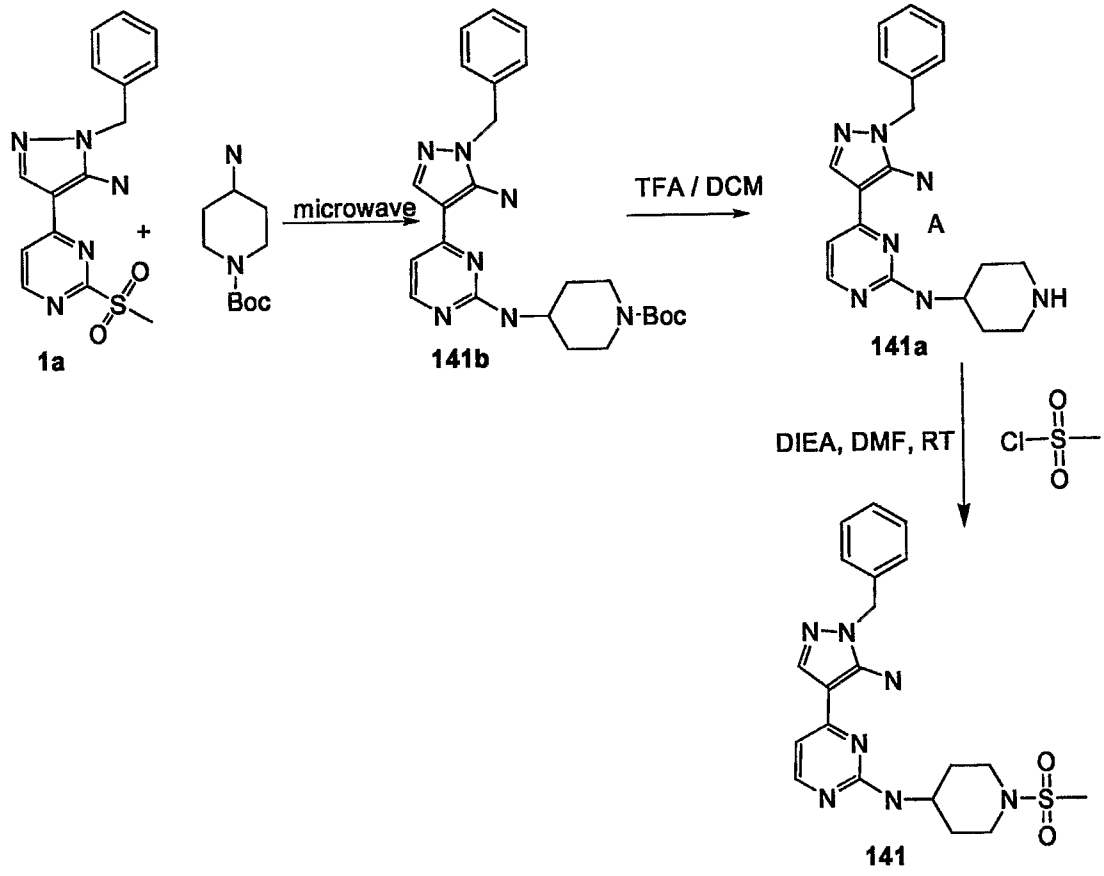
Preparation of [4-(5-Amino-1-methyl-1H-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methanesulfonyl-piperidin-4-yl)-amine (133)

Methane sulfonyl chloride (25 mg, 0.22 mmol) was added drop wise to a mixture of **128a** (50 mg, 0.18 mmol) and DIEA (59 mg, 0.46 mmol) in DMF (1 mL) at 0 C. The resulting mixture was stirred at room temperature for 15 minutes. DMF and DIEA were removed under reduced pressure at 85 °C. The residue triturated with 10% K_2CO_3 aqueous solution. The solid product was then filtered and washed with water, ethyl acetate to gain 52 mg colorless solid product **133**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, J = 5.0 Hz, 1 H), 7.67 (s, 1 H), 6.65 (d, J = 5.3 Hz, 1 H), 5.53 (s, 2 H), 4.90 (d, J = 3.5 Hz, 1 H), 3.90 - 4.13 (m, 1 H), 3.76 (d, J = 12.1 Hz, 2 H), 3.68 (s, 3 H), 2.94 (t, J = 10.7 Hz, 2 H), 2.82 (s, 3 H), 2.21 (d, J = 11.3 Hz, 2 H), 1.66 - 1.79 (m, 2 H). LRMS m/z calcd. for $C_{14}H_{22}N_7O_2S$ $[M+H]^+$ 352. Found: 352.

Table 7. Compounds 134-140 were prepared according to the method H as described above.

#	Structure	Compound name	LRMS m/z	1H NMR
133		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methanesulfonyl-piperidin-4-yl)-amine	352	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, J = 5.0 Hz, 1 H), 7.67 (s, 1 H), 6.65 (d, J = 5.3 Hz, 1 H), 5.53 (s, 2 H), 4.90 (d, J = 3.5 Hz, 1 H), 3.90 - 4.13 (m, 1 H), 3.76 (d, J = 12.1 Hz, 2 H) 3.68 (s, 3 H) 2.94 (t, J = 10.7 Hz, 2 H), 2.82 (s, 3 H), 2.21 (d, J=11.3 Hz, 2 H), 1.66 - 1.79 (m, 2 H)
134		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-benzenesulfonyl-piperidin-4-yl)-amine	414	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (d, J = 5.3 Hz, 1 H), 7.79 (d, J=7.3 Hz, 2 H), 7.65 (s, 1 H), 7.61 - 7.66 (m, 1 H), 7.58 (d, J=6.6 Hz, 1 H), 7.54 - 7.57 (m, 1 H), 6.61 (d, J = 5.3 Hz, 1 H), 5.48 (s, 2 H), 4.82 (d, J = 7.6 Hz, 1 H), 3.73 - 3.87 (m, 1 H), 3.67 - 3.74 (m, 2 H), 3.66 (s, 3 H), 2.61 (t, J=9.8 Hz, 2 H), 2.14 (dd, J=13.1, 3.3 Hz, 2 H), 1.64 - 1.74 (m, 2 H)
135		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-phenylmethanesulfonyl-piperidin-4-yl)-amine	428	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (d, J = 5.3 Hz, 1 H), 7.66 (s, 1 H), 7.41 (s, 5 H), 6.62 (d, J=5.3 Hz, 1 H), 5.50 (s, 2 H), 4.86 (d, J = 4.5 Hz, 1 H), 4.25 (s, 2 H), 3.76 - 3.97 (m, 1 H), 3.67 (s, 3 H), 3.56 - 3.68 (m, 2 H), 2.80 (t, J=11.1 Hz, 2 H), 1.99 - 2.09 (m, 2 H), 1.36 - 1.57 (m, 2 H).
136		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[1-(toluene-4-sulfonyl)-piperidin-4-yl]-amine	428	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (d, J = 5.3 Hz, 1 H), 7.67 (d, J = 8.1 Hz, 2 H), 7.65 (s, 1 H), 7.35 (d, J = 8.1 Hz, 2 H), 6.61 (d, J = 5.3 Hz, 1 H), 5.48 (s, 2 H), 4.83 (d, J = 3.8 Hz, 1 H), 3.72 - 3.86 (m, 1 H), 3.66 (s, 3 H), 3.58 - 3.72 (m, 2 H), 2.54 - 2.73 (m, 2 H), 2.47 (s, 3 H), 2.14 (d, J=12.6 Hz, 2 H), 1.63 - 1.77 (m, 2 H)
137		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[1-(2-methyl-propane-1-sulfonyl)-piperidin-4-yl]-amine	394	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, J = 5.5 Hz, 1 H), 7.67 (s, 1 H), 6.64 (d, J = 5.5 Hz, 1 H), 5.53 (s, 2 H), 4.91 (d, J = 6.6 Hz, 1 H), 3.87 - 4.07 (m, 1 H), 3.76 (d, J = 12.3 Hz, 2 H), 3.67 (s, 3 H), 2.98 (t, J = 10.7 Hz, 2 H), 2.78 (d, J = 6.6 Hz, 2 H), 2.24 - 2.39 (m, 1 H), 2.18 (dd, J = 13.1, 2.8 Hz, 2 H), 1.55 - 1.73 (m, 2 H), 1.13 (d, J = 6.8 Hz, 6 H)
138		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[1-(toluene-2-sulfonyl)-piperidin-4-yl]-amine	428	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (d, J = 5.3 Hz, 1 H), 7.92 (d, J = 8.1 Hz, 1 H), 7.66 (s, 1 H), 7.48 (t, J = 7.4 Hz, 1 H), 7.29 - 7.38 (m, 2 H), 6.62 (d, J = 5.5 Hz, 1 H), 5.53 (s, 2 H), 4.91 (d, J = 7.1 Hz, 1 H), 3.82 - 3.98 (m, 1 H), 3.71 (d, J = 12.6 Hz, 2 H), 3.66 (s, 3 H), 2.84 - 2.95 (m, 2 H), 2.65 (s, 3 H), 2.15 (dd, J = 13.1, 3.0 Hz, 2 H), 1.50 - 1.68 (m, 2 H)

#	Structure	Compound name	LRMS m/z	1H NMR
139		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[1-(4-isopropyl-benzenesulfonyl)-piperidin-4-yl]-amine	456	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (d, J = 5.3 Hz, 1 H),7.70 (d, J = 8.1 Hz, 2 H), 7.65 (s, 1 H), 7.40 (d, J = 8.1 Hz, 2 H), 6.61 (d, J = 5.5 Hz, 1 H), 5.48 (s, 2 H), 4.82 (d, J = 7.6 Hz, 1 H), 3.72 - 3.84 (m, 1 H), 3.66 (s, 3 H), 3.59 - 3.71 (m, 2 H), 2.91 - 3.09 (m, 1 H), 2.52 - 2.71 (m, 2 H), 2.14 (d, J = 13.6 Hz, 2 H), 1.62 - 1.74 (m, 2 H), 1.31 (d, J = 7.1 Hz, 6 H)
140		4-{4-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-piperidine-1-sulfonyl}-benzonitrile	439	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.08 (d, J = 5.5 Hz, 1 H), 7.89 (q, J = 8.1 Hz, 4 H), 7.66 (s, 1 H), 6.63 (d, J = 5.3 Hz, 1 H), 5.46 (s, 2 H), 4.79 (d, J = 7.1 Hz, 1 H), 3.77 - 3.90 (m, 1 H), 3.68 - 3.77 (m, 2 H), 3.67 (s, 3 H), 2.68 (t, J = 11.6 Hz, 2 H), 2.17 (d, J = 12.6 Hz, 2 H), 1.62 - 1.76 (m, 2 H)



Preparation of [4-(5-Amino-1-benzyl-1H-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methanesulfonyl-piperidin-4-yl)-amine (141)

Compound **141** was prepared according to the method described for preparation of **133** starting from compound **141a** . 1H NMR (400 MHz, DMSO-d6) δ ppm 8.05 (d, J = 5.3 Hz, 1 H), 7.80 (s, 1 H), 7.32 (t, J

= 7.3 Hz, 2 H), 7.25 (t, J = 7.3 Hz, 1 H), 7.15 (d, J = 7.3 Hz, 2 H), 7.08 (d, J = 7.6 Hz, 1 H), 6.87 (s, 2 H), 6.68 (d, J = 5.3 Hz, 1 H), 5.20 (s, 2 H), 3.67 - 3.92 (m, 1 H), 3.55 (d, J = 12.1 Hz, 2 H), 2.87 (s, 3 H), 2.80 - 2.91 (m, 2 H), 1.90 - 2.09 (m, 2 H), 1.39 - 1.61 (m, 2 H). LRMS m/z calcd. for $C_{20}H_{26}N_7O_2S$ $[M+H]^+$ 428. Found: 428.

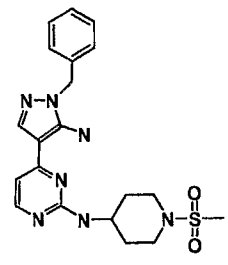
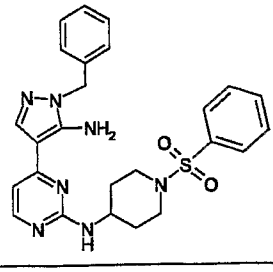
Preparation of [4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-piperidin-4-yl-amine (141a)

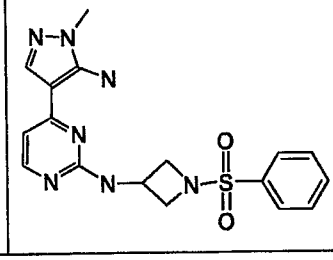
Compound **141a** was prepared according to the method described for preparation of **128a** starting from compound **141b**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (s, 1 H) 7.29 - 7.40 (m, 3 H) 7.21 (d, J = 6.8 Hz, 2 H), 6.63 (d, J = 5.3 Hz, 1 H), 5.47 (s, 2 H), 5.22 (s, 2 H), 4.93 (d, J = 5.0 Hz, 1 H), 3.69 - 3.95 (m, 1 H), 2.99 - 3.16 (m, 2 H), 2.59 - 2.81 (m, 2 H), 2.06 (dd, J = 12.2, 3.2 Hz, 2 H), 1.94 (s, 2 H), 1.30 - 1.46 (m, 2 H). LRMS m/z calcd. for $C_{19}H_{24}N_7$ $[M+H]^+$ 350. Found: 350.

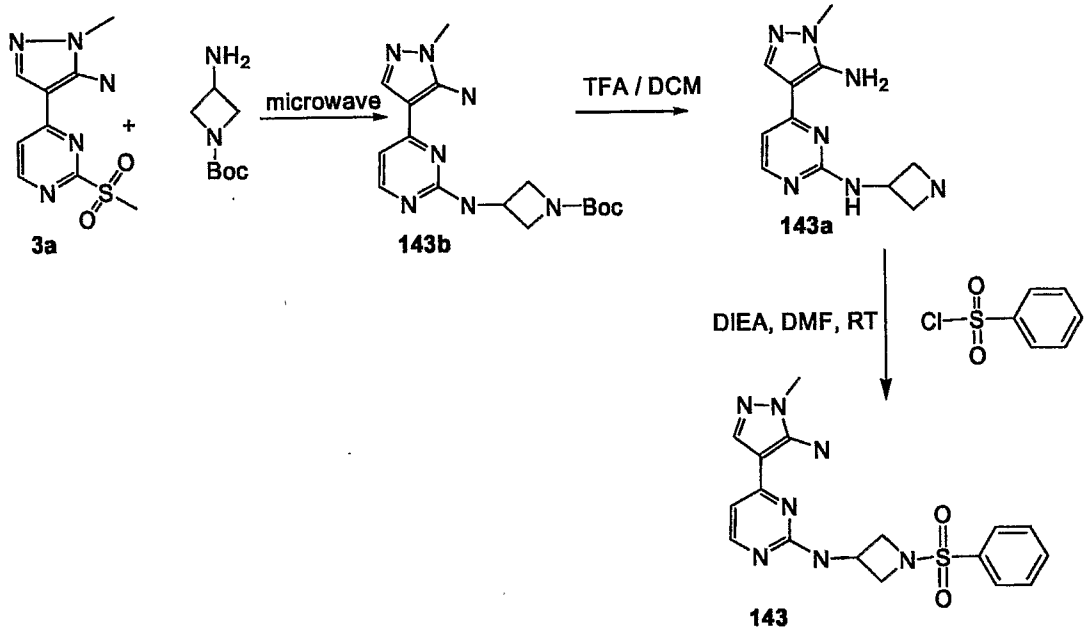
Preparation of 4-[4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (141b)

Compound **141b** was prepared according to the method described for preparation of **128b** starting from compound **1a** instead of **3a**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, J = 5.5 Hz, 1 H), 7.75 (s, 1 H), 7.36 (d, J = 7.8 Hz, 2 H), 7.30 - 7.40 (m, 1 H), 7.21 (d, J = 7.6 Hz, 2 H), 6.65 (d, J = 5.5 Hz, 1 H), 5.43 (s, 2 H), 5.22 (s, 2 H), 4.87 (d, J = 2.3 Hz, 1 H), 4.03 (d, J = 12.3 Hz, 2 H), 3.90 (dd, J = 7.3, 3.8 Hz, 1 H), 2.93 (t, J = 12.3 Hz, 2 H), 2.03 (dd, J = 12.3, 2.0 Hz, 2 H), 1.46 (s, 9 H) 1.32 - 1.45 (m, 2 H). LRMS m/z calcd. for $C_{24}H_{32}N_7O_2$ $[M+H]^+$ 450. Found: 450.

Table 8. Compounds **141-143** were prepared according to the method of preparation of compound **141** as described above. Compound **142** was prepared according to the method described for preparation of **141** with the substitution of benzenesulfonyl chloride instead of methanesulfonyl chloride.

#	Structure	Compound name	LRMS m/z	1H NMR
141		[4-(5-Amino-1-benzyl-1H-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methanesulfonyl-piperidin-4-yl)-amine	428	1H NMR (400 MHz, DMSO-d6) δ ppm 8.05 (d, J = 5.3 Hz, 1 H), 7.80 (s, 1 H), 7.32 (t, J = 7.3 Hz, 2 H), 7.25 (t, J = 7.3 Hz, 1 H), 7.15 (d, J = 7.3 Hz, 2 H), 7.08 (d, J = 7.6 Hz, 1 H), 6.87 (s, 2 H), 6.68 (d, J = 5.3 Hz, 1 H), 5.20 (s, 2 H), 3.67 - 3.92 (m, 1 H), 3.55 (d, J = 12.1 Hz, 2 H), 2.87 (s, 3 H), 2.80 - 2.91 (m, 2 H), 1.90 - 2.09 (m, 2 H), 1.39 - 1.61 (m, 2 H).
142		[4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-benzenesulfonyl-piperidin-4-yl)-amine	490	1H NMR (400 MHz, DMSO-d6) δ ppm 7.99 (d, J = 5.3 Hz, 1 H), 7.77 (d, J = 3.5 Hz, 2 H), 7.8 (s, 1 H), 7.70 - 7.74 (m, 1 H), 7.66 (t, J = 7.4 Hz, 2 H), 7.3 (t, J = 7.3 Hz, 2 H), 7.25 (t, J = 7.3 Hz, 1 H), 7.14 (d, J = 7.1 Hz, 2 H), 7.02 (d, J = 7.3 Hz, 1 H), 6.82 (s, 2 H), 6.65 (d, J = 5.3 Hz, 1 H), 5.18 (s, 2 H), 3.61 - 3.72 (m, 1 H), 3.57 (d, J = 11.8 Hz, 2 H), 2.45 - 2.53 (m, 2 H), 1.97 (dd, J=13.9, 3.0

#	Structure	Compound name	LRMS m/z	1H NMR
				Hz, 2 H), 1.46 - 1.60 (m, 2 H)
143		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-benzenesulfonyl-azetidin-3-yl)-amine	386	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (d, J = 4.0 Hz, 1 H), 7.88 (d, J = 7.1 Hz, 2 H), 7.66 - 7.74 (m, 1 H), 7.65 (s, 1 H), 7.62 (d, J = 7.6 Hz, 2 H), 6.67 (d, J = 4.3 Hz, 1 H), 5.49 (s, 2 H), 5.12 (d, J = 5.8 Hz, 1 H), 4.46 - 4.69 (m, 1 H), 4.18 (t, J = 7.4 Hz, 2 H), 3.68 - 3.73 (m, 2 H), 3.67 (s, 3 H).



Preparation of [4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-benzenesulfonyl-azetidin-3-yl)-amine (143)

Compound **143** was prepared according to the method described for preparation of **142** starting from compound **143a**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (d, J = 4.0 Hz, 1 H), 7.88 (d, J = 7.1 Hz, 2 H), 7.66 - 7.74 (m, 1 H), 7.65 (s, 1 H), 7.62 (d, J = 7.6 Hz, 2 H), 6.67 (d, J = 4.3 Hz, 1 H), 5.49 (s, 2 H), 5.12 (d, J = 5.8 Hz, 1 H), 4.46 - 4.69 (m, 1 H), 4.18 (t, J = 7.4 Hz, 2 H), 3.68 - 3.73 (m, 2 H), 3.67 (s, 3 H). LRMS m/z calcd. for $C_{17}H_{20}N_7O_2S$ $[M+H]^+$ 386. Found: 386.

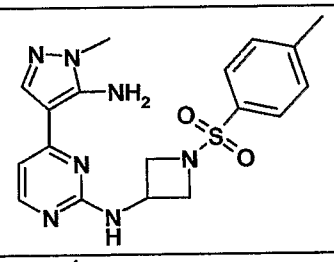
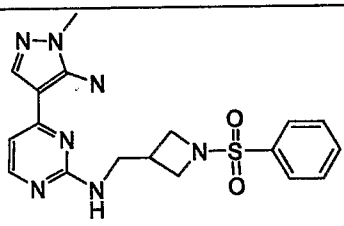
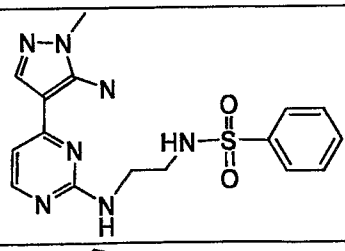
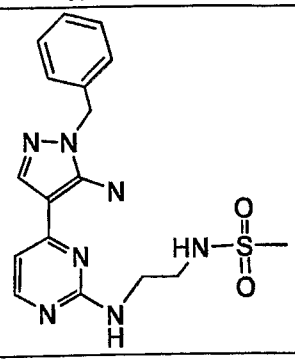
Preparation of [4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-azetidin-3-yl-amine (143a)

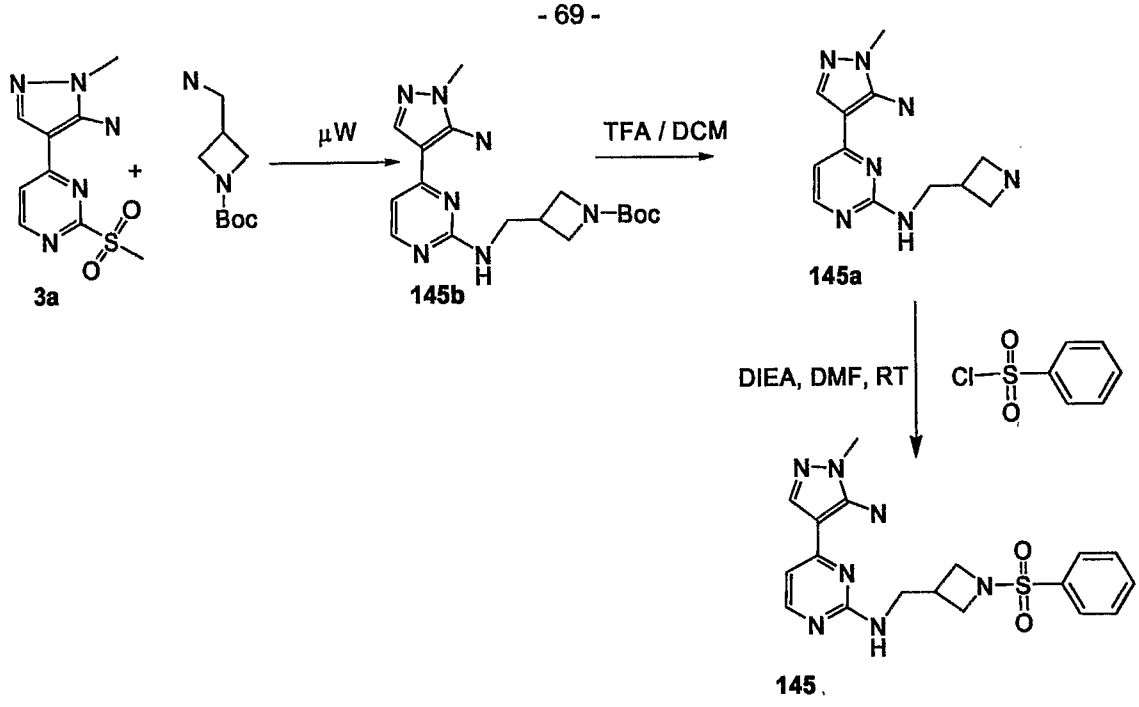
Compound **143a** was prepared according to the method described for preparation of **128a** starting from compound **143b**. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.20 (d, J=7.3 Hz, 1 H), 8.03 (s, 1 H), 7.69 - 7.85 (m, 1 H), 7.32 (s, 2 H), 7.03 (d, J = 7.1 Hz, 1 H), 6.68 (d, J = 7.3 Hz, 1 H), 4.38 - 4.57 (m, 1 H), 4.17 - 4.28 (m, 2 H), 4.09 - 4.17 (m, 1 H), 3.85 - 4.01 (m, 1 H), 3.59 (s, 3 H). LRMS m/z calcd. for $C_{11}H_{16}N_7$ $[M+H]^+$ 246. Found: 246.

Preparation of 4-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-azitidine-1-carboxylic acid *tert*-butyl ester (143b)

Compound (**143b**) was prepared according to method A starting with **3a** and 3-amino-1-boc-azetidine 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, J = 4.8 Hz, 1 H), 7.67 (s, 1 H), 6.68 (d, J=5.0 Hz, 1 H), 5.54 (s, 2 H), 5.39 (d, J = 4.3 Hz, 1 H), 4.50 - 4.80 (m, 1 H), 4.31 (t, J = 8.1 Hz, 2 H), 3.76 - 3.95 (m, 2 H), 3.67 (s, 3 H), 1.46 (s, 9 H). LRMS m/z calcd. for $C_{16}H_{24}N_7O_2$ $[M+H]^+$ 346. Found: 346.

Table 9. Compounds **144-147** were prepared according to the method described for preparation of **143** as described above.

#	Structure	Compound name	LRMS m/z	1H NMR
144		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[1-(toluene-4-sulfonyl)-azetidin-3-yl]-amine	400	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (d, J = 5.3 Hz, 1 H), 7.75 (d, J = 8.3 Hz, 2 H), 7.65 (s, 1 H), 7.40 (d, J = 8.1 Hz, 2 H), 6.66 (d, J = 5.3 Hz, 1 H), 5.52 (s, 2 H), 5.20 (d, J = 7.1 Hz, 1 H), 4.48 - 4.68 (m, 1 H), 4.15 (t, J = 7.3 Hz, 2 H), 3.67 (s, 3 H), 3.64 - 3.68 (m, 2 H), 2.48 (s, 3 H)
145		[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-benzenesulfonyl-azetidin-3-ylmethyl)-amine	400	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (d, J = 5.5 Hz, 1 H) 7.77 - 7.87 (m, 2 H) 7.67 (s, 1 H) 7.61 - 7.66 (m, 1 H) 7.54 - 7.60 (m, 2 H) 6.64 (d, J = 5.3 Hz, 1 H) 5. Hz, 2 H) 3.68 (s, 3 H) 3.66 (d, J = 5.0 Hz, 1 H) 3.64 (d, J=5.0 Hz, 1 H) 3.56 (t, J = 6.6 Hz, 2 H) 2.63 - 2.74 (m, 1 H).
146		*N*-[2-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-ethyl]-benzenesulfonamide	374	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (d, J=5.5 Hz, 1 H), 7.82 (d, J = 7.6 Hz, 2 H), 7.67 (s, 1 H), 7.51 - 7.59 (m, 1 H), 7.48 (d, J = 7.6 Hz, 2 H), 6.66 (d, J = 5.3 Hz, 1 H), 5.77 (s, 1 H), 5.51 (s, 2 H), 5.03 - 5.18 (m, 1 H), 3.68 (s, 3 H), 3.58 (q, J = 6.0 Hz, 2 H), 3.23 (q, J = 5.7 Hz, 2 H).
147		*N*-[2-[4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-ethyl]-methanesulfonamide	388	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (d, J = 5.5 Hz, 1 H), 7.70 (s, 1 H), 7.30 (d, J = 7.3 Hz, 2 H), 7.25 - 7.36 (m, 1 H), 7.16 (d, J = 7.1 Hz, 2 H), 6.62 (d, J = 5.3 Hz, 1 H), 5.53 - 5.82 (m, 2 H), 5.27 (s, 2 H), 5.16 (s, 2 H), 3.50 (t, J = 5.9 Hz, 2 H), 3.38 (s, 3 H), 3.25 (t, J = 5.8 Hz, 2 H).



Preparation of 3-{[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-methyl}-azetidine-1-carboxylic acid *tert*-butyl ester (145b)

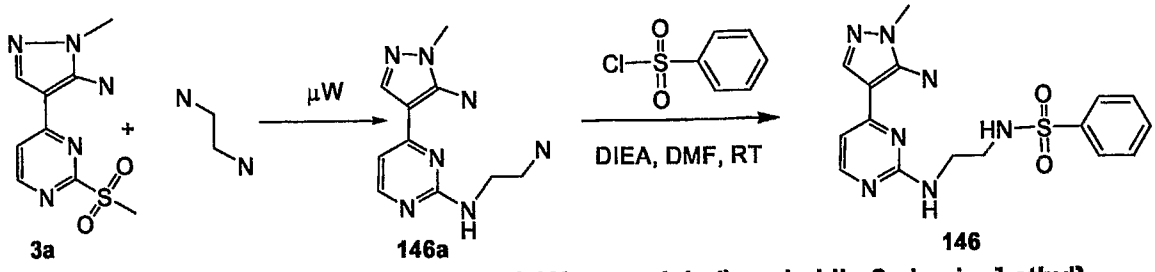
Compound (**145b**) was prepared according to method A as described above starting with **3a** and displacing the sulfonyl with 3-aminomethyl-1-boc-azitidine. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (d, J = 5.5 Hz, 1 H), 7.67 (s, 1 H), 6.65 (d, J = 5.5 Hz, 1 H), 5.56 (s, 2 H), 5.22 (d, J = 4.3 Hz, 1 H), 4.05 (t, J = 8.4 Hz, 2 H), 3.69 - 3.72 (m, 2 H), 3.67 (s, 3 H), 3.63 - 3.66 (m, 2 H), 2.83 - 2.90 (m, 1 H), 1.44 (s, 9 H). LRMS m/z calcd. for $C_{17}H_{26}N_7O_2$ $[M+H]^+$ 360. Found: 360.

Preparation of [4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-azetidin-3-ylmethyl-amine (145a)

Compound **145a** was prepared according to the method described for preparation of **128a** starting from compound **145b**. LRMS m/z calcd. for $C_{12}H_{18}N_7$ $[M+H]^+$ 260. Found: 260.

Preparation of [4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-benzenesulfonyl-azetidin-3-ylmethyl)-amine (145)

Compound **145** was prepared according to the method described for preparation of **143** starting from compound **145a**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (d, J = 5.5 Hz, 1 H) 7.77 - 7.87 (m, 2 H) 7.67 (s, 1 H) 7.61 - 7.66 (m, 1 H) 7.54 - 7.60 (m, 2 H) 6.64 (d, J = 5.3 Hz, 1 H) 5. Hz, 2 H) 3.68 (s, 3 H) 3.66 (d, J = 5.0 Hz, 1 H) 3.64 (d, J=5.0 Hz, 1 H) 3.56 (t, J = 6.6 Hz, 2 H) 2.63 - 2.74 (m, 1 H). LRMS m/z calcd. for $C_{18}H_{22}N_7O_2S$ $[M+H]^+$ 400. Found: 400.



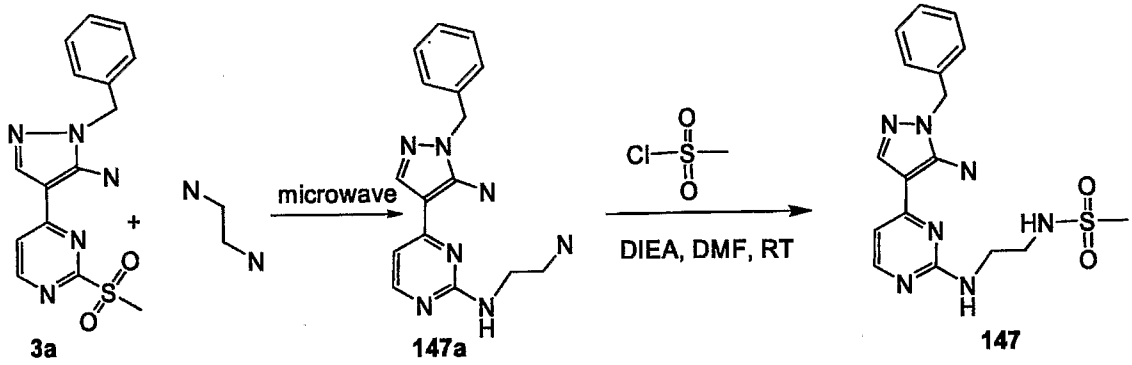
3a 146a 146

Preparation of *N*-{2-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-ethyl}-benzenesulfonamide (146)

Compound **146** was prepared according to the method described for preparation of **143** starting from compound **146a**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (d, J=5.5 Hz, 1 H), 7.82 (d, J = 7.6 Hz, 2 H), 7.67 (s, 1 H), 7.51 - 7.59 (m, 1 H), 7.48 (d, J = 7.6 Hz, 2 H), 6.66 (d, J = 5.3 Hz, 1 H), 5.77 (s, 1 H), 5.51 (s, 2 H), 5.03 - 5.18 (m, 1 H), 3.68 (s, 3 H), 3.58 (q, J = 6.0 Hz, 2 H), 3.23 (q, J = 5.7 Hz, 2 H). LRMS m/z calcd. for $C_{16}H_{20}N_7O_2S$ $[M+H]^+$ 374. Found: 374.

Preparation of N^1-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-ethane-1, 2-diamine. (146a)

Compound (**146a**) was prepared according to method A as described above starting with **3a** and displacing the sulfone with 1, 2-diaminoethane. LRMS m/z calcd. for $C_{10}H_{15}N_7$ $[M+H]^+$ 234. Found: 234.



3a 147a 147

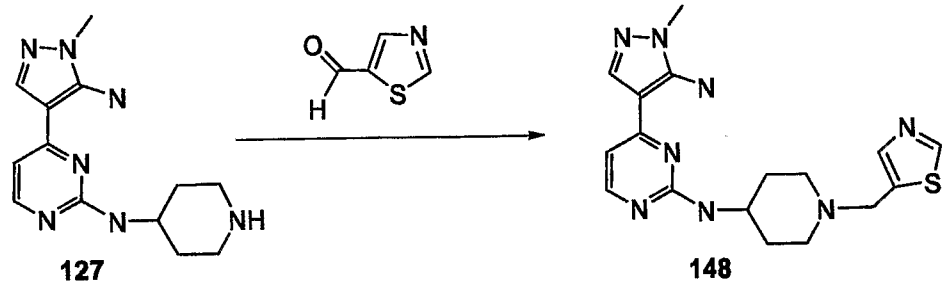
Preparation of *N*-{2-[4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-ethyl}-methanesulfonamide (147)

Compound **147** was prepared according to the method described for preparation of **146** starting from compound **147a**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (d, J = 5.5 Hz, 1 H), 7.70 (s, 1 H), 7.30 (d, J = 7.3 Hz, 2 H), 7.25 - 7.36 (m, 1 H), 7.16 (d, J = 7.1 Hz, 2 H), 6.62 (d, J = 5.3 Hz, 1 H), 5.53 - 5.82 (m, 2 H), 5.27 (s, 2 H), 5.16 (s, 2 H), 3.50 (t, J = 5.9 Hz, 2 H), 3.38 (s, 3 H), 3.25 (t, J = 5.8 Hz, 2 H). LRMS m/z calcd. for $C_{17}H_{22}N_7O_2S$ $[M+H]^+$ 388. Found: 388.

Preparation of N^1-[4-(5-Amino-1-benzyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-ethane-1,2-diamine. (147a)

Compound (**147a**) was prepared according to method A as described above starting with **1a** and displacing the sulfone with 1,2-diaminoethane. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.03 (d, J = 5.3 Hz,

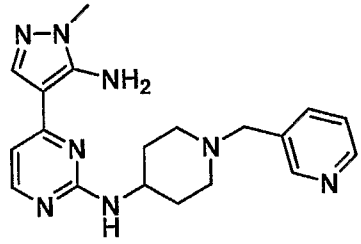
1 H), 7.79 (s, 1 H), 7.32 (t, J = 7.3 Hz, 2 H), 7.21 - 7.28 (m, 1 H), 7.16 (d, J = 7.1 Hz, 2 H), 7.02 (s, 1 H), 6.87 (s, 2 H), 6.66 (d, J = 5.3 Hz, 1 H), 5.20 (s, 2 H), 3.25 (q, J = 6.1 Hz, 2 H), 2.97 - 3.50 (m, 2 H), 2.69 (t, J = 6.3 Hz, 2 H). LRMS m/z calcd. for $C_{16}H_{20}N_7$ $[M+H]^+$ 310. Found: 310.



127 148

Preparation of [4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-thiazol-5-ylmethyl-piperidin-4-yl)-amine (148)

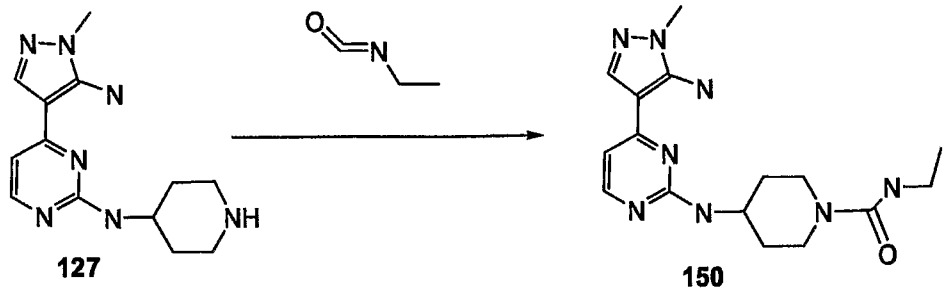
Sodium triacetoxyhydroborate (97 mg, 0.45 mmol) was added to a mixture of **127** (50 mg, 0.18 mmol), thiazole-5-carboxaldehyde (52 mg, 0.46 mmol) and acetic acid (22 mg, 0.37 mmol) in dichloroethane (1.5 mL) at room temperature. The resulting was stirred at 45 °C for 45 minutes. After cooling to room temperature, the mixture was diluted with $CHCl_3$ (55 mL) and washed with 10% aqueous Na_2CO_3 solution. The organic layer was separated, dried over MgSO4, then concentrated. The crude product was purified by ISCO silica gel column chromatography, eluting with CHCl3: MeOH (9:1) to gain 45 mg (66%) of colorless solid **148**. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.77 (s, 1 H) 8.11 (d, J = 5.3 Hz, 1 H), 7.72 (s, 1 H), 7.66 (s, 1 H), 6.61 (d, J = 5.3 Hz, 1 H), 5.56 (s, 2 H), 4.80 - 5.14 (m, 1 H), 3.81 - 3.99 (m, 1 H), 3.79 (s, 2 H), 3.67 (s, 3 H), 2.89 (d, J = 11.6 Hz, 2 H), 2.16 - 2.36 (m, 2 H), 2.02 - 2.13 (m, 2 H), 1.43 - 1.68 (m, 2 H). LRMS m/z calcd. for $C_{17}H_{23}N_8S$ $[M+H]^+$ 371. Found: 371.



149

Preparation of [4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-N-(1-(pyridin-3-ylmethyl)piperidin-4-yl)pyrimidin-2-amine (149)

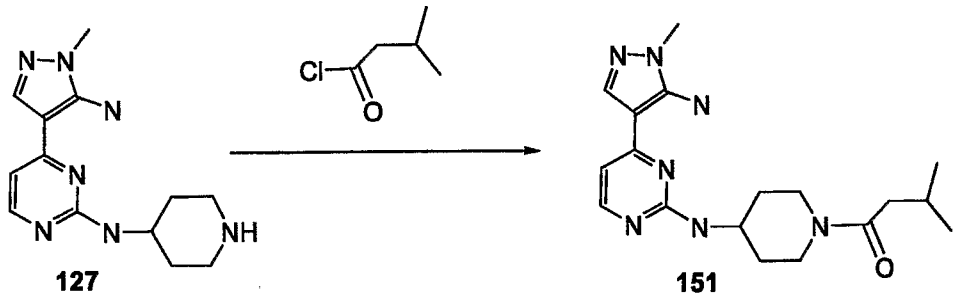
Compound **149** was prepared according to the method described for preparation of **148** starting from 3-nicotinaldehyde instead of thiazole-5-carboxaldehyde. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.55 (d, J = 1.8 Hz, 1 H), 8.52 (dd, J = 4.8, 1.5 Hz, 1 H), 8.11 (d, J = 5.3 Hz, 1 H), 7.68 (d, J = 7.8 Hz, 1 H), 7.66 (s, 1 H), 7.26 - 7.30 (m, 1 H), 6.60 (d, J = 5.5 Hz, 1 H), 5.57 (s, 2 H), 4.98 (s, 1 H), 3.75 - 3.87 (m, 1 H), 3.67 (s, 3 H), 3.54 (s, 2 H), 2.85 (d, J = 11.6 Hz, 2 H), 2.21 (t, J = 11.2 Hz, 2 H), 2.03 - 2.12 (m, 2 H), 1.52 - 1.66 (m, 2 H). LRMS m/z calcd. for $C_{19}H_{25}N_8$ $[M+H]^+$ 365. Found: 365.



127 150

Preparation of 4-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid ethylamide (150)

Ethyl isocyanate (13 mg, 0.18 mmol) was added to a mixture of **127** (45 mg, 0.17 mmol) and DIEA (32 mg, 0.25 mmol) in DMF (1mL) at 0 °C. The resulting mixture was stirred at room temperature for 15 min. DMF was evaporated under reduced pressure. The residue was diluted with $CHCl_3$ (15 mL) and washed with 10% $NaCO_3$ aq. solution. The organic layer was separated and concentrated to dryness. The crude product was washed with diethyl ether to gain 36 mg (63%) of colorless solid product. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.02 (d, J = 5.5 Hz, 1 H), 7.71 (s, 1 H), 7.00 (d, J = 7.6 Hz, 1 H), 6.67 (s, 2 H), 6.63 (d, J = 5.3 Hz, 1 H), 6.47 (t, J = 5.0 Hz, 1 H), 3.91 (d, J = 13.4 Hz, 2 H), 3.83 (s, 1 H), 3.56 (s, 3 H), 2.91 - 3.13 (m, 2 H), 2.77 (t, J = 11.8 Hz, 2 H), 1.85 (d, J = 10.3 Hz, 2 H), 1.30 (q, J = 11.1 Hz, 2 H), 1.01 (t, J = 7.2 Hz, 3 H). LRMS m/z calcd. for $C_{16}H_{25}N_8O$ $[M+H]^+$ 345. Found: 345.



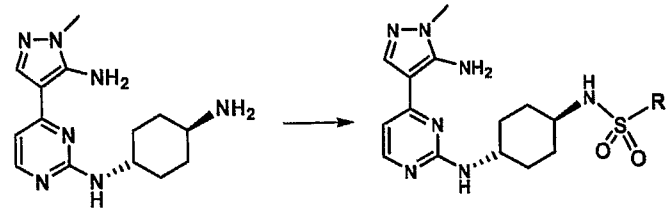
127 151

Preparation of 1-{4-[4-(5-Amino-1-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-3-methyl-butan-1-one (151)

Isovaleryl chloride (27 mg, 0.22 mmol) was added to a mixture of **127** (55 mg, 0.20 mmol) and DIEA (52 mg, 0.40 mmol) in DMF (1.0 mL) at 0 °C. The resulting mixture was stirred at room temperature for 15 min. The mixture was diluted with ethyl acetate (15 mL) and washed with 10% NaCO3 aqueous solution (1 mL). The organic layer was separated and concentrated. The crude product was purified by ISCO silica gel column chromatography, eluting with CHCl3: MeOH (9:1), to gain 30 mg (42%) of colorless solid product. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (d, J = 5.5 Hz, 1 H), 7.66 (s, 1 H), 6.62 (d, J = 5.5 Hz, 1 H), 5.59 (s, 2 H), 5.04 (s, 1 H), 4.52 (d, J = 13.3 Hz, 1 H), 4.01 (d, J = 7.3 Hz, 1 H), 3.87 (d, J = 13.6 Hz, 1 H), 3.66 (s, 3 H), 3.20 (t, J = 11.5 Hz, 1 H), 2.87 (t, J = 11.7 Hz, 1 H), 2.23 (d, J = 7.1 Hz, 2 H), 2.06 - 2.21

(m, 3 H), 1.32 - 1.55 (m, 2 H), 0.98 (d, J = 6.6 Hz, 6 H). LRMS m/z calcd. for $C_{18}H_{28}N_7O$ $[M+H]^+$ 358. Found: 358.

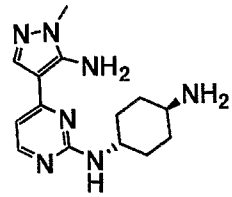
General method I:



107 (trans)

Trans-N-[4-(5-amino-1-methyl-1*H*-pyrazol-4-yl)pyrimidin-2-yl]cyclohexane-1,4-diamine (**107 trans**) (100 mg, 0.35 mmol), sulfonyl chloride (1 eq, 0.35 mmol) and triethylamine (35 mg, 0.35 mmol) were mixed in 7 mL of dichloroethane:dimethoxyethane (1:2) and the solution was stirred at room temperature for 16 h. The reaction mixture was filtered and the crude materials were purified by HPLC to give the sulfonamide product with yield 30-65% varying with different sulfonyl chlorides used.

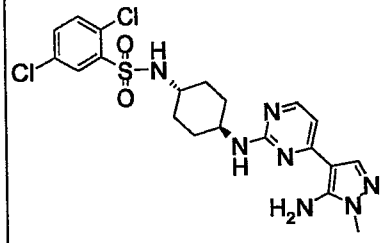
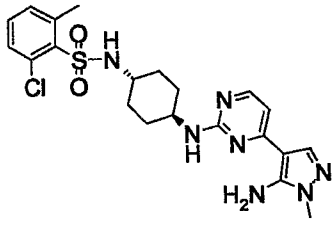
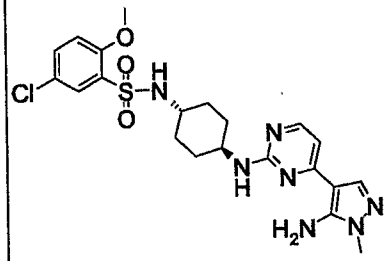
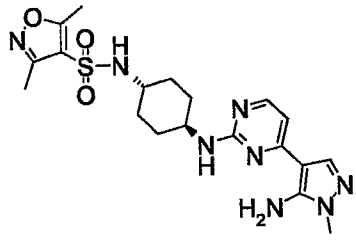
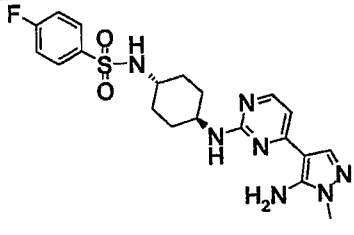
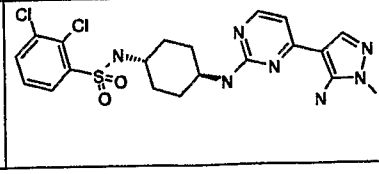
***Trans-N*-[4-(5-amino-1-methyl-1*H*-pyrazol-4-yl)pyrimidin-2-yl]cyclohexane-1,4-diamine (107 trans)**

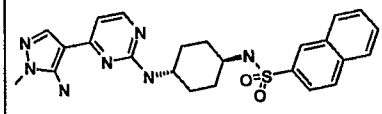
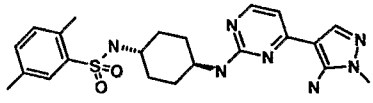
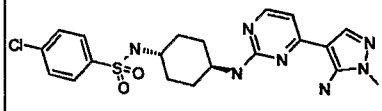
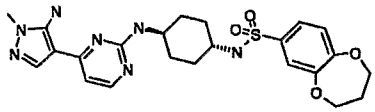
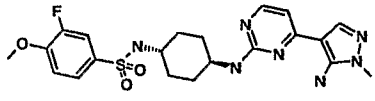
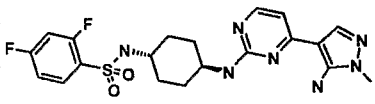
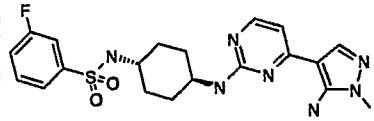


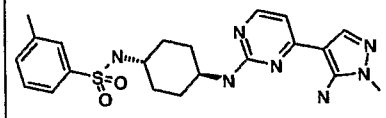
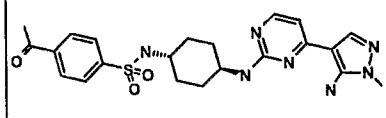
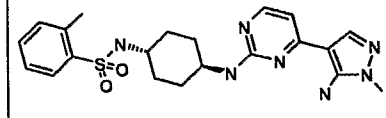
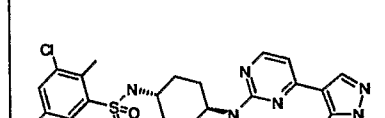
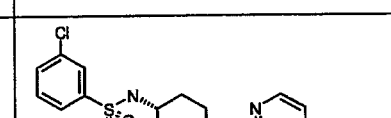
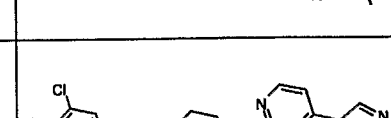
107 (trans)

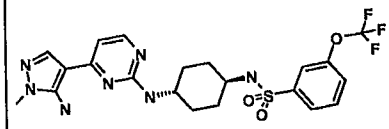
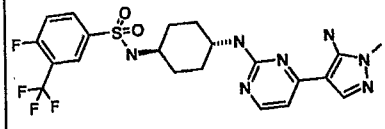
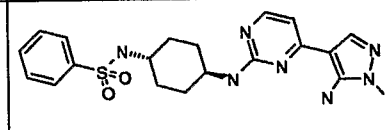
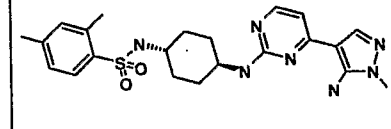
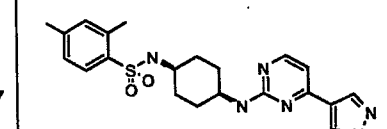
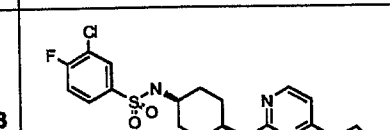
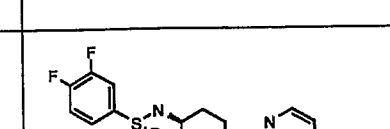
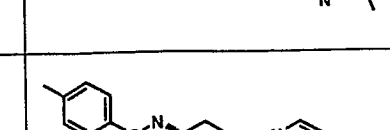
4-(1,5-dimethyl-1H-pyrazol-4-yl)-2-(methylsulfonyl)pyrimidine (10.0 g, 39.5 mmol) and *trans*-cyclohexane-1,4-diamine (9.0 g, 79.0 mmol) were dissolved in 40 mL isopropanol. This mixture was transferred into a microwave-reaction tube, and was heated to 140 °C under microwave radiation for 1.5 hrs. After cooling down to room temperature, the solvent was evaporated and the crude product was precipitated from EA. Collected the solid material and washed with ether many times to remove the excess diamino-cyclohexane. The product was place under vacuum to dry and yielded 4.02 g of solid. The mother liquid was further purified by a silica gel column with 10 % MeOH in ethyl acetate to give additional 2.1 g of the product (total 6.12 g, 56%). 1H NMR (400 MHz, D_2O) ppm δ 0.99 - 1.21 (m, 4 H), 1.64 - 1.93 (m, 4 H), 2.49 - 2.79 (m, 1 H), 3.07 - 3.22 (m, 1 H), 3.41 (s, 3 H), 6.20 (d, *J* = 5.5 Hz, 1 H), 7.35 (s, 1 H), 7.64 (d, *J* = 5.5 Hz, 1 H). LRMS : 287. $[(M + H)^+$.

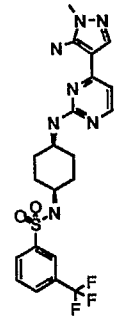
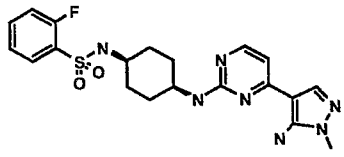
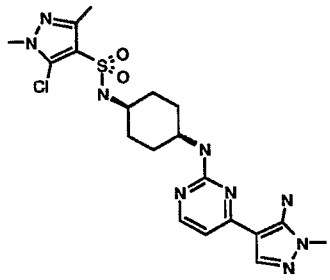
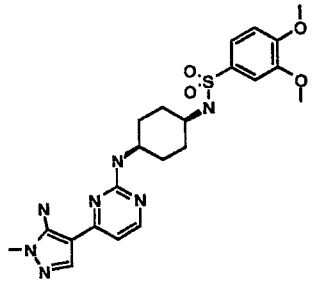
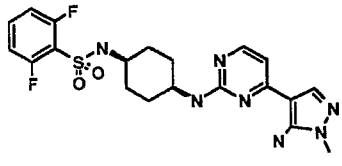
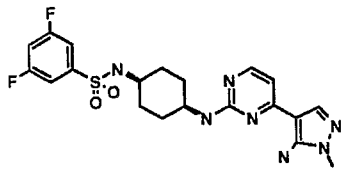
Table 10. Compounds 152-207 were prepared according to the method I as described above.

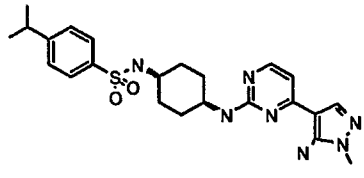
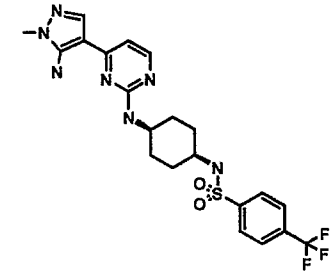
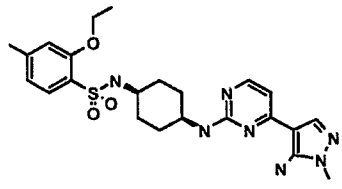
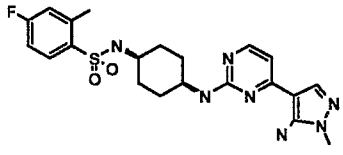
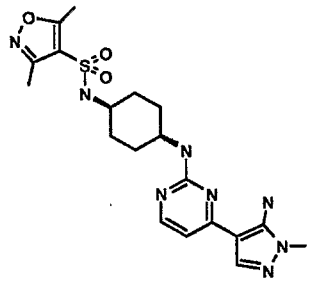
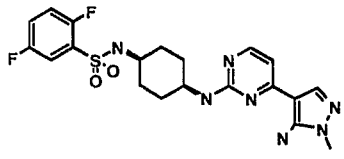
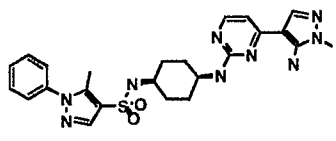
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
152		*N*-(*trans*-4-{[4-(5-amino-1-methyl-1*H*-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2,5-dichlorobenzenesulfonamide	496	1H NMR (400 MHz, DMSO-d6) δ ppm 1.19 (m, 2 H), 1.31 - 1.48 (m, 2 H), 1.60 - 1.76 (m, 2 H), 1.82 - 1.96 (m, 3 H), 2.96 - 3.13 (m, 1 H), 3.55 (s, 3 H), 6.60 (d, J =,5.29 Hz, 1 H), 6.64 (s, 2 H), 7.67 - 7.77 (m, 3 H), 7.94 - 8.02 (m, 2 H), 8.15 (d, J = 8.06 HZ, 1H)
153		N-((1r,4r)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)-2-chloro-6-methylbenzenesulfonamide	476	1H NMR (400 MHz, DMSO-d6) δ ppm 1.16 - 1.30 (m, 2 H), 1.58 - 1.74 (m, 2 H), 1.82 - 1.99 (m, 2 H), 2.65 (s, 3 H), 2.96 - 3.15 (m, 2 H), 3.55 - 3.61 (m, 3 H), 6.92 (d, *J* = 6.55 Hz, 1 H), 7.17 (d, *J* = 15.86 Hz, 1 H), 7.34 - 7.41 (m, 2 H), 7.40 - 7.54 (m, 2 H), (d, *J* = 7.55 Hz, 1H), 7.97 (s, 1H), 8.59 (s, 1H)
154		N-((1r,4r)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)-5-chloro-2-methoxybenzenesulfonamide	492	1H NMR (400 MHz, DMSO-d6) δ ppm 1.09 - 1.25 (m, 2 H), 1.24 - 1.42 (m, 2 H), 1.55 - 1.77 (m, 2 H), 1.78 - 1.99 (m, 3 H), 2.85 - 3.14 (m, 1 H), 3.60 (m, 3 H), 3.97 (m, 3 H), 6.49 - 6.69 (m, 3 H), 6.74 - 6.91 (m, 1 H), 7.27 (d, *J* = 8.81 Hz, 1 H), 7.60 - 7.77 (m, 3 H), 7.99 (d, *J* = 5.29 Hz, 1H)
155		N-((1r,4r)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)-3,5-dimethylisoxazole-4-sulfonamide	447	1H NMR (400 MHz, DMSO-d6) δ ppm 1.22 - 1.49 (m, 4 H), 1.65 - 1.82 (m, 2 H), 1.85 - 2.05 (m, 2 H), 2.35 (s, 3 H), 2.60 (s, 3 H), 3.02 (s, 1 H), 3.46 (s, 1 H), 3.59 (s, 3 H), 6.97 (d, *J* = 6.80 Hz, 1 H), 7.14-7.42 (m, 1 H), 7.85-8.15 (m, 3 H), 8.60-9.04 (m, 1 H)
156		N-((1r,4r)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)-4-fluorobenzenesulfonamide	466	1H NMR (400 MHz, DMSO-d6) δ ppm 1.16 - 1.36 (m, 4 H), 1.60 - 1.77 (m, 2 H), 1.81 - 1.97 (m, 2 H), 3.04-3.05 (m, 1 H), 3.41 (s, 1 H), 3.56 (s, 3 H), 6.95 (d, *J* = 6.55 Hz, 1 H), 7.26 (d, *J* = 12.34 Hz, 1 H), 7.40 - 7.48 (m, 2 H), 7.84 (d, *J* = 7.30 Hz, 1 H),7.87-7.93 (m, 3 H), 7.98-8.04 (m, 1 H), 8.74 (s, 1 H)
157		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2,3-	497	

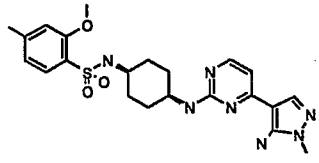
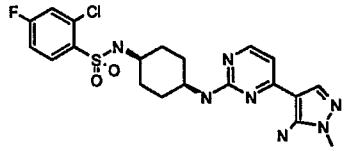
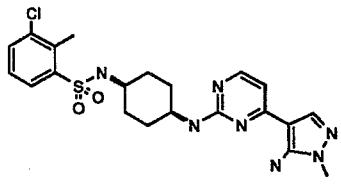
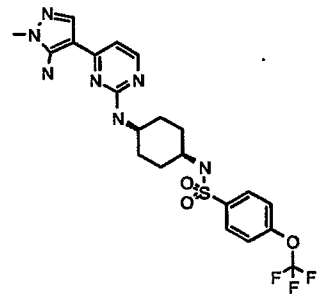
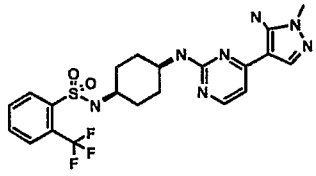
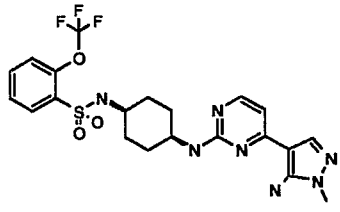
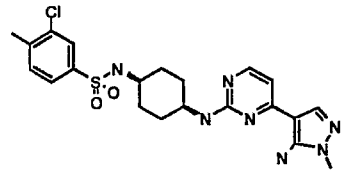
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
		dichlorobenzenesulfonamide		
158		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)naphthalene-2-sulfonamide	478	
159		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2,5-dimethylbenzenesulfonamide	456	
160		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-chlorobenzenesulfonamide	462	
161		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3,4-dihydro-2H-1,5-benzodioxepine-7-sulfonamide	500	
162		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-fluoro-4-methoxybenzenesulfonamide	476	
163		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2,4-difluorobenzenesulfonamide	464	
164		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-fluorobenzenesulfonamide	446	

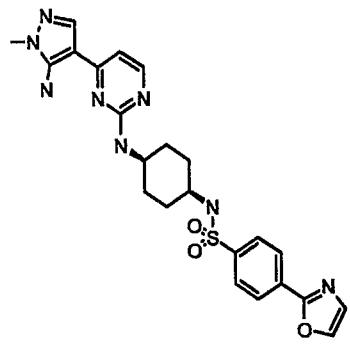
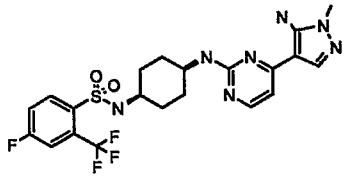
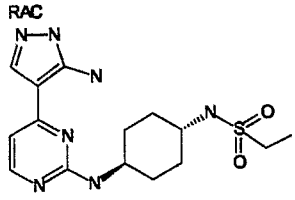
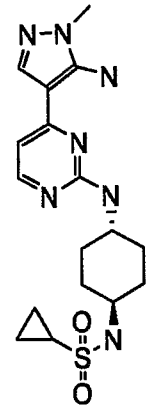
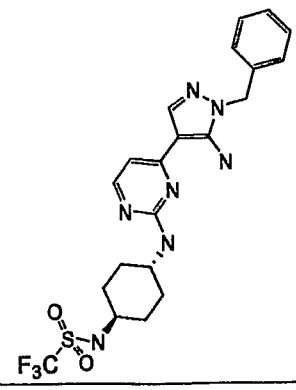
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
165		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-methylbenzenesulfonamide	442	
166		4-acetyl-N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)benzenesulfonamide	470	
167		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-methylbenzenesulfonamide	442	
168		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-chloro-5-fluoro-2-methylbenzenesulfonamide	494	
169		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-chlorobenzenesulfonamide	462	
170		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3,4-dichlorobenzenesulfonamide	497	
171		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-ethylbenzenesulfonamide	456	
172		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-5-fluoro-2-methylbenzenesulfonamide	460	

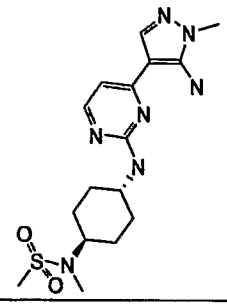
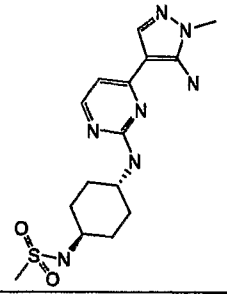
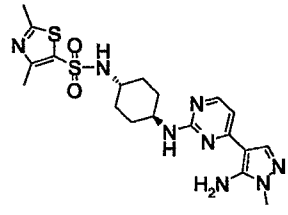
#	Structure	Compound Name	LRMS m/z	^{1}H NMR
173		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(trifluoromethoxy)benzenesulfonamide	512	
174		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-fluoro-3-(trifluoromethyl)benzenesulfonamide	514	
175		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)benzenesulfonamide	428	
176		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2,4-dimethylbenzenesulfonamide	456	
177		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-24-dimethylbenzenesulfonamide	457	
178		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-chloro-4-fluorobenzenesulfonamide	481	I
179		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-34-difluorobenzenesulfonamide	465	
180		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-methylbenzenesulfonamide	443	

#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
181		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(trifluoromethyl)benzenesulfonamide	497	
182		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-fluorobenzenesulfonamide	447	
183		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-5-chloro-13-dimethyl-1H-pyrazole-4-sulfonamide	481	
184		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-34-dimethoxybenzenesulfonamide	489	
185		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-26-difluorobenzenesulfonamide	465	
186		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-35-difluorobenzenesulfonamide	465	

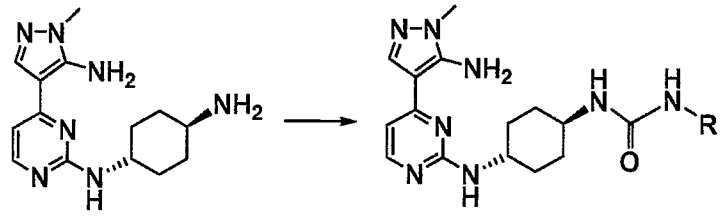
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
187		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-isopropylbenzenesulfonamide	471	
188		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-(trifluoromethyl)benzenesulfonamide	497	
189		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-ethoxy-4-methylbenzenesulfonamide	487	
190		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-fluoro-2-methylbenzenesulfonamide	461	
191		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-35-dimethylisoxazole-4-sulfonamide	448	
192		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-25-difluorobenzenesulfonamide	465	
193		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-5-methyl-1-phenyl-1H-pyrazole-4-sulfonamide	509	

#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
194		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-methoxy-4-methylbenzenesulfonamide	473	
195		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-chloro-4-fluorobenzenesulfonamide	481	
196		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-chloro-2-methylbenzenesulfonamide	477	
197		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide	513	
198		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(trifluoromethyl)benzenesulfonamide	497	
199		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(trifluoromethoxy)benzenesulfonamide	513	
200		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-chloro-4-methylbenzenesulfonamide	477	

#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
201		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-(13-oxazol-2-yl)benzenesulfonamide	496	
202		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-fluoro-2-(trifluoromethyl)benzenesulfonamide	515	
203		N-(trans-4-{[4-(5-amino-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-ethanesulfonamide	366	1H NMR (400 MHz, MeOD) δ ppm 1.32 - 1.41 (m, 3 H) 1.52 - 1.64 (m, 1 H) 1.78 - 1.96 (m, 6 H) 2.15 (s, 1 H) 2.99 - 3.19 (m, 2 H) 3.47 - 3.58 (m, 1 H) 3.62 - 3.80 (m, 1 H) 7.20 (d, J=6.06 Hz, 1 H) 8.06 (t, J=6.57 Hz, 1 H) 8.52 - 8.71 (m, 1 H).
204		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)cyclopropanesulfonamide	392	1H NMR (400 MHz, METHANOL-d4) δ ppm 0.94 - 1.10 (m, 4 H) 1.33 - 1.54 (m, 4 H) 2.00 - 2.19 (m, 4 H) 2.47 - 2.60 (m, 1 H) 3.10 - 3.23 (m, 1 H) 3.63 (s, 3 H) 3.63 - 3.69 (m, 1 H) 6.69 (d, J=5.56 Hz, 1 H) 7.73 (s, 1 H) 7.98 (d, J=5.56 Hz, 1 H)
205		N-(trans-4-{[4-(5-amino-1-benzyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1,1,1-trifluoromethanesulfonamide	496	1H NMR (400 MHz, METHANOL-d4) δ ppm 1.35 - 1.64 (m, 4 H) 2.00 - 2.07 (m, 2 H) 2.08 - 2.18 (m, 2 H) 3.36 - 3.44 (m, 1 H) 3.58 - 3.71 (m, 1 H) 5.21 (s, 2 H) 6.72 (d, J=5.56 Hz, 1 H) 7.18 (d, J=7.07 Hz, 2 H) 7.22 - 7.42 (m, 3 H) 7.81 (s, 1 H) 8.01 (d, J=5.56 Hz, 1 H)

#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
206		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-N-methylmethanesulfonamide	380	1H NMR (400 MHz, METHANOL-d4) δ ppm 1.36 - 1.54 (m, 2 H) 1.68 - 1.89 (m, 4 H) 2.11 - 2.22 (m, 2 H) 2.81 (s, 3 H) 2.88 (s, 3 H) 3.62 (s, 3 H) 3.65 (m, 1H) 3.69 - 3.81 (m, 1 H) 6.71 (d, J=5.56 Hz, 1 H) 7.74 (s, 1 H) 7.97 (d, J=5.81 Hz, 1 H)
207		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl) methanesulfonamide	366.2	1H NMR (400 MHz, METHANOL-d4) δ ppm 1.42 - 1.63 (m, 4 H) 2.07 - 2.24 (m, 4 H) 2.95 - 3.02 (s, 3 H) 3.25 - 3.30 (m, 1H) 3.40 - 3.57 (m, 1 H) 3.64 (s, 3 H) 6.98 (d, J=7.07 Hz, 1 H) 7.83 (br. s., 1 H) 7.95 (br. s., 1 H)
208		N-((1r,4r)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)-2,4-dimethylthiazole-5-sulfonamide	466	1H NMR (400 MHz, DMSO-d6) δ ppm 1.20 - 1.45 (m, 4 H), 1.58 - 2.08 (m, 4 H), 2.51 (s, 3 H), 2.64(s, 3 H), 3.01 - 3.20 (m, 1 H), 3.59 (m, 3 H), 6.96 (d, *J* = 6.6 Hz, 1 H), 7.05 - 7.39 (m, 2 H), 7.82 - 8.10 (m, 2 H), 8.21 (d, *J* =7.6 Hz, 1 H), 8.74 (s, 1 H)

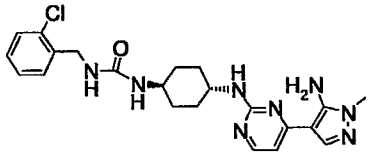
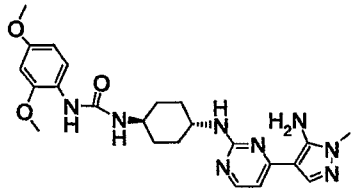
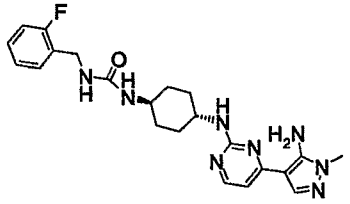
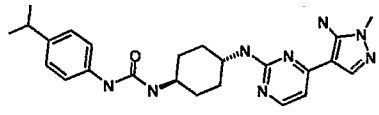
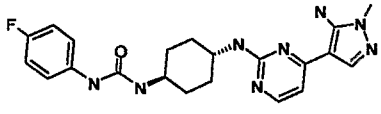
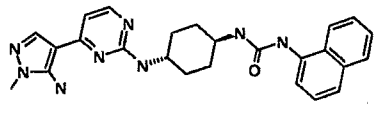
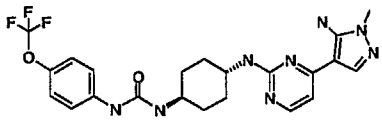
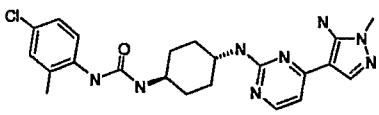
General method J:

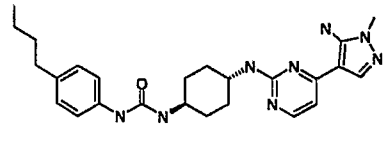
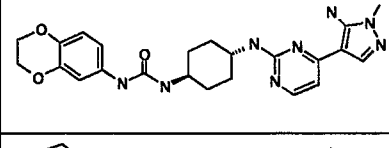
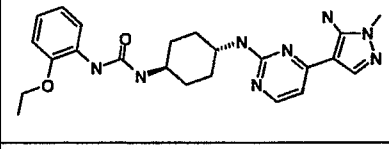
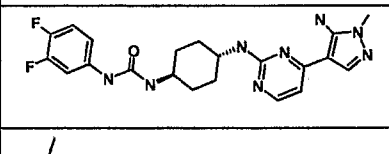
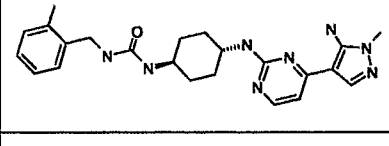
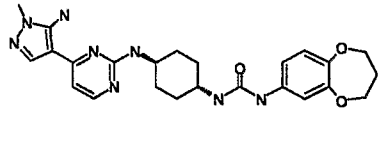
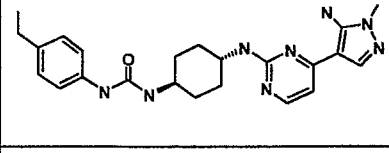
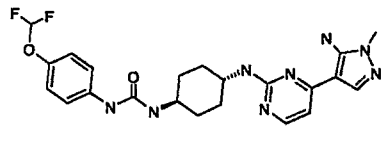
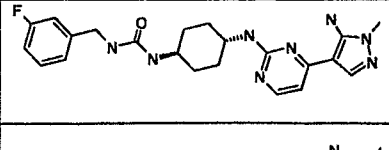
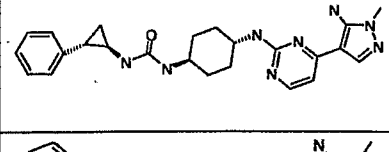
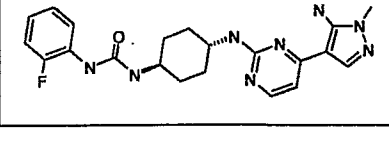


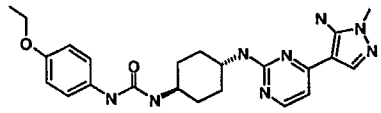
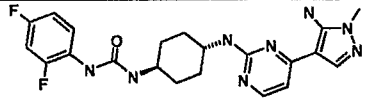
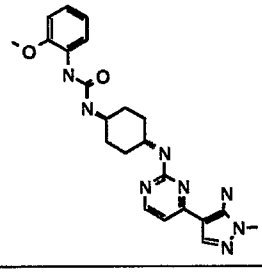
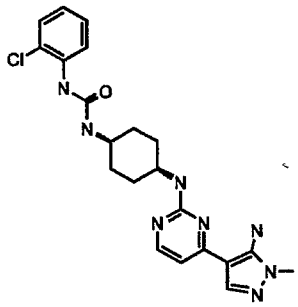
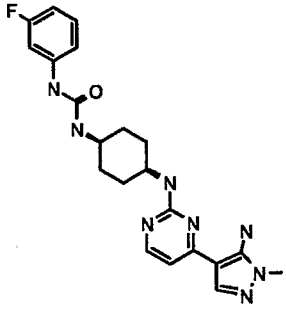
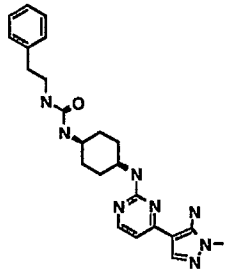
107 (trans)

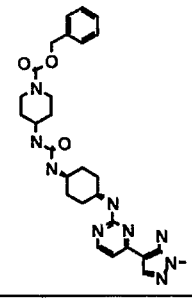
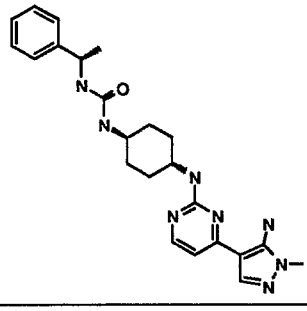
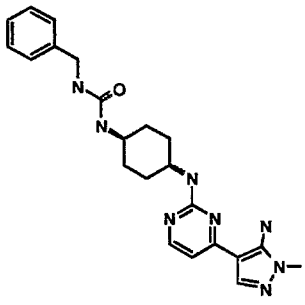
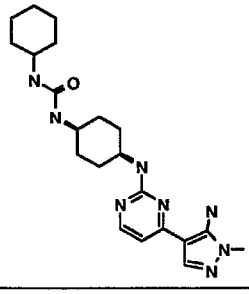
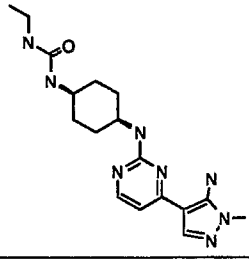
Trans-N-[4-(5-amino-1-methyl-1*H*-pyrazol-4-yl)pyrimidin-2-yl]cyclohexane-1,4-diamine (**107 trans**) was prepared above as described in method I. **107 trans** (35 mmol) and various isocyanatomethylbenzene (1 eq, 0.35 mmol) were dissolved in 5 mL of DMF. The reaction was stirred at 75 °C for 16 hours. The reaction mixture was filtrated and the crude materials were purified by HPLC to give the urea product with yield from 9- 60%.

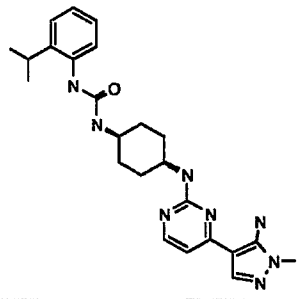
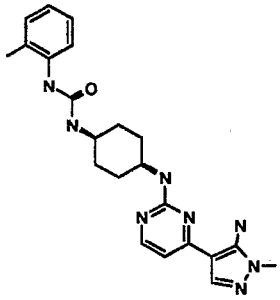
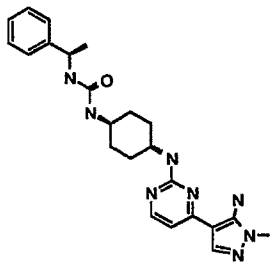
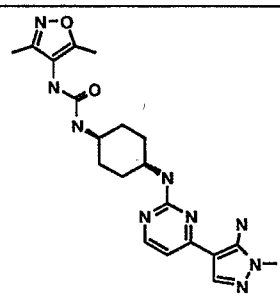
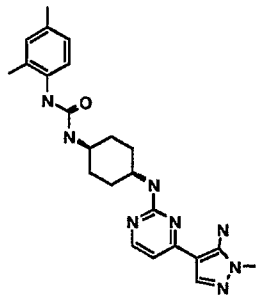
Table 11. Compounds **209-273** were prepared according to the method **J** as described above.

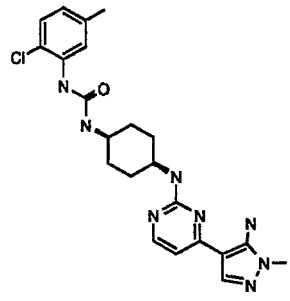
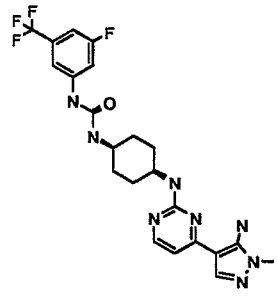
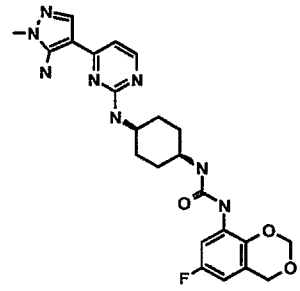
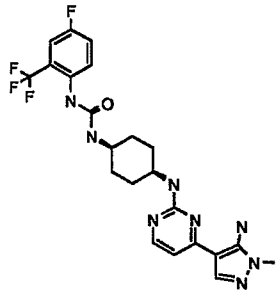
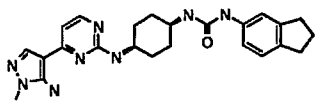
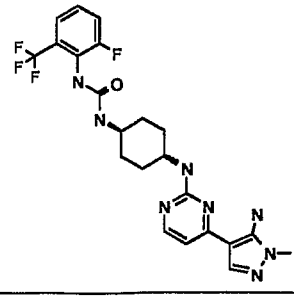
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
209		1-(2-chlorobenzyl)-3-((1r,4r)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)urea	455	1H NMR (400 MHz, DMSO-d6) δ ppm 1.07 - 1.34 (m, 4 H), 1.82 - 2.01 (m, 4 H), 3.56 (s, 3 H) ,4.26 (d, *J* = 6.04 Hz, 2 H), 5.99 (d, *J* = 7.81 Hz, 1 H), 6.26 (t, *J* =,5.92 Hz, 1 H), 6.61 (d, *J* =,5.29 Hz, 1 H), 6.67 (s, 1 H), 6.92 (s, 1 H), 7.22 - 7.30 (m, 1 H), 7.30 - 7.34 (m, 2 H), 7.42 (d, *J* =7,.55 Hz, 1 H), 7.70 (s, 1 H), 8.01 (d, *J* = 5.29 Hz, 1 H)
210		1-((1r,4r)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)-3-(2,4-dimethoxyphenyl)urea	467	1H NMR (400 MHz, DMSO-d6) δ ppm 1.12 - 1.41 (m, 4 H), 1.90 - 2.04 (m, 4 H), 3.56 (s, 3 H), 3.64 - 3.73 (m, 3 H), 3.81 (s, 3 H), 6.42 (dd, *J* = 8.94, 2.64 Hz, 1 H), 6.56 (d, *J* = 2.77 Hz, 1 H), 6.58 - 6.67 (m, 2 H), 6.69 (s, 1 H), 6.95 (s, 1 H), 7.71 (s, 1 H), 7.88 (d, *J* = 8.81 Hz, 1 H), 8.01 (d, *J* = 5.29 Hz, 1 H)
211		1-(2-fluorobenzyl)-3-((1r,4r)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)urea	439	1H NMR (400 MHz, DMSO-d6) δ ppm 1.09 - 1.39 (m, 4 H), 1.80 - 2.02 (m, 4 H), 4.24 (d, *J* = 6.04 Hz, 2 H), 5.91 (d, *J* = 7.55 Hz, 1 H), 6.22 (t, *J* = 5.79 Hz, 1 H), 6.61 (d, *J* = 5.29 Hz, 1 H), 6.68 (s, 2 H), 6.94 (s, 1 H), 7.10 - 7.20 (m, 2 H), 7.23 - 7.35 (m, 2 H), 7.71 (s, 1 H), 8.01 (d, *J 12*= 5.54 Hz, 1 H)
212		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-isopropylphenyl)urea	449	
213		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-fluorophenyl)urea	425	
214		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(1-naphthyl)urea	458	
215		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[4-(trifluoromethoxy)phenyl]urea	491	
216		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-chloro-2-methylphenyl)urea	456	

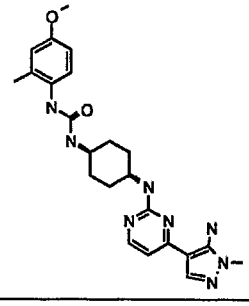
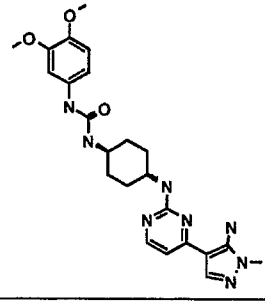
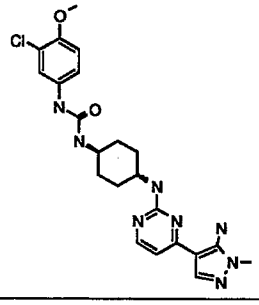
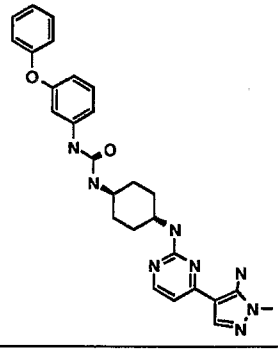
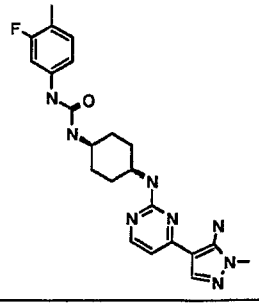
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
217		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-butylphenyl)urea	463	
218		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)urea	465	
219		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-ethoxyphenyl)urea	451	
220		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3,4-difluorophenyl)urea	443	
221		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-methylbenzyl)urea	435	
222		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-methylbenzyl)urea	479	
223		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-ethylphenyl)urea	435	
224		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[4-(difluoromethoxy)phenyl]urea	473	
225		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-fluorobenzyl)urea	439	
226		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[(1R,2S)-2-phenylcyclopropyl]urea	447	
227		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-fluorophenyl)urea	425	

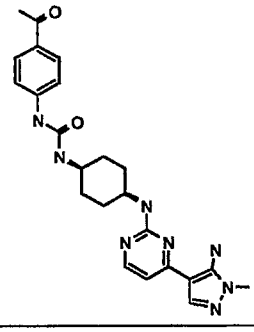
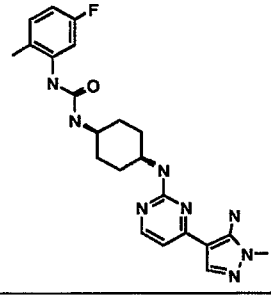
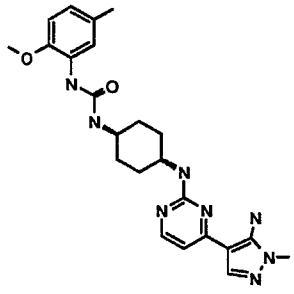
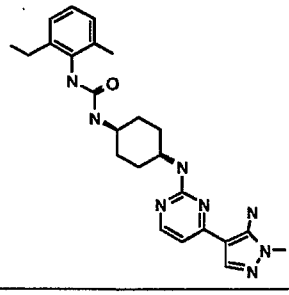
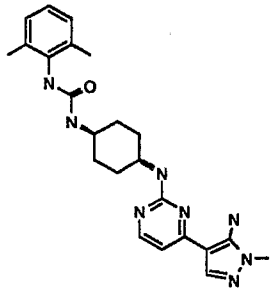
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
228		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-ethoxyphenyl)urea	451	
229		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2,4-difluorophenyl)urea	443	
230		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-methoxyphenyl)urea	438	
231		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-chlorophenyl)urea	442	
232		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-fluorophenyl)urea	425	
233		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-phenylethyl)urea	436	

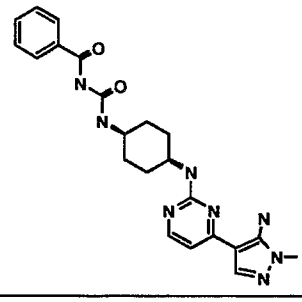
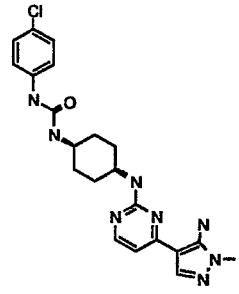
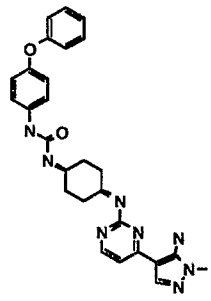
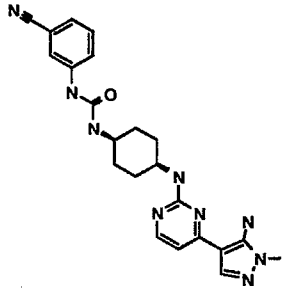
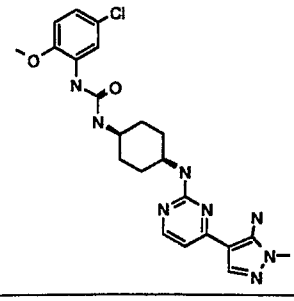
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
234		benzyl 4-({[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]carbonyl}amino)piperidine-1-carboxylate	549	
235		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[(1S)-1-phenylethyl]urea	436	
236		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-benzylurea	422	
237		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-cyclohexylurea	414	
238		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-ethylurea	359	

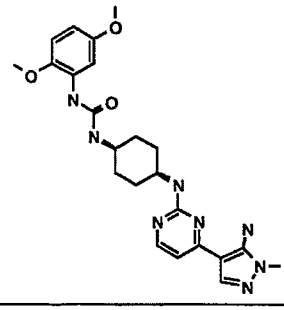
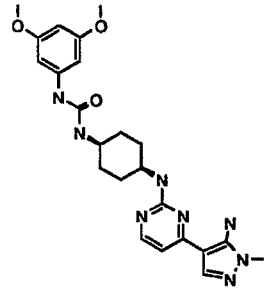
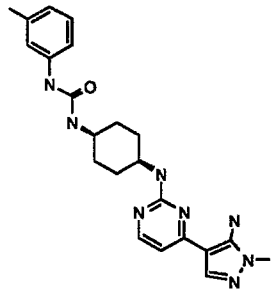
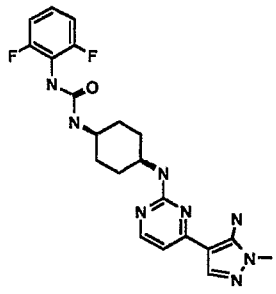
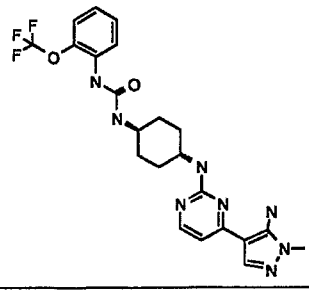
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
239		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-isopropylphenyl)urea	450	
240		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-methylphenyl)urea	422	
241		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[(1R)-1-phenylethyl]urea	436	
242		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(35-dimethylisoxazol-4-yl)urea	426	
243		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(24-dimethylphenyl)urea	436	

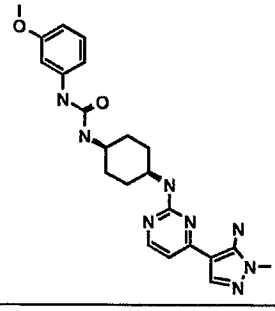
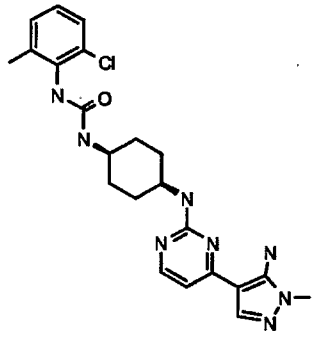
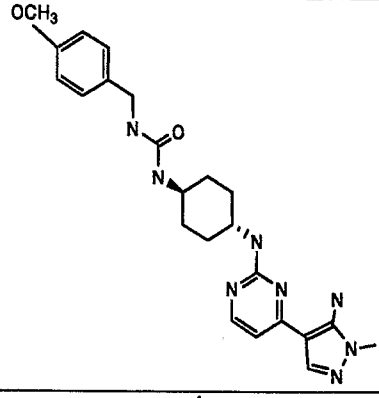
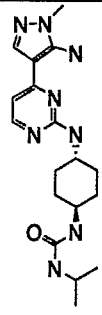
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
244		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-chloro-5-methylphenyl)urea	456	
245		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[3-fluoro-5-(trifluoromethyl)phenyl]urea	493	
246		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(6-fluoro-4H-13-benzodioxin-8-yl)urea	484	
247		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[4-fluoro-2-(trifluoromethyl)phenyl]urea	493	
248		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(23-dihydro-1H-inden-5-yl)urea	448	
249		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[2-fluoro-6-(trifluoromethyl)phenyl]urea	493	

#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
250		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-methoxy-2-methylphenyl)urea	452	
251		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(34-dimethoxyphenyl)urea	468	
252		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-chloro-4-methoxyphenyl)urea	472	
253		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-phenoxyphenyl)urea	500	
254		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-fluoro-4-methylphenyl)urea	440	

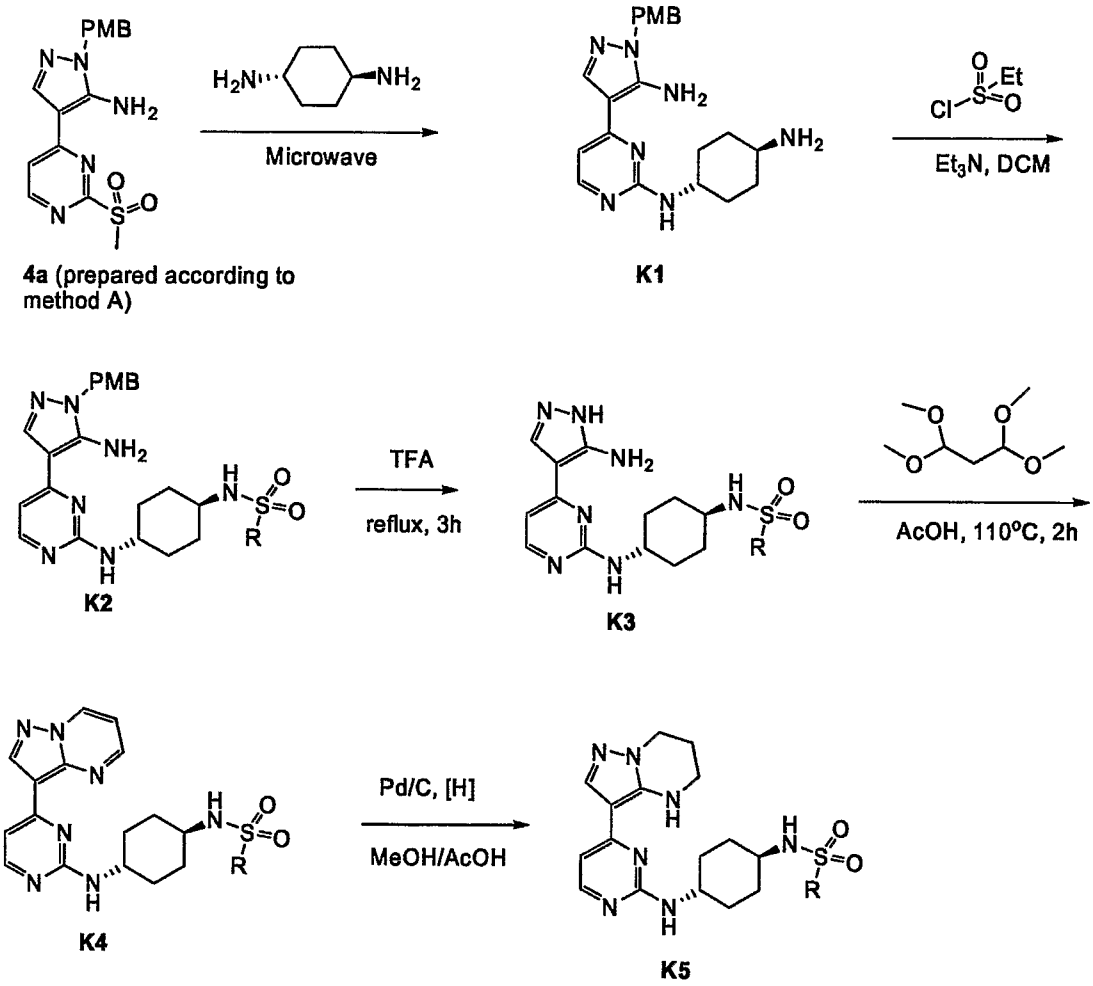
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
255		1-(4-acetylphenyl)-3-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)urea	450	
256		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(5-fluoro-2-methylphenyl)urea	440	
257		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-methoxy-5-methylphenyl)urea	452	
258		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-ethyl-6-methylphenyl)urea	450	
259		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(26-dimethylphenyl)urea	436	

#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
260		N-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]carbonyl}benzamide	435	
261		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-chlorophenyl)urea	442	
262		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-phenoxyphenyl)urea	500	
263		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-cyanophenyl)urea	432	
264		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(5-chloro-2-methoxyphenyl)urea	472	

#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
265		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(25-dimethoxyphenyl)urea	468	
266		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(35-dimethoxyphenyl)urea	468	
267		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-methylphenyl)urea	422	
268		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(26-difluorophenyl)urea	443	
269		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[2-(trifluoromethoxy)phenyl]urea	491	

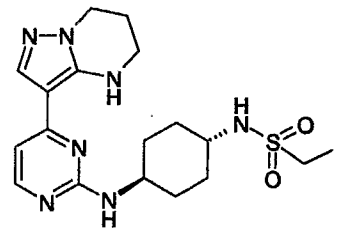
#	Structure	Compound Name	LRMS *m/z*	^{1}H NMR
270		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-methoxyphenyl)urea	438	
271		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-chloro-6-methylphenyl)urea	456	
272		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-methoxybenzyl)urea	452	
273		1-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-isopropylurea	373	1H NMR (400 MHz, METHANOL-d4) δ ppm 1.11 (d, J=6.57 Hz, 6 H) 1.22 - 1.50 (m, 4 H) 1.93 - 2.05 (m, 2 H) 2.05 - 2.14 (m, 2 H) 3.44 - 3.55 (m, 1 H) 3.62 (s, 3 H) 3.63 - 3.69 (m, 1 H) 3.75 - 3.85 (m, 1 H) 6.68 (d, J=5.31 Hz, 1 H) 7.73 (s, 1 H) 7.98 (d, J=5.31 Hz, 1 H)

Method K



General method K is described below using the preparation of **274** *as an example of* ***K5:***

Preparation of *N*-(*trans*)-4-{[4-(4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-3-yl)pyrimidin-2-yl]amino}cyclohexyl) ethanesulfonamide (274)



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Preparation of (*trans*)-N1-(4-(1-(4-methoxybenzyl)-5-amino-1H-pyrazol-4-yl)pyrimidin-2-yl)cyclohexane-1,4-diamine(K1)

Methylsulfonylpyrimidine **4a** (2.0 g, 6.0 mmol) was suspended in a mixed solvent 1,4-dioxane (8 mL) and isopropanol (3 mL). *Trans*-1, 4-diaminocyclohexane (1.6 g, 13.9 mmol) was added at room temperature.

The resulting suspension was heated at 130 °C for 1.5 hours by microwave in a sealed tube. The solution was cooled to room temperature, and the resulting suspension was filtrated to remove remaining diamine. The solution thus obtained was extracted with EtOAc (100 mL x 2), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0 – 15% methanol in CH_2Cl_2) to yield 1.9 g (81%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.15 - 1.32 (m, 4 H), 1.61 (br s, 2 H), 1.92 (br s, 2 H), 2.13 (br s, 2 H), 2.75 (br s, 1 H), 3.67 (br s, 1 H), 3.80 (s, 3 H), 4.80 (br s, 1 H), 5.15 (s, 2 H), 5.45 (br s, 2 H), 6.57 - 6.66 (m, 1 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 7.18 (d, *J* = 8.3 Hz, 2 H), 7.73 (s, 1 H), 8.11 (d, *J* = 4.3 Hz, 1 H).

Preparation of N-((*trans*)-4-(4-(1-(4-methoxybenzyl)-5-amino-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)ethanesulfonamide(274c)

To a solution of (*trans*)-N1-(4-(1-(4-methoxybenzyl)-5-amino-1H-pyrazol-4-yl)pyrimidin-2-yl)cyclohexane-1,4-diamine (1.00 g, 2.54 mmol)) and triethylamine (5.08 mmol, 0.71 mL) in dichloromethane (8.5 mL) was added ethane sulfonyl chloride (3.05 mmol, 0.29 mL) at 0 °C. The solution was stirred for 30 mins, poured into water (15 mL)and extracted with EtOAc (25 mL X 2). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give (1.1g) the title compound as brown oil, which was carried on crude.

1H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 - 1.25 (m, 3 H), 1.51 - 1.98 (m, 8 H), 2.94 - 3.04 (m, 2 H), 3.24 - 3.41 (m, 2 H), 3.64 - 3.73 (m, 3 H), 5.07 - 5.14 (m, 2 H), 6.82 - 6.94 (m, 4 H), 7.10 - 7.19 (m, 2 H), 7.72 - 7.80 (m, 1 H), 7.98 - 8.08 (m, 1 H). LRMS m/z calcd. for $C_{23}H_{32}N_7O_3S$ $[M+H]^+$ 486. Found: 486.

Preparation of *N*-(*trans*)-4-{[4-(5-amino-1*H*-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl) ethanesulfonamide(274b)

Crude N-((*trans*)-4-(4-(1-(4-methoxybenzyl)-5-amino-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)ethanesulfonamide (1.1 g, ~80% pure) was dissolved in 10 mL of neat TFA. The dark brown solution was heated to reflux for 3 hours. TFA was removed by evaporation under vacuum to give crude product as dark oil (0.83g). 150 mg of the crude material was purified by HPLC (10-40% CH_3CN in water) to yield 30 mg of the title compound as a white powder.

1H NMR (400 MHz, CD_3OD) δ ppm 1.32 - 1.41 (m, 3 H), 1.52 - 1.64 (m, 1 H), 1.78 - 1.96 (m, 6 H), 2.15 (s, 1 H), 2.99 - 3.19 (m, 2 H), 3.47 - 3.58 (m, 1 H), 3.62 - 3.80 (m, 1 H), 7.20 (d, *J* = 6.1 Hz, 1 H), 8.06 (t, *J* = 6.6 Hz, 1 H), 8.52 - 8.71 (m, 1 H). LRMS m/z calcd. for $C_{15}H_{24}N_7O_2S$ $[M+H]^+$ 366. Found: 366

Preparation of N-(*trans*)-4-(4-(pyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexyl)ethanesulfonamide(274a)

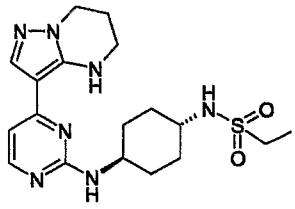
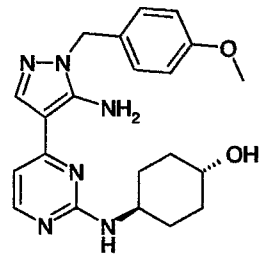
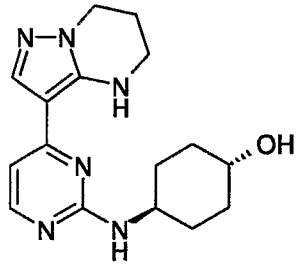
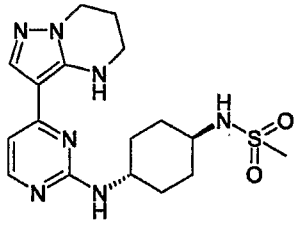
A solution of *N*-(*trans*)-4-{[4-(5-amino-1*H*-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl) ethanesulfonamide (600 mg, 1.64 mmol) and 1, 1, 3, 3-tetramethoxy propane (540 mg, 3.29 mmol) in acetic acid was heated to reflux for 2 hours. Evaporation yielded 0.59 g (90%) the title compound.

Preparation of *N*-(*trans*)-4-{[4-(4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-3-yl)pyrimidin-2-yl]amino}cyclohexyl) ethanesulfonamide(274)

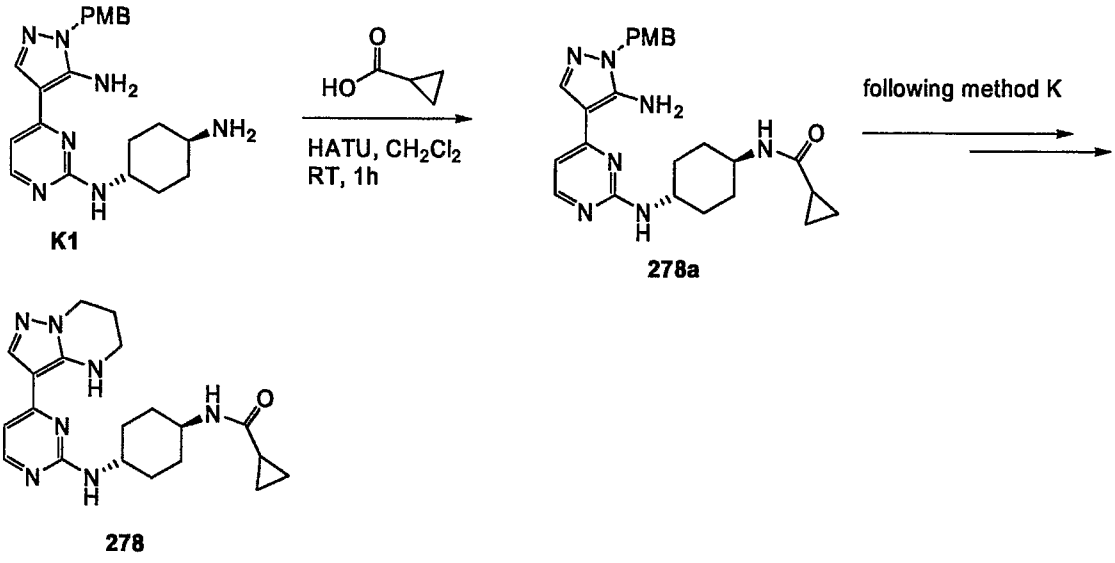
A solution of N-(*trans*)-4-(4-(pyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexyl)ethanesulfonamide (250mg, 0.62 mmol) and 10% Pd/C (10 mg) in MeOH (20 mL) was hydrogenated at room temperature under 50 psi pressure of hydrogen. The reaction was held at room temperature for 24 hours. The solution was filtrated and evaporated. The residue was purified by HPLC (10-40% CH_3CN) to give 89 mg (35%)of the title compound.

1H NMR (400 MHz, CD_3OD) δ ppm 1.11 - 1.29 (m, 3 H), 1.37 - 1.51 (m, 1 H), 1.66 - 1.85 (m, 5 H), 1.87 - 2.07 (m, 2 H), 2.07 - 2.21 (m, 2 H), 2.87 - 3.07 (m, 2 H), 3.36 - 3.67 (m, 4 H), 3.98 - 4.19 (m, 2 H), 6.89 - 7.07 (m, 1 H), 7.79 - 7.95 (m, 1 H), 8.31 (s, 1 H). LRMS m/z calcd. for $C_{15}H_{28}N_7O_2S$ $[M+H]^+$ 406. Found: 406.

Table 12. Compounds **274-277** were prepared according to the method **K** as described above.

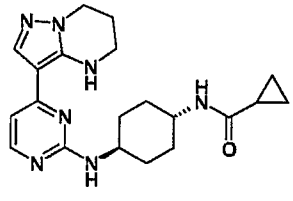
#	Structure	Compound Name	M+1	NMR Data
274		*N*-(*trans*-4-{[4-(4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidin-3-yl)pyrimidin-2-yl]amino}cyclohexyl) ethanesulfonamide	406	1H NMR (400 MHz, CD_3OD) δ ppm 1.11 - 1.29 (m, 3 H) 1.37 - 1.51 (m, 1 H) 1.66 - 1.85 (m, 5 H) 1.87 - 2.07 (m, 2 H) 2.07 - 2.21 (m, 2 H) 2.87 - 3.07 (m, 2 H) 3.36 - 3.67 (m, 4 H) 3.98 - 4.19 (m, 2 H) 6.89 - 7.07 (m, 1 H) 7.79 – 7.95 (m, 1 H) 8.31 (s, 1 H).
275		trans-4-({4-[5-amino-1-(4-methoxybenzyl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	395	1H NMR (400 MHz, DMSO-d6) δ ppm 1.13 - 1.32 (m, 4 H) 1.85 (br. s., 2 H) 1.92 (br. s., 2 H) 3.35 - 3.47 (m, 2 H) 3.56 (d, J=24.76 Hz, 1 H) 3.71 (s, 3 H) 5.11 (s, 2 H) 6.62 (d, J=5.31 Hz, 1 H) 6.79 - 6.97 (m, 5 H) 7.14 (d, J=8.08 Hz, 2 H) 7.76 (s, 1 H) 8.02 (d, J=5.30 Hz, 1 H)
276		*N*-(*trans*-4-methylcyclohexyl)-4-(4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-3-yl)pyrimidin-2-amine	315	1H NMR (400 MHz, CD_3CN) δ ppm 1.12 - 1.41 (m, 6 H) 1.99 - 2.18 (m, 4 H) 2.69 - 2.75 (m, 1 H) 3.35 - 3.46 (m, 2 H) 3.48 - 3.59 (m, 1 H) 3.66 (dd, J=7.07, 3.28 Hz, 1 H) 4.01 (t, J=6.06 Hz, 2 H) 5.70 (s, 1 H) 6.55 (d, J=5.56 Hz, 1 H) 6.91 (s, 1 H) 7.59 (s, 1 H) 7.88 - 8.02 (m, 1
277		N-(trans-4-{[4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-yl]amino}cyclohexyl)methanesulfonamide	392	1H NMR (400 MHz, DMSO-d6) δ ppm 1.19 - 1.41 (m, 4 H) 1.91 - 2.01 (m, 4 H) 2.07 (s, 2 H) 2.92 (s, 3 H) 3.07 - 3.20 (m, 1 H) 3.34 - 3.41 (m, 2 H) 3.50 - 3.64 (m, 1 H) 4.00 (t, J=5.68 Hz, 2 H) 6.61 (d, J=4.80 Hz, 1 H) 6.77 - 6.96 (m, 1 H) 7.03 (d, J=7.33 Hz, 1 H) 7.28 - 7.44 (m, 1 H) 7.72

Method L

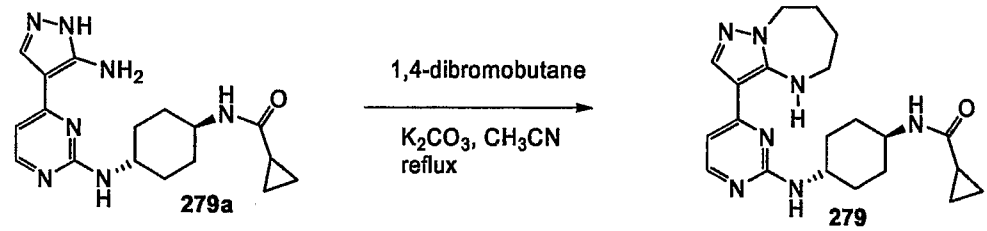


Preparation of N-((trans)-4-((4-(5-amino-1-(4-methoxybenzyl) -1H-pyrazol-4-yl)pyrimidin-2-yl)methyl)cyclohexyl)cyclopropanecarboxamide (278a)

To a solution of N-((trans)-4-(1-(4-methoxybenzyl)-5-amino-1H-pyrazol-4-yl)pyrimidin-2-yl)cyclohexane-1,4-diamine (2g, 5.08 mmol) and triethylamine (10.16 mmol, 1.42 mL) in dichloromethane (32 mL) was added HATU (6.10 mmol, 2.33 g). The reaction was held at room temperature for 5 minutes, then treated with cyclopropane carboxylic acid (6.10 mmol, 0.49 mL). The solution was stirred for 1h at room temperature, then washed with brine (2x30 mL) and extracted with CH_2Cl_2 (75 mL), then and concentrated. Purification by silica gel chromatography (0-30% MeOH-EtOAc) yielded 1.8g (77%) of N-((trans)-4-(4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino) cyclohexyl)cyclopropanecarboxamide.

#	Structure	Compound Name	M+1	NMR Data
278		*N*-(*trans*-4-{[4-(4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-3-yl)pyrimidin-2-yl]amino}cyclohexyl) cyclopropanecarboxamide	382	1H NMR (400 MHz, CD_3OD) δ ppm 0.53 - 0.67 (m, 2 H) 0.71 - 0.84 (m, 2 H) 1.20 - 1.36 (m, 4 H) 1.40 - 1.49 (m, 1 H) 1.80 - 1.91 (m, 3 H) 1.97 - 2.15 (m, 4 H) 3.32 - 3.42 (m, 2 H) 3.51 - 3.68 (m, 2 H) 3.97 (t, J=5.94 Hz, 2 H) 6.53 (d, J=5.56 Hz, 1 H) 7.60 (s, 1 H) 7.86 (d, J=5.56 Hz, 1 H).

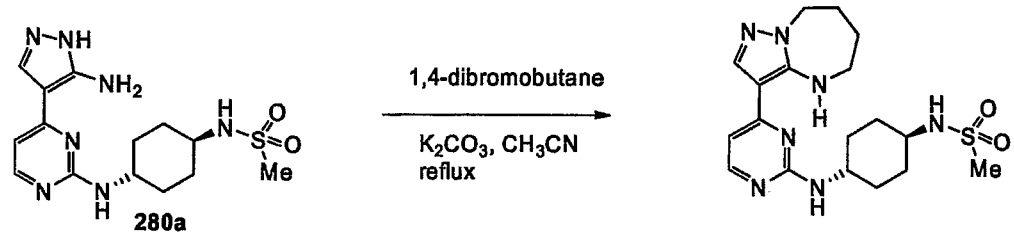
Method M



279a

279

Prepared by method L



280a

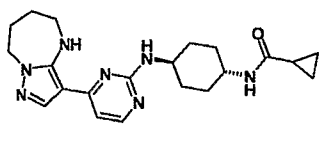
280

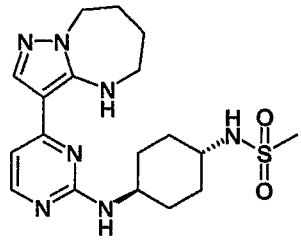
Prepared by method K

Preparation of N-(*trans*-4-{[4-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-3-yl)pyrimidin-2-yl]amino}cyclohexyl) cyclopropanecarboxamide (280)

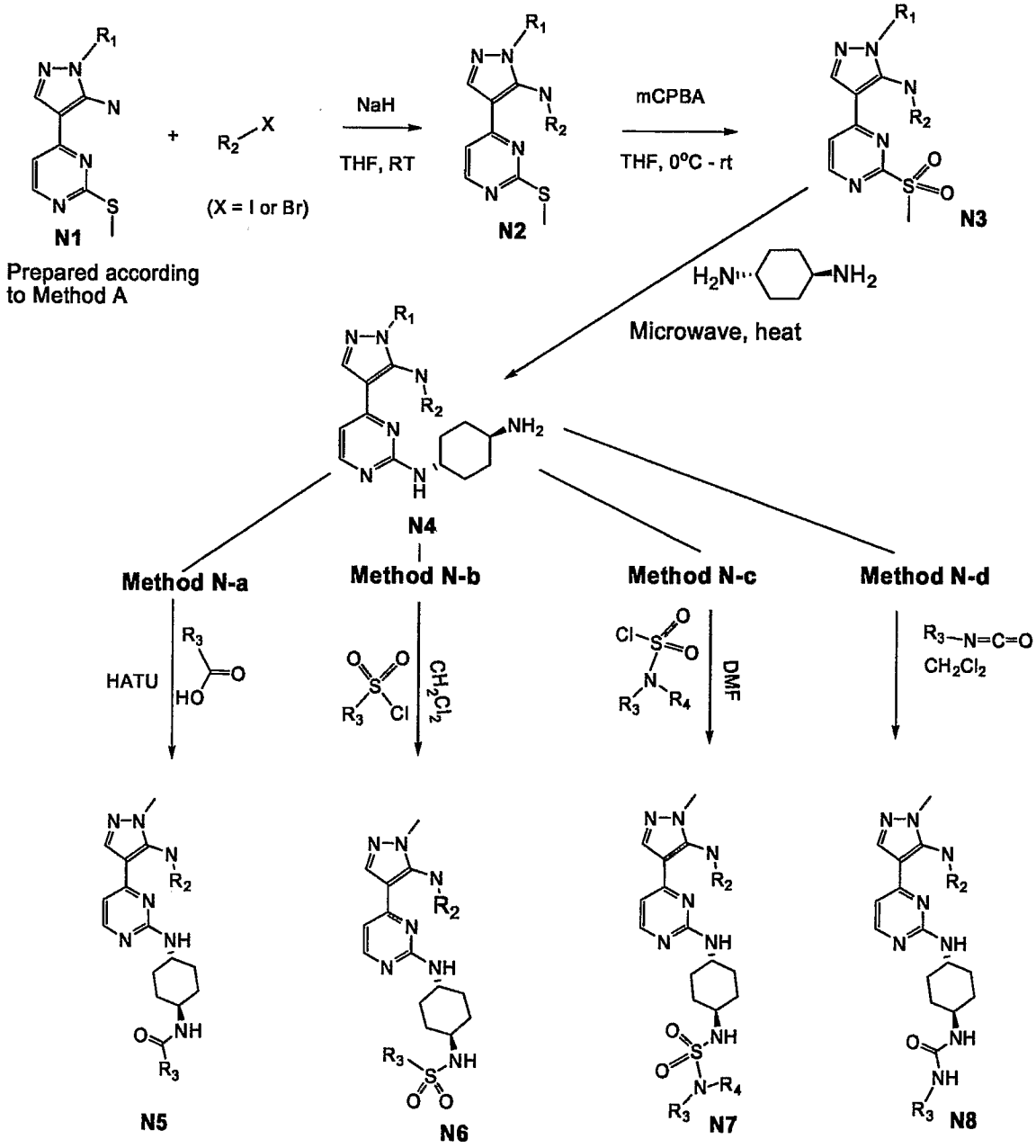
A solution of containing N-(trans-4-(4-(5-amino-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexyl)cyclopropanecarboxamide (**280a**) (0.73 mmol, 250 mg), 1,4-dibromobutane (471 mg, 2.20 mmol) and K_2CO_3 (507 mg, 3.67 mmol) in CH_3CN (5 mL) was heated to reflux overnight. The solution was extracted with EtOAc (50 mL x 2). The combined oil layer was concentrated to dry under vacuum. The residue was purified by HPLC (10-50% CH_3CN in water) to yield 52 mg (18%) of product. $C_{21}H_{30}N_7O$ $[M+H]^+$ 396. Found: 396.

Table 13. Compounds **279-280** were prepared according to the method **M** as described above.

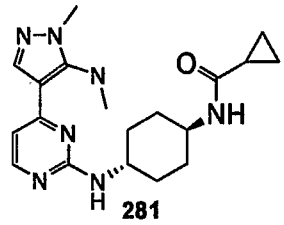
#	Structure	Compound Name	M+1	NMR Data
279		*N*-(*trans*-4-{[4-(5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-3-yl)pyrimidin-2-yl]amino}cyclohexyl) cyclopropanecarboxamide	396	1H NMR (400 MHz, CD_3OD) δ ppm 0.48 – 0.82 (m, 4 H) 1.19 – 1.37 (m, 4 H) 1.40 – 1.55 (m, 1 H) 1.69 – 1.93 (m, 4 H) 1.95 – 2.15 (m, 4 H) 3.41 – 3.71 (m, 3 H) 3.96 – 4.06 (m, 2 H) 4.06 – 4.17 (m, 2 H) 6.70 (d, J=4.55 Hz, 1 H) 8.11 (d, J=5.05 Hz, 1 H) 8.50 (s, 1 H).

#	Structure	Compound Name	M+1	NMR Data
280		N-(trans-4-{[4-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-3-yl)pyrimidin-2-yl]amino}cyclohexyl)methanesulfonamide	406	1H NMR (400 MHz, DMSO-d6) δ ppm 1.27 – 1.39 (m, 4 H) 1.78 (s, 4 H) 1.90 – 2.04 (m, 4 H) 2.92 (s, 3 H) 3.16 (s, 4 H) 3.99 – 4.10 (m, 2 H) 6.67 (d, J=3.79 Hz, 1 H) 7.05 (d, J=7.07 Hz, 2 H) 7.76 (s, 2 H) 8.06 (d, J=5.31 Hz, 1 H)

Method N



Preparation of N-[trans-4-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]cyclopropanecarboxamide (281)



281

The above compound **281** was prepared according to the general procedure Method **N-a** as described above.

Preparation of N,1-dimethyl-4-[2-(methylthio)pyrimidin-4-yl]-1H-pyrazol-5-amine (281c)

1-methyl-4-[2-(methylthio)pyrimidin-4-yl]-1H-pyrazol-5-amine (1.0 g, 3.2 mmol) was dissolved in THF (10 mL) and NaH (0.39 g, 9.6 mmol, 60 % dispersion in oil) was added in one portion. The mixture was stirred at room temperature for 10 minutes, Methyl iodide (0.4 mL, 6.4 mmol) was added dropwise. The mixture was stirred for 24 hour(s). The mixture was quenched with $NaHCO_3$ (saturated aq.) and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* .This crude was used without further purification.

Preparation of N,1-dimethyl-4-[2-(methylsulfonyl)pyrimidin-4-yl]-1H-pyrazol-5-amine (281b)

A solution of N,1-dimethyl-4-[2-(methylthio)pyrimidin-4-yl]-1H-pyrazol-5-amine (0.5g, 2.1 mmol) in THF (10 mL) was cooled to 0°C. To the solution was added 3-chloroperoxy benzoic acid (mCPBA) (0.86g, 5.25 mmol, 77 % tech grade). After being stirred for 30 minutes the ice bath was removed and the reaction was allowed to be stirred at RT for 6 hours. The solution was basified with $NaHCO_3$, saturated with NaCl and extracted with THF. The organic layer was concentrated to give N,1-dimethyl-4-[2-(methylsulfonyl)pyrimidin-4-yl]-1H-pyrazol-5-amine and the corresponding sulfoxide . The mixture was used in next step without purification.

Preparation of trans-N-{4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}cyclohexane-1,4-diamine (281a)

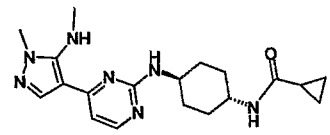
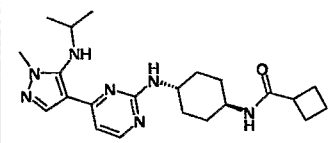
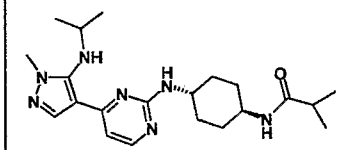
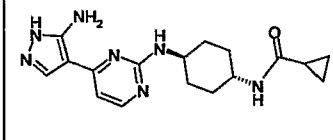
N,1-dimethyl-4-[2-(methylsulfonyl)pyrimidin-4-yl]-1H-pyrazol-5-amine (0.5 g crude, 1.78 mmol) and trans-cyclohexane-1,4-diamine (0.406 g, 3.55 mmol) were dissolved in 10 mL of isopropanol The solution was heated in the automated Microwave Reactor at 140°C for 1.5h. The resulting suspension was filtrated to remove remaining diamine. The solution thus obtained was extracted with EtOAc (50 mL X 2), dried over $MgSO_4$ and concentrated *in vacuo.* The mixture was used in next step without purification.

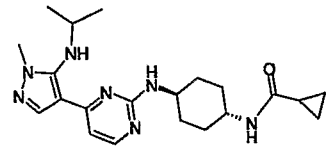
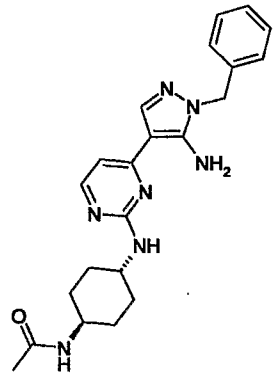
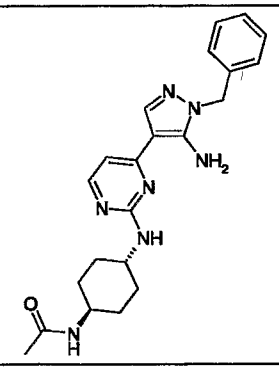
Preparation of N-[trans-4-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]cyclopropanecarboxamide (281)

To a solution of cyclopropane carboxylic acid (62 mg, 0.72 mmol) and triethylamine (0.13 mL, 0.9 mmol) in 10 mL of dichloromethane was added HATU (0.34 g, 0.9 mmol). After being stirred for 5 minutes, to the solution was added trans-N-{4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}cyclohexane-1,4-diamine (0.18 g, 0.6 mmol). The solution was stirred for 1h, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by HPLC (20-100% CH_3CN/H_2O gradient) to afford 32 mg (21%) of the desired product.

1H NMR (400 MHz, CD_3OD) δ ppm 0.52 - 0.66 (m, 2 H), 0.68 - 0.80 (m, 2 H), 1.32 (t, *J* = 9.7 Hz, 4 H), 1.41 - 1.52 (m, 1 H), 1.85 - 2.13 (m, 4 H), 2.88 - 3.01 (m, 3 H), 3.49 - 3.64 (m, 1 H), 3.74 (s, 3 H), 6.61 (d, *J* = 5.6 Hz, 1 H), 7.68 (s, 1 H), 7.87 - 7.95 (m, 1 H). LRMS m/z calcd. for $C_{19}H_{28}N_7O$ $[M+H]^+$ 370. Found: 370.

Table 14. Compounds **281-287** were prepared according to the method **N-a** as described above.

#	Structure	Compound Name	M+1	NMR Data
281		*N*-[*trans*-4-({4-[1-methyl-5-(methylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] cyclopropanecarboxamide	370	1H NMR (400 MHz, CD_3OD) δ ppm 0.52 - 0.66 (m, 2 H) 0.68 - 0.80 (m, 2 H) 1.32 (t, J=9.73 Hz, 4 H) 1.41 - 1.52 (m, 1 H) 1.85 - 2.13 (m, 4 H) 2.88 - 3.01 (m, 3 H) 3.49 - 3.64 (m, 1 H) 3.74 (s, 3 H) 6.61 (d, J=5.56 Hz, 1 H) 7.68 (s, 1 H) 7.87 - 7.95 (m, 1 H).
282		*N*-[*trans*-4-({4-[5-(isopropylamino)-1-methyl-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] cyclobutanecarboxamide	412	1H NMR (400 MHz, CD_3OD) δ ppm 1.14 (d, J=6.32 Hz, 6 H) 1.19 - 1.42 (m, 6 H) 1.68 - 1.92 (m, 4 H) 2.01 - 2.24 (m, 4 H) 2.86 - 3.04 (m, 2 H) 3.47 - 3.58 (m, 2 H) 3.61 - 3.69 (m, 3 H) 6.64 (d, J=5.31 Hz, 1 H) 7.72 (s, 1 H) 7.95 (d, J=5.56 Hz, 1 H)
283		*N*-[*trans*-4-({4-[5-(isopropylamino)-1-methyl-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]-2-methylpropanamide	400	1H NMR (400 MHz, CD_3OD) δ ppm 0.94 - 1.07 (m, 6 H) 1.10 - 1.20 (m, 6 H) 1.29 - 1.51 (m, 4 H) 1.82 - 2.07 (m, 4 H) 2.22 - 2.37 (m, 1 H) 3.52 - 3.77 (m, 3 H) 3.61 - 3.67 (m, 3 H) 6.55 - 6.69 (m, 1 H) 7.72 (s, 1 H) 7.95 (d, J=5.31 Hz, 1 H)
284		*N*-(*trans*-4-{[4-(5-amino-1*H*-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl) cyclopropane carboxamide	342	1H NMR (400 MHz, DMSO-d6) δ ppm 0.44 - 0.76 (m, 4 H) 1.12 - 1.38 (m, 4 H) 1.43 - 1.58 (m, 1 H) 1.73 - 2.05 (m, 4 H) 3.50 - 3.69 (m, 2 H) 4.05 (s, 1 H) 6.74 (d, J=5.81 Hz, 1 H) 7.85 - 8.11 (m, 2 H) 11.96 (s, 1 H).

#	Structure	Compound Name	M+1	NMR Data
285		*N*-[*trans*-4-({4-[5-(isopropylamino)-1-methyl-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]cyclopropanecarboxamide	398	1H NMR (400 MHz, CD_3OD) δ ppm 0.53 - 0.68 (m, 2 H) 0.70 - 0.78 (m, 2 H) 1.11 - 1.19 (m, 6 H) 1.25 - 1.38 (m, 4 H) 1.40 - 1.53 (m, 1 H) 1.84 - 2.09 (m, 4 H) 3.47 - 3.61 (m, 2 H) 3.60 - 3.69 (m, 3 H) 4.51 (s, 1 H) 6.64 (d, J=5.56 Hz, 1 H) 7.63 - 7.80 (m, 1 H) 7.95 (d, J=5.56 Hz, 1 H).
286		N-(trans-4-{[4-(5-amino-1-benzyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)acetamide	406	1H NMR (400 MHz, CD_3OD) δ ppm 1.28 - 1.51 (m, 4 H) 1.86 - 1.96 (m, 2 H) 1.98 (s, 3 H) 2.05 - 2.18 (m, 2 H) 3.54 - 3.79 (m, 2 H) 5.21 (s, 2 H) 6.71 (d, J=5.56 Hz, 1 H) 7.18 (d, J=7.33 Hz, 2 H) 7.22 - 7.40 (m, 3 H) 7.82 (s, 1 H) 7.99 (d, J=5.56 Hz, 1 H)
287		N-(trans-4-{[4-(5-amino-1-benzyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)acetamide	406	1H NMR (400 MHz, DMSO-d6) δ ppm 1.14 - 1.37 (m, 4 H) 1.77 (s, 3 H) 1.79 - 1.86 (m, 2 H) 1.92 - 2.01 (m, 2 H) 3.42 - 3.55 (m, 1 H) 3.55 - 3.70 (m, 1 H) 5.20 (s, 2 H) 6.64 (d, J=4.80 Hz, 1 H) 6.87 (br. s., 2 H) 6.95 (s, 1 H) 7.15 (d, J=7.33 Hz, 2 H) 7.26 (t, 1 H) 7.32 (t, 2 H) 7.71 - 7.8

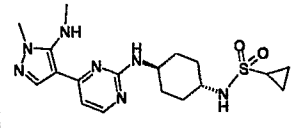
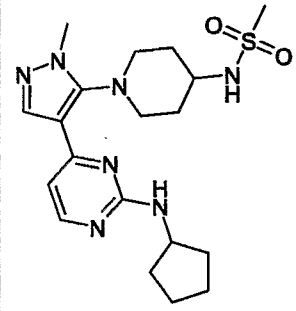
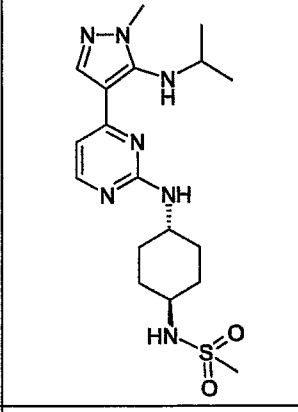
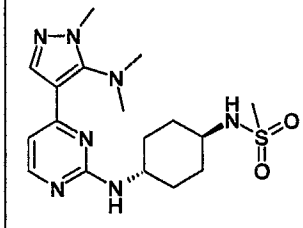
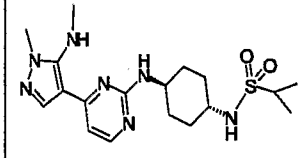
Preparation of N-[trans-4-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]cyclopropanesulfonamide (288)

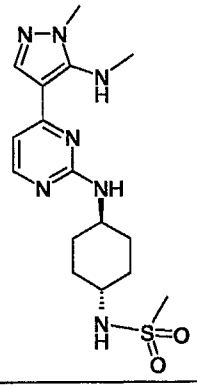
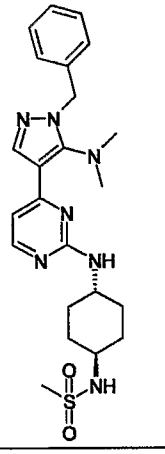
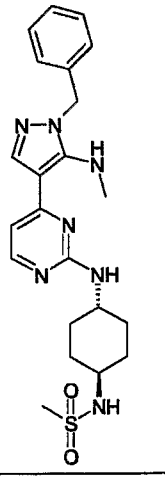
The above compound **288** was prepared according to the general procedure Method **N-b**.

To a solution of trans-N-{4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}cyclohexane-1,4-diamine (0.25 g crude containing ~50% of the compound **288a**, 0.42 mmol) and triethylamine (0.115 mL, 0.84 mmol) in 5 mL of dichloromethane was added cyclopropanesulfonyl chloride (0.085 mL , 0.84 mmol) at 0 °C. The solution was stirred for 30 mins, poured into water and extracted with EtOAc (100 mL X 2). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by HPLC (20-100% CH_3CN/H_2O gradient) to afford the title compound **288**.

1H NMR (400 MHz, CD_3OD) δ ppm 0.87 - 0.97 (m, 4 H),1.26 - 1.47 (m, 4 H), 1.91 - 2.11 (m, 4 H), 2.13 - 2.22 (m, 1 H), 2.93 - 3.05 (m, 3 H), 3.06 - 3.11 (m, 1 H), 3.49 - 3.56 (m, 1 H), 3.71 - 3.79 (m, 3 H), 6.63 - 6.72 (m, 1 H), 7.72 (s, 1 H), 7.86 (d, *J* = 6.1 Hz, 1 H). LRMS m/z calcd. for $C_{18}H_{28}N_7O_2S$ $[M+H]^+$ 406. Found: 406.

Table 15. Compounds **288-295** were prepared according to the method **N-b** as described above.

#	Structure	Compound Name	M+1	NMR Data
288		*N*-[*trans*-4-({4-[1-methyl-5-(methylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] cyclopropanesulfonamide	406	1H NMR (400 MHz, CD_3OD) δ ppm 0.87 - 0.97 (m, 4 H) 1.26 - 1.47 (m, 4 H) 1.91 - 2.11 (m, 4 H) 2.13 - 2.22 (m, 1 H) 2.93 - 3.05 (m, 3 H) 3.06 - 3.11 (m, 1 H) 3.49 - 3.56 (m, 1 H) 3.71 - 3.79 (m, 3 H) 6.63 - 6.72 (m, 1 H) 7.72 (s, 1 H) 7.86 (d, J=6.06 Hz, 1 H).
289		N-(1-{4-[2-(cyclopentylamino)pyrimidin-4-yl]-1-methyl-1H-pyrazol-5-yl}piperidin-4-yl)methanesulfonamide	420	1H NMR (400 MHz, DMSO-d6) δ ppm 1.41-1.49(m,2 H) 1.52 (d, J=7.33 Hz., 2H), 1.60 (d, J=7.58 Hz., 2H),1.68(d, J=5.56 Hz., 2H) 1.79-1.87 (m, 2H) 1.91(d, J=7.58 Hz., 4H) 2.88 (s, 3 H) 2.92 (s, 3H) 3.70 (s, 3 H) 4.35(d, J=4.80 Hz., 1H) 6.76 (d, J=5.05 Hz, 1 H) 7.77 (s, 1 H) 8.15 (d, J
290		*N*-[*trans*-4-({4-[5-(isopropylamino)-1-methyl-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] methanesulfonamide	408	1H NMR (400 MHz, CD_3OD) δ ppm 1.15 (t, J=6.57 Hz, 6 H) 1.33 - 1.42 (m, 4 H) 1.96 - 2.07 (m, 4 H) 3.16 (dd, J=3.16, 1.64 Hz, 2 H) 3.46 - 3.57 (m, 1 H) 3.59 - 3.68 (m, 3 H) 6.65 (d, J=5.31 Hz, 1 H) 7.66 - 7.79 (m, 1 H) 7.95 (d, J=5.56 Hz, 1 H)
291		*N*-[*trans*-4-({4-[5-(dimethylamino)-1-methyl-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] methanesulfonamide	394	1H NMR (400 MHz, CD_3OD) δ ppm 1.33 - 1.41 (m, 4 H) 1.96 - 2.04 (m, J=6.82 Hz, 4 H) 2.59 - 2.63 (m, 1 H) 2.79 - 2.83 (m, 6 H) 2.86 (s, 3 H) 2.92 - 2.97 (m, 1 H) 3.14 - 3.18 (m, 1 H) 3.66 - 3.71 (m, 3 H) 3.79 (s, 1 H) 6.83 (d, J=5.81 Hz, 1 H) 7.76 - 7.84 (m, 1 H) 7.97 - 8.05 (m, 1 H)
292		*N*-[*trans*-4-({4-[1-methyl-5-(methylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] propane-2-sulfonamide	408	1H NMR (400 MHz, CD_3OD) δ ppm 1.10 - 1.50 (m, 12 H) 1.87 - 2.09 (m, 4 H) 2.94 - 3.01 (m, 3 H) 3.03 - 3.11 (m, 3 H) 3.47 - 3.59 (m, 1 H) 3.67 - 3.78 (m, 3 H) 6.60 (d, J=5.56 Hz, 1 H) 7.64 - 7.71 (m, 1 H) 7.92 (t, J=5.81 Hz, 1 H). Ms + 1 = 408.2.

#	Structure	Compound Name	M+1	NMR Data
293		*N*-[*trans*-4-({4-[1-methyl-5-(methylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] methanesulfonamide	380	1H NMR (400 MHz, CD_3OD) δ ppm 1.26 - 1.40 (m, 4 H) 1.88 - 2.06 (m, 4 H) 2.84 - 2.90 (m, 3 H) 2.92 - 2.99 (m, 3 H) 3.46 - 3.60 (m, 2 H) 3.68 - 3.77 (m, 3 H) 6.60 (d, J=5.31 Hz, 1 H) 7.62 - 7.73 (m, 2 H) 7.92 (d, J=5.31 Hz, 1 H).
294		N-[trans-4-({4-[1-benzyl-5-(dimethylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]methanesulfonamide	470	1H NMR (400 MHz, DMSO-d6) δ ppm 1.21 - 1.44 (m, 4 H) 1.85 - 1.96 (m, 4 H) 2.74 (s, 6 H) 2.91 (s, 3 H) 3.03 - 3.16 (m, 1 H) 3.64 - 3.96 (m, 1 H) 5.27 (s, 2 H) 6.78 (d, J=5.05 Hz, 1 H) 7.17 (d, J=7.07 Hz, 2 H) 7.28 (t, 1 H) 7.34 (t, 2 H) 7.92 (s, 1 H) 8.17 (d, 1 H)
295		N-[trans-4-({4-[1-benzyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]methanesulfonamide	456	1H NMR (400 MHz, CD_3OD) δ ppm 1.40 - 1.54 (m, 4 H) 2.05 - 2.17 (m, 4 H) 2.96 (s, 3 H) 3.03 (s, 3 H) 3.22 - 3.28 (m, 1 H) 3.50 - 3.67 (m, 1 H) 5.48 (s, 2 H) 6.91 (d, J=6.57 Hz, 1 H) 7.14 (d, J=7.33 Hz, 2 H) 7.24 - 7.31 (m, 1 H) 7.35 (t, 2 H) 7.91 (d, J=6.57 Hz, 1 H) 8.00 (s, 1 H)

Further modification of compounds produced by Method N-b:

Preparation of N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-N-methylmethanesulfonamide (296) and N-methyl-N-[trans-4-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]methanesulfonamide (297)

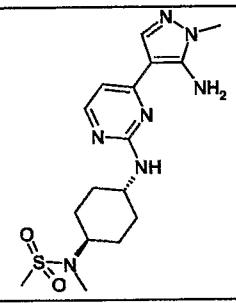
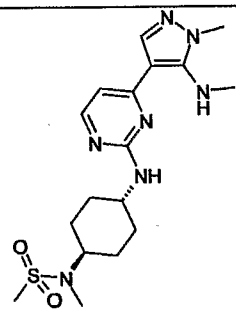
N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl) methanesulfonamide (**296a**) was prepared according to method **N-b**. To a solution of **296a**

(0.175 g, 0.48 mmol) in THF (10 mL) at 0°C, NaH (0.019 g, 0.48 mmol, 60 % dispersion in oil) was added in one portion. The mixture was stirred at 0°C for 10 minutes, and methyl iodide (0.05 mL, 0.72 mmol) was added dropwise. The mixture was allowed to warm up gradually to room temperature and was stirred for 16 hour(s). The mixture was quenched with $NaHCO_3$ (saturated aq.) and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, and concentrated *in vacuo* This residue was purified by HPLC (20-100% CH_3CN/H_2O gradient) to yield N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-N-methylmethanesulfonamide (**296**) and N-methyl-N-[trans-4-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]methanesulfonamide (**297**).

296:. LRMS m/z calcd. for $C_{16}H_{26}N_7O_2S$ $[M+H]^+$380. Found: 380.

297: LRMS m/z calcd. for $C_{17}H_{28}N_7O_2S$ $[M+H]^+$ 394. Found: 394.

Table 16. Compounds **296-297** were prepared according to the modified method **N-b** as described above.

#	Structure	Compound Name	M+1	NMR Data
296		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-N-methylmethanesulfonamide	380	1H NMR (400 MHz, CD_3OD) δ ppm 1.36 - 1.54 (m, 2 H), 1.68 - 1.89 (m, 4 H), 2.11 - 2.22 (m, 2 H), 2.81 (s, 3 H), 2.88 (s, 3 H), 3.62 (s, 3 H), 3.65 (m, 1H), 3.69 - 3.81 (m, 1 H), 6.71 (d, *J* = 5.6 Hz, 1 H), 7.74 (s, 1 H), 7.97 (d, *J* = 5.8 Hz, 1 H).
297		N-methyl-N-[trans-4-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]methanesulfonamide	394	1H NMR (400 MHz, CD_3OD) δ ppm 1.37 - 1.57 (m, 2 H), 1.70 - 1.91 (m, 4 H), 2.11 - 2.24 (m, 2 H), 2.83 (s, 3 H), 2.90 (s, 3 H), 3.08 (s, 3 H), 3.55 - 3.68 (m, 1 H), 3.71 - 3.81 (m, 1 H), 3.84 (s, 3 H), 6.74 (d, *J* = 5.8 Hz, 1 H), 7.80 (s, 1 H), 7.99 (d, *J* = 5.8 Hz, 1 H).

Preparation of N-[trans-4-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]morpholine-4-sulfonamide (298)

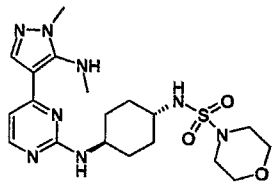
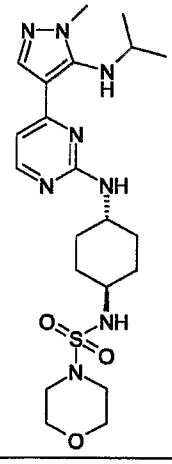
The above compound **298** was prepared according to the general procedure Method **N-c** as described above.

To a solution of trans-N-{4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}cyclohexane-1,4-diamine (0.25 g crude containing ~50% of the compound, 0.42 mmol) in 5 mL of DMF was added triethylamine (0.115 mL, 0.84 mmol) and 4-Morpholinesulfonyl chloride (0.154 g, 0.84 mmol). The mixture was heated in the automated Microwave Reactor to 80°C for 30 minutes. The solution was extracted with

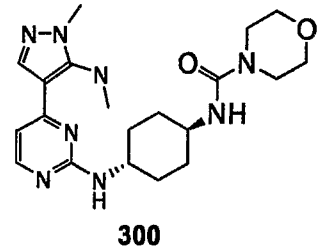
EtOAc, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by HPLC (20-100% CH_3CN/H2O gradient) to yield 76 mg (37%) of the title compound **298.**

1H NMR (400 MHz, CD_3OD) δ ppm 1.26 - 1.58 (m, 2 H), 4.00 (d, *J* = 11.1 Hz, 2 H), 3.07 (s, 3 H) 3.12 - 3.18 (m, 4 H), 3.20 - 3.29 (m, 9 H), 3.21 - 3.28 (m, 4 H), 3.58 - 3.68 (m, 1 H), 3.81 - 3.90 (m, 3 H), 6.71 (d, *J* = 5.6 Hz, 1 H), 7.79 (s, 1 H), 8.04 (d, *J* = 5.3 Hz, 1 H). LRMS m/z calcd. for $C_{19}H_{31}N_8O_3S$ $[M+H]^+$ 451. Found: 451.

Table 17. Compounds **298-299** were prepared according to the method **N-c** as described above.

#	Structure	Compound Name	M+1	NMR Data
298		*N*-[*trans*-4-({4-[1-methyl-5-(methylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] morpholine-4-sulfonamide	451	1H NMR (400 MHz, CD_3OD) δ ppm 1.26 - 1.58 (m, 2 H) 4.00 (d, J=11.12 Hz, 2 H) 3.07 (s, 3 H) 3.12 - 3.18 (m, 4 H) 3.20 - 3.29 (m, 9 H) 3.21 - 3.28 (m, 4 H) 3.58 - 3.68 (m, 1 H) 3.81 - 3.90 (m, 3 H) 6.71 (d, J=5.56 Hz, 1 H) 7.79 (s, 1 H) 8.04 (d, J=5.30 Hz, 1 H).
299		N-[trans-4-({4-[5-(isopropylamino)-1-methyl-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]morpholine-4-sulfonamide	479	1H NMR (400 MHz, CD_3OD) δ ppm 1.23 (d, 6 H) 1.38 - 1.54 (m, 4 H) 2.07 - 2.16 (m, 4 H) 3.06 - 3.15 (m, 4 H) 3.15 - 3.24 (m, 1 H) 3.57 - 3.67 (m, 1 H) 3.68 - 3.74 (m, 5 H) 3.74 (s, 3 H) 6.74 (d, J=5.56 Hz, 1 H) 7.82 (s, 1 H) 8.05 (d, 1 H)

Preparation of N-[trans-4-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]morpholine-4-carboxamide (300)



300

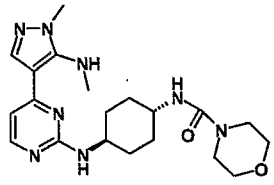
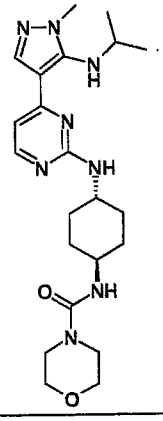
The above compound **300** was prepared according to the general procedure Method **N-d** as described above.

To a solution of trans-N-{4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}cyclohexane-1,4-diamine (0.25 g crude containing ~50% of compound **300a**, 0.42 mmol) in 5 mL of DMF was added

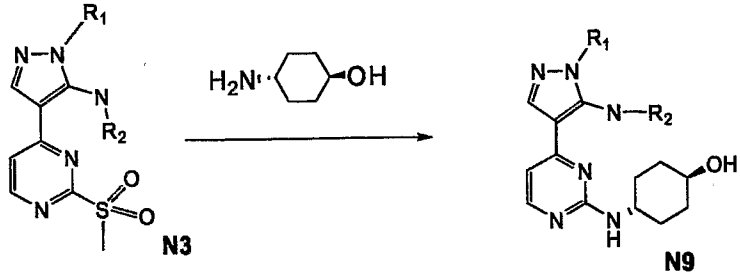
triethylamine (0.115 mL, 0.84 mmol) and 4-Morpholine-carbonyl chloride (0.1 mL, 0.84 mmol). The mixture was stirred at rt for 15 minutes. The solution was extracted with 2-methyl tetrahydrofuran, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by HPLC (20-100% CH_3CN/H2O gradient) to yield 19 mg (6%) of the title compound **300**.

LRMS m/z calcd. for $C_{20}H_{31}N_8O_2$ $[M+H]^+$ 415. Found: 415.

Table 18. Compounds **300-301** were prepared according to the method **N-d** as described above.

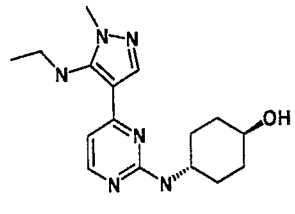
#	Structure	Compound Name	M+1	NMR Data
300		*N*-[*trans*-4-({4-[1-methyl-5-(methylamino)-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl] morpholine-4-carboxamide	415	1H NMR (400 MHz, CD_3OD) δ ppm 1.24 - 1.43 (m, 4 H) 1.79 - 1.93 (m, 2 H) 1.94 - 2.07 (m, 2 H) 2.91 - 2.99 (m, 3 H) 3.25 - 3.34 (m, 4 H) 3.37 - 3.49 (m, 2 H) 3.49 - 3.60 (m, 4 H) 3.74 (s, 3 H) 6.60 (d, J=5.56 Hz, 1 H) 7.68 (s, 1 H) 7.88 - 7.96 (m, 1 H).
301		N-[trans-4-({4-[5-(isopropylamino)-1-methyl-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexyl]morpholine-4-carboxamide	443	1H NMR (400 MHz, CD_3OD) δ ppm 1.23 (d, J=6.57 Hz, 6 H) 1.37 - 1.53 (m, 4 H) 1.95 - 2.03 (m, 2 H) 2.05 - 2.15 (m, 2 H) 3.34 - 3.41 (m, 4 H) 3.55 - 3.62 (m, 2 H) 3.63 - 3.68 (m, 4 H) 3.74 (s, 3 H) 3.75 - 3.77 (m, 1 H) 6.73 (d, J=5.56 Hz, 1 H) 7.82 (s, 1 H) 8.05 (d, J=5.56 Hz, 1 H)

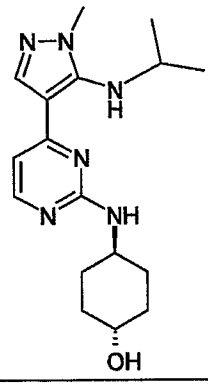
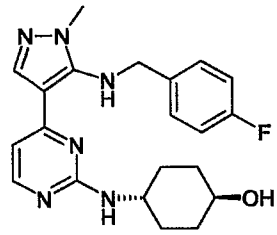
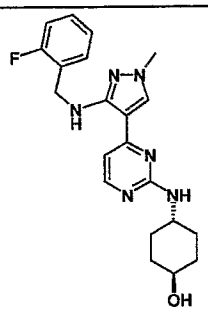
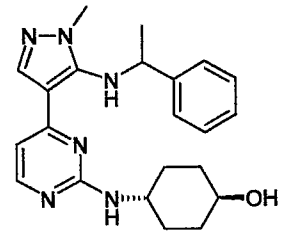
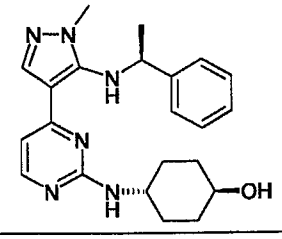
Method N-e

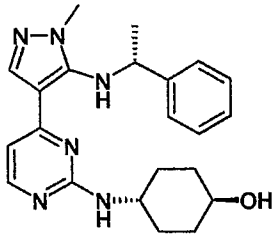
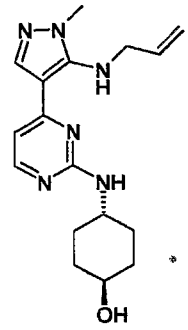
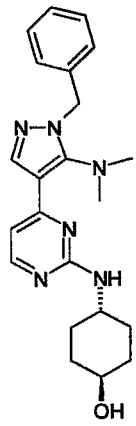
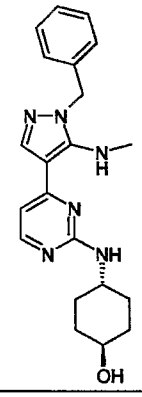


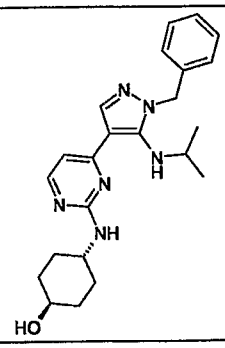
N3 N9

Table 19. Compounds **302-312** were prepared according to the method **N-e** as described above.

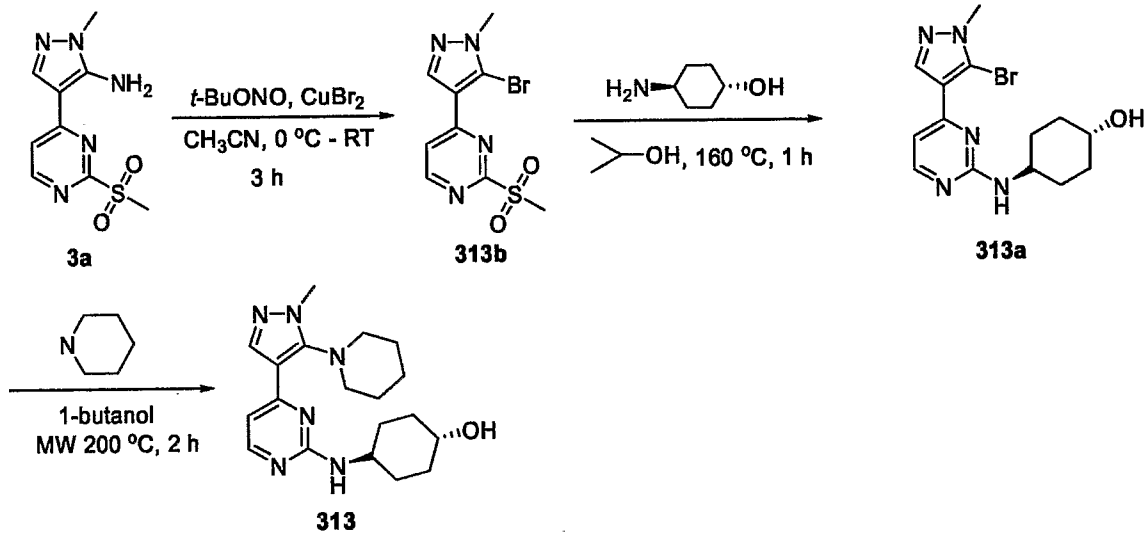
#	Structure	Compound Name	M+1	NMR Data
302		trans-4-({4-[5-(ethylamino)-1-methyl-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	317	1H NMR (400 MHz, DMSO-d6) δ ppm 1.07 - 1.35 (m, 7 H) 1.81 - 1.89 (m, 2 H) 1.93 (br. s., 2 H) 3.21 - 3.30 (m, 2 H) 3.37 - 3.47 (m, 1 H) 3.58 (d, J=18.69 Hz, 1 H) 3.71 (s, 3 H) 6.68 (d, J=5.31 Hz, 1 H) 6.91 (d, J=8.08 Hz, 1 H) 7.08 (br. s., 1 H) 7.81 (s, 1 H) 8.06 (d, J=5.30 Hz, 1 H)

#	Structure	Compound Name	M+1	NMR Data
303		*trans*-4-({4-[5-(isopropylamino)-1-methyl-1*H*-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	331	1H NMR (400 MHz, CD_3OD) δ ppm 1.20 – 1.30 (m, 6 H) 1.39 – 1.56 (m, 4 H) 1.99 – 2.17 (m, J=28.42, 8.46 Hz, 4 H) 3.27 – 3.41 (m, 2 H) 3.57 – 3.70 (m, 1 H) 3.72 – 3.82 (m, 3 H) 6.75 (d, J=5.31 Hz, 1 H) 7.83 (s, 1 H) 8.06 (d, J=5.31 Hz, 1 H)
304		*trans*-4-[(4-{5-[(4-fluorobenzyl)amino]-1-methyl-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]cyclohexanol	397	1H NMR (400 MHz, CD_3OD) δ ppm 1.18 - 1.42 (m, 4 H) 1.77 - 2.00 (m, 4 H) 3.25 (s, 3 H) 3.36 - 3.50 (m, 2 H) 3.57 - 3.72 (m, 3 H) 4.38 - 4.57 (m, 2 H) 6.52 - 6.67 (m, 1 H) 6.82 - 7.00 (m, 2 H) 7.15 - 7.36 (m, 2 H) 7.71 - 7.98 (m, 2 H)
305		4-[(4-{3-[(2-fluorophenyl)amino]-1-methyl-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]cyclohexanol	397	1H NMR (400 MHz, CD_3OD) δ ppm 1.08 - 1.33 (m, 4 H) 1.68 - 1.98 (m, 4 H) 3.31 - 3.47 (m, 2 H) 3.59 - 3.70 (m, 3 H) 4.45 (s, 2 H) 6.61 (d, J=6.06 Hz, 1 H) 6.79 - 6.99 (m, 2 H) 7.06 - 7.15 (m, 1 H) 7.14 - 7.25 (m, 1 H) 7.68 (s, 1 H) 7.81 (d, J=5.81 Hz, 1 H)
306		*trans*-4-[(4-{1-methyl-5-[(1-phenylethyl)amino]-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]cyclohexanol	393	1H NMR (400 MHz, CD_3OD) δ ppm 1.28 - 1.47 (m, 4 H) 1.59 - 1.69 (m, 3 H) 1.91 - 2.02 (m, 3 H) 2.05 - 2.17 (m, 2 H) 3.67 - 3.75 (m, 3 H) 3.74 - 3.83 (m, 1 H) 4.76 (d, J=6.06 Hz, 1 H) 7.07 - 7.38 (m, 5 H) 7.72 (s, 1 H) 8.05 (d, J=5.30 Hz, 1 H)
307	Chiral 	*trans*-4-{[4-(1-methyl-5-{[(1*S*)-1-phenylethyl]amino}-1*H*-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	393	1H NMR (400 MHz, CD_3OD) δ ppm 1.19 - 1.40 (m, 4 H) 1.54 (d, J=6.57 Hz, 3 H) 1.88 (s, 2 H) 1.93 - 2.09 (m, 2 H) 3.41 - 3.54 (m, 1 H) 3.57 - 3.64 (m, 3 H) 3.67 (dd, J=7.58, 3.79 Hz, 1 H) 4.66 (d, J=5.81 Hz, 1 H) 6.58 (d, J=5.56 Hz, 1 H) 6.99 - 7.25 (m, 5 H) 7.50 - 7.68 (m, 1 H) 7.86 - 8.02

#	Structure	Compound Name	M+1	NMR Data
308	Chiral 	*trans*-4-{[4-(1-methyl-5-{[(1*R*)-1-phenylethyl]amino}-1*H*-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	393	1H NMR (400 MHz, CD_3OD) δ ppm 1.14 - 1.39 (m, 4 H) 1.54 (d, J=6.82 Hz, 3 H) 1.88 (s, 2 H) 1.93 - 2.11 (m, 2 H) 3.56 - 3.64 (m, 3 H) 3.64 - 3.73 (m, 1 H) 4.65 (d, 1 H) 6.58 (d, J=5.56 Hz, 1 H) 7.01 - 7.28 (m, 5 H) 7.61 (s, 1 H) 7.94 (d, J=5.31 Hz, 1 H).
309		trans-4-({4-[5-(allylamino)-1-methyl-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	329	1H NMR (400 MHz, CD_3OD) δ ppm 1.27 - 1.52 (m, 4 H) 1.94 - 2.04 (m, 2 H) 2.04 - 2.16 (m, 2 H) 3.53 - 3.72 (m, 2 H) 3.79 (s, 3 H) 3.94 - 4.04 (m, 2 H) 5.17 (d, J=10.11 Hz, 1 H) 5.31 (d, J=17.18 Hz, 1 H) 5.88 - 6.10 (m, 1 H) 6.73 (d, J=5.56 Hz, 1 H) 7.81 (s, 1 H) 8.04 (d, J=5.30 Hz,
310		trans-4-({4-[1-benzyl-5-(dimethylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	393	1H NMR (400 MHz, CD_3OD) δ ppm 1.29 - 1.47 (m, 4 H) 1.92 - 2.02 (m, 2 H) 2.02 - 2.11 (m, 2 H) 2.80 (s, 6 H) 3.52 - 3.64 (m, 1 H) 3.86 - 4.08 (m, 1 H) 5.33 (s, 2 H) 6.81 (d, J=5.31 Hz, 1 H) 7.19 (d, J=7.07 Hz, 2 H) 7.27 (t, 1 H) 7.33 (t, 2 H) 7.93 (s, 1 H) 8.13 (d, J=5.31 Hz, 1 H)
311		trans-4-({4-[1-benzyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	379	1H NMR (400 MHz, CD_3OD) δ ppm 1.27 - 1.47 (m, 4 H) 1.89 - 2.02 (m, 2 H) 2.02 - 2.11 (m, 2 H) 2.91 (s, 3 H) 3.50 - 3.68 (m, 2 H) 5.39 (s, 2 H) 6.71 (d, 1 H) 7.13 (d, J=4.80 Hz, 2 H) 7.19 - 7.37 (m, 3 H) 7.88 (d, 1 H) 8.00 (s, 1 H)

#	Structure	Compound Name	M+1	NMR Data
312		trans-4-({4-[1-benzyl-5-(isopropylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	407	1H NMR (400 MHz, CD_3OD) δ ppm 1.13 (d, 6 H) 1.34 - 1.48 (m, 4 H) 1.96 - 2.03 (m, 2 H) 2.03 - 2.12 (m, 2 H) 3.39 - 3.51 (m, 1 H) 3.55 - 3.66 (m, 1 H) 3.69 - 3.81 (m, 1 H) 5.30 (s, 2 H) 6.78 (d, J=5.56 Hz, 1 H) 7.19 (d, J=7.33 Hz, 2 H) 7.24 - 7.31 (m, 1 H) 7.33 (t, 2 H) 7.94 (s, 1

Method O



3a 313b 313a

313

Preparation of (*trans*)-4-(4-(1-methyl-5-(piperidin-1-yl)-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol (313):

Preparation of 4-(5-bromo-1-methyl-1H-pyrazol-4-yl)-2-(methylsulfonyl)pyrimidine (313b)

To a suspension of 1-methyl-4-(2-(methylsulfonyl)pyrimidin-4-yl)-1H-pyrazol-5-amine (**3a**) (0.95 g, 3.75 mmol), which was prepared as described in Method A above, and $CuBr_2$ (1.0 g) in acetonitrile at O °C, t-Butyl nitrite (90%, 0.65 mL) was added dropwise. The solution was allowed to warm to room temperature overnight, then diluted with ethyl acetate (50 mL) and washed with 1N HCl (3X 20mL), water (1X 20mL), and brine (1 X 20mL). The organic layer was dried over $MgSO_4$ and concentrated to yield 4-(5-bromo-1-methyl-1H-pyrazol-4-yl)-2-(methylsulfonyl)pyrimidine (0.68g, 58% yield).

Preparation of trans-4-(4-(5-bromo-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol (313a)

In a 20mL microwave tube, 4-(5-bromo-1-methyl-1H-pyrazol-4-yl)-2-(methylsulfonyl)pyrimidine (0.90g, 2.84 mmol) and *trans*-4-aminocyclohexanol was dissolved in isopropanol (15 mL), sealed and heated to 160°C in the Biotage microwave for 1 hour. The solvent was concentrated and residue purified on

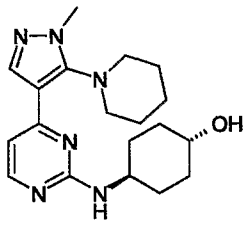
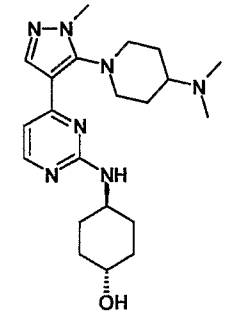
Biotage column eluting with 5% CH_3OH in CH_2Cl_2 to yield *trans*-4-(4-(5-bromo-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol (0.97g, 96.8% yield)

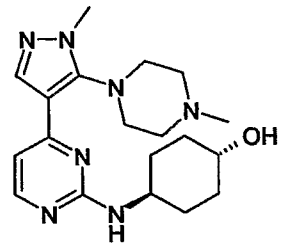
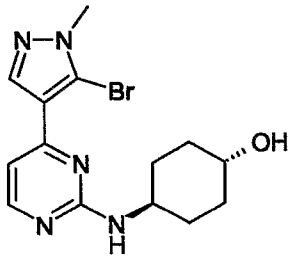
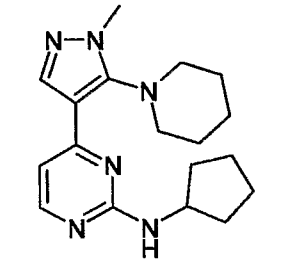
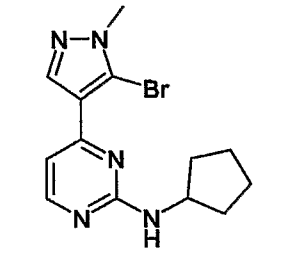
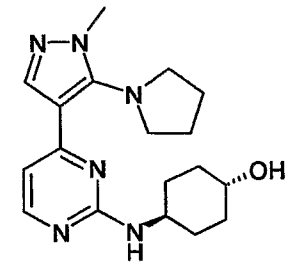
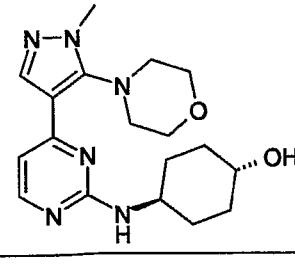
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.16 - 1.35 (m, 4 H), 1.78 - 1.87 (m, 2 H), 1.90 (d, *J* = 10.1 Hz, 2 H), 3.37 (br s, 1 H), 3.66 - 3.81 (m, 1 H), 3.89 (s, 3 H), 4.55 (br s, 1 H), 6.93 (br s, 2 H), 8.10 (br s, 1 H), 8.24 (br s, 1 H).

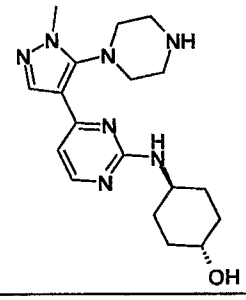
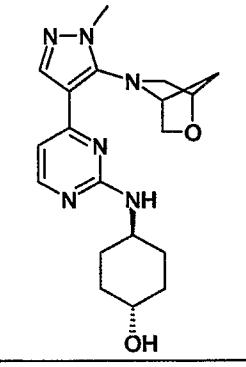
Preparation of (*trans*)-4-(4-(1-methyl-5-(piperidin-1-yl)-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol (313):

In a 10mL microwave tube, *trans*-4-(4-(5-bromo-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol (0.3g, 0.85mmol) and piperidine (0.75mL, 5.06mmol) was dissolve in 1-butanol. The reaction mixture was heated in the Biotage microwave to 200°C for 4 h. Solvent was evaporated and the residue was purified by HPLC (20-100% MeOH-CH_3CN) to yield 59 mg (20%) ((*trans*)-4-(4-(1-methyl-5-(piperidin-1-yl)-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.28 - 1.48 (m, 5 H), 1.71 (d, *J* = 3.8 Hz, 6 H), 1.99 (s, 2 H), 2.08 (br s, 3 H), 3.13 (br s, 4 H), 3.51 - 3.64 (m, 1 H), 3.76 (s, 3 H), 3.99 (br s, 1 H), 6.80 (d, *J* = 5.3 Hz, 1 H), 7.75 (s, 1 H), 8.11 (d, *J* = 5.1 Hz, 1 H). LRMS m/z calcd. for $C_{19}H_{29}N_6O$ $[M+H]^+$ 357. Found: 357.

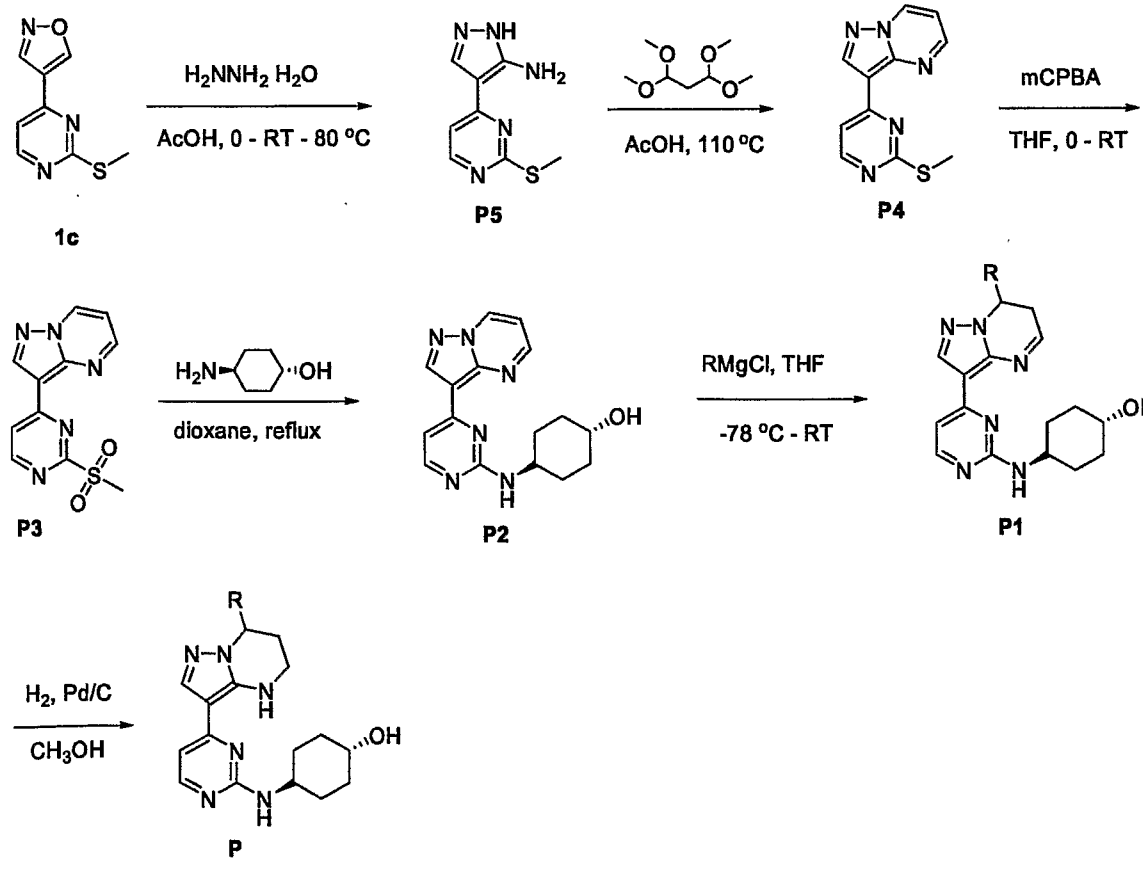
Table 20. Compounds **313-322** were prepared according to the method **O** as described above.

#	Structure	Compound Name	M+1	NMR Data
313		trans-4-{[4-(1-methyl-5-piperidin-1-yl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	357	1H NMR (400 MHz, CD_3OD) δ ppm 1.28 - 1.48 (m, 5 H) 1.71 (d, J=3.79 Hz, 6 H) 1.99 (s, 2 H) 2.08 (br. s., 3 H) 3.13 (br. s., 4 H) 3.51 - 3.64 (m, 1 H) 3.76 (s, 3 H) 3.99 (br. s., 1 H) 6.80 (d, J=5.31 Hz, 1 H) 7.75 (s, 1 H) 8.11 (d, J=5.05 Hz, 1 H)
314		trans-4-[(4-{5-[4-(dimethylamino)piperidin-1-yl]-1-methyl-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]cyclohexanol	400	1H NMR (400 MHz, DMSO-d6) δ ppm 1.08 - 1.34 (m, 4 H) 1.41 - 1.65 (m, 2 H) 1.72 - 1.89 (m, 6 H) 2.23 (s, 6 H) 2.86 (d, J=11.12 Hz, 2 H) 3.29 (br. s., 3 H) 3.28 - 3.39 (m, 3 H) 3.63 (s, 3 H) 6.66 (d, J=5.05 Hz, 1 H) 7.67 (s, 1 H) 8.08 (d, J=4.04 Hz, 1 H)

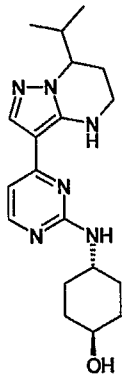
#	Structure	Compound Name	M+1	NMR Data
315		trans-4-({4-[1-methyl-5-(4-methylpiperazin-1-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	372	1H NMR (400 MHz, CD_3OD) δ ppm 1.37-1.47(m, 4H) 1.96 (s, 3H) 1.97-2.09 (m, 4H) 2.47 (s, 3H) 2.72 (br.s., 4H) 3.43 (br.s., 1H) 3.53-3.63 (m,1H) 3.79 (s, 3H), 6.82 (d, J= 5.56 Hz, 1H) 7.87-7.91 (m, 1H) 8.12 (d, J= 5.31 Hz, 1H)
316		trans-4-{[4-(5-bromo-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	353	1H NMR (400 MHz, DMSO-d6) δ ppm 1.16 - 1.35 (m, 4 H) 1.78 - 1.87 (m, 2 H) 1.90 (d, J=10.11 Hz, 2 H) 3.37 (br. s., 1 H) 3.66 - 3.81 (m, 1 H) 3.89 (s, 3 H) 4.55 (br. s., 1 H) 6.93 (br. s., 2 H) 8.10 (br. s., 1 H) 8.24 (br. s., 1 H)
317		N-cyclopentyl-4-(1-methyl-5-piperidin-1-yl-1H-pyrazol-4-yl)pyrimidin-2-amine	327	1H NMR (400 MHz, DMSO-d6) δ ppm 1.42 - 1.58 (m, 6 H) 1.61 (d, J=4.04 Hz, 4 H) 1.70 (br. s., 2 H) 1.83 - 1.98 (m, 2 H) 3.07 (br. s., 4 H) 3.69 (s, 3 H) 4.39 (br. s., 1 H) 6.76 (d, J=5.05 Hz, 1 H) 6.92 (br. s., 1 H) 7.75 (s, 1 H) 8.14 (d, J=5.05 Hz, 1 H)
318		4-(5-bromo-1-methyl-1H-pyrazol-4-yl)-N-cyclopentylpyrimidin-2-amine	322	1H NMR (400 MHz, DMSO-d6) δ ppm 1.42 - 1.57 (m, 4 H) 1.61 - 1.73 (m, 2 H) 1.85 - 1.98 (m, 2 H) 3.88 (s, 3 H) 4.24 (br. s., 1 H) 6.95 (d, J=5.05 Hz, 1 H) 7.06 (d, J=5.81 Hz, 1 H) 8.08 (br. s., 1 H) 8.25 (d, J=3.28 Hz, 1 H)
319		trans-4-{[4-(1-methyl-5-pyrrolidin-1-yl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	343	1H NMR (400 MHz, DMSO-d6) δ ppm 1.11 - 1.43 (m, 4 H) 1.84 (d, J=9.09 Hz, 4 H) 1.96 (br. s., 4 H) 3.21 (br. s., 4 H) 3.37 (br. s., 2 H) 3.67 (s, 3 H) 3.72 (br. s., 1 H) 4.57 (br. s., 1 H) 6.66 (d, J=5.31 Hz, 1 H) 7.77 (s, 1 H) 8.14 (d, J=4.55 Hz, 1 H)
320		trans-4-{[4-(1-methyl-5-morpholin-4-yl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	359	1H NMR (400 MHz, DMSO-d6) δ ppm 1.20 - 1.39 (m, 4 H) 1.81 (br. s., 2 H) 1.83 - 1.95 (m, 2 H) 3.15 (br. s., 4 H) 3.36 (br. s., 1 H) 3.71 (d, J=4.29 Hz, 4 H) 3.74 (s, 3 H) 4.01 (br. s., 1 H) 4.53 (br. s., 1 H) 6.75 (d, J=5.05 Hz, 1 H) 6.83 (br. s., 1 H) 7.80 (s, 1 H) 8.14 (d, J=3.79 Hz,

#	Structure	Compound Name	M+1	NMR Data
321		trans-4-{[4-(1-methyl-5-piperazin-1-yl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexanol	358	1H NMR (400 MHz, CD_3OD) δ ppm 1.25 (br. s., 4 H) 1.83 (br. s., 2 H) 1.90 (br. s., 2 H) 3.06 - 3.17 (m, 4 H) 3.26 (br. s., 4 H) 3.42 (br. s., 1 H) 3.60 (br. s., 1 H) 3.64 (br. s., 3 H) 6.64 (d, J=4.55 Hz, 1 H) 7.72 (s, 1 H) 7.98 (d, J=4.55 Hz, 1 H)
322		trans-4-({4-[1-methyl-5-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)cyclohexanol	371	1H NMR (400 MHz CD_3OD) δ ppm 1.26 - 1.50 (m, 5 H) 1.66 (br. s., 1 H) 1.86 - 2.00 (m, 3 H) 2.00 - 2.09 (m, 2 H) 2.19 (dd, J=9.60, 2.02 Hz, 1 H) 3.33 (br. s., 1 H) 3.52 - 3.63 (m, 1 H) 3.66 - 3.73 (m, 1 H) 3.76 (s, 3 H) 3.80 (d, J=8.84 Hz, 2 H) 4.11 (d, J=7.07 Hz, 1 H) 4.28 (br. s., 1 H)

Method P



Preparation of (1s,4s)-4-(4-(7-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexanol (323, which is an example of compound P):



(323)

Preparation of 4-(2-(methylthio)pyrimidin-4-yl)-1H-pyrazol-5-amine (P5)

4-(Isoxazol-4-yl)-2-(methylthio)pyrimidine **1c**, which was prepared via method A, (6.3g, 32.6 mmol) was dissolved in AcOH (50 mL). The solution was cooled to 0°C in an ice bath. To the solution was added hydrazinemonohydrate (5.0 mL, 94.9 mmol) dropwise over 10 minutes. The solution was warmed up to room temperature in 2 hours. The solution was warmed to 50°C for 30 minutes, and then to 85°C for 3 hours. The reaction mixture was allowed to cool to room temperature, basified with NH_4OH to pH 9. The precipitate thus formed was filtered, washed thoroughly with water, and dried *in vacuo* to yield 4-(2-(methylthio)pyrimidin-4-yl)-1H-pyrazol-5-amine as an orange solid (4.85 g, 67 %). The filtrate was saturated with NaCl and extracted with THF, concentrated to give an orange which consisting of the desired product and unreacted isoxazole **1c**.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.58 (s, 3 H), 7.32 – 7.42 (m, 1 H), 8.28 (s, 1 H), 8.49 (d, J = 5.3 Hz, 1 H).

Preparation of 3-(2-(methylthio)pyrimidin-4-yl)pyrazolo[1,5-a]pyrimidine (P4)

To a suspension of 4-(2-(methylthio)pyrimidin-4-yl)-1H-pyrazol-5-amine (**P5**) (1.0g, 4.8 mmol) in AcOH (20 mL) was added 1,1,3,3-tetramethoxypropane (1.0 mL, 6.0 mmol). The solution was heated to 110°C overnight. The solution was cooled to RT, poured into water, basified with NH_4OH and extracted with EtOAc, dried over $MgSO_4$ and concentrated under vacuum to give 1.33 g (99%) of the title compound.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.59 (s, 3 H), 7.29 (dd, J = 7.0, 4.2 Hz, 1 H), 8.10 (d, J = 5.3 Hz, 1 H), 8.61 (d, J = 5.3 Hz, 1 H), 8.84 (dd, J = 4.0, 1.8 Hz, 1 H), 8.92 (s, 1 H), 9.32 (dd, J = 7.1, 1.8 Hz, 1 H).

Preparation of 3-(2-(methylsulfonyl)pyrimidin-4-yl)pyrazolo[1,5-a]pyrimidine (P3)

A solution of 3-(2-(methylthio)pyrimidin-4-yl)pyrazolo[1,5-a]pyrimidine (**P4**) (1.0g, 4.1 mmol) in THF (20 mL) was cooled to 0°C. To the solution was added 3-chloroperoxybenzoic acide (mCPBA) (3.0g, 13.3 mmol, 77 % tech grade). After being stirred for 30 minutes the ice bath was removed and the reaction was allowed to be stirred at RT for 6 hours. The solution was basified with $NaHCO_3$, saturated with NaCl and extracted with THF. The organic layer was concentrated to give 3-(2-(methylsulfonyl)pyrimidin-4-yl)pyrazolo[1,5-a]pyrimidine and the corresponding sulfoxide (980 mg). The mixture was used in next step without purification.

Preparation of *trans*-4-[(4-pyrazolo[1,5-*a*]pyrimidin-3-ylpyrimidin-2-yl)amino]cyclohexanol (P2)

Crude 3-(2-(methylsulfonyl)pyrimidin-4-yl)pyrazolo[1,5-a]pyrimidine (**P3**) (500 mg) and (trans)-4-aminocyclohexanol were dissolved in 20 mL of dioxane. The solution was heated to reflux for 4 hours, cooled to RT and extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was purified by a silica gel chromatography (0-5% MeOH in CH_2Cl_2) to give *trans*-4-[(4-pyrazolo[1,5-*a*]pyrimidin-3-ylpyrimidin-2-yl)amino]cyclohexanol (310mg).

1H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 - 1.54 (m, 4 H) 1.82 - 2.07 (m, 4 H) 3.48 (s, 1 H) 3.75 - 4.19 (m, 1 H) 7.42 (dd, *J* = 6.8, 4.3 Hz, 1 H) 7.93 (d, *J* = 6.6 Hz, 1 H) 8.39 (d, *J* = 5.3 Hz, 1 H) 8.95 (dd, *J* = 4.3, 1.8 Hz, 1 H) 9.10 (d, 1 H) 9.43 (d, *J* = 6.1 Hz, 1 H).

Preparation of (*trans*)-4-(4-(7-isopropyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexanol (323a)

A solution of *trans*-4-[(4-pyrazolo[1,5-*a*]pyrimidin-3-ylpyrimidin-2-yl)amino]cyclohexanol (**321b**) (600 mg, 1.9 mmol) in THF (20 mL) was cooled to -78°C under N_2. To the solution was added CH_3MgCl (3.5 mL, 2M in THF, 7 mmol) dropwise. The reaction was warmed up to room temperature slowly and stirred for 18 hours. The reaction was quenched by NH_4Cl and extracted with EtOAc The organic layer was dried over $MgSO_4$ and concentrated to give 800 mg of crude product (trans)-4-(4-(7-isopropyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexanol. 100mg of crude material was purified by HPLC (10-40% CH_3CN in water).

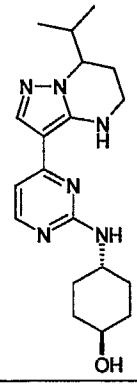
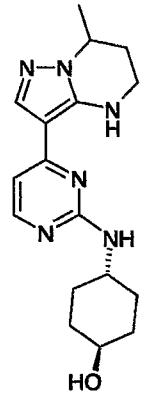
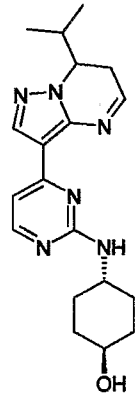
1H NMR (400 MHz, CD_3OD) δ ppm 0.75 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 7.1 Hz, 3 H), 1.26 - 1.54 (m, 4 H), 1.94 - 2.05 (m, 2 H), 2.05 - 2.17 (m, 2 H), 2.38 - 2.52 (m, 1 H), 3.55 - 3.78 (m, 2 H), 4.57 - 4.66 (m, 2 H), 4.68 - 4.77 (m, 1 H), 6.51 (d, *J* = 8.1 Hz, 1 H), 6.72 (d, *J* = 5.6 Hz, 1 H), 7.87 (s, 1 H), 8.04 (d, *J* = 5.6 Hz, 1 H).

Preparation of (*trans*)-4-(4-(7-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexanol (323)

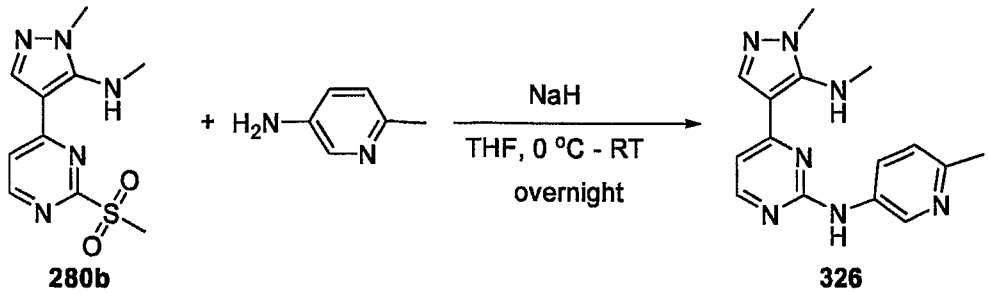
The hydrogenation of crude material (700 mg) containing (trans)-4-(4-(7-isopropyl-6,7-dihydropyrazolo[1,5-a] pyrimidin -3-yl) pyrimidin-2-ylamino)cyclohexanol and 10% Pd/C in MeOH (10 mL) was curried out by a balloon filled with H_2 for 66 hours. LCMC indicated 70% starting material was converted. The solution was filtrated and concentrated. The residue was purified by HPLC (10-40% CH_3CN in water) to give 17 mg (3%) of the title compound.

1H NMR (400 MHz, CD_3OD) δ ppm 0.88 (d, *J* = 6.8 Hz, 3 H), 1.05 (d, *J* = 7.1 Hz, 2 H), 1.28 - 1.50 (m, 4 H), 1.93 - 2.04 (m, 2 H), 2.04 - 2.18 (m, 4 H), 2.39 - 2.51 (m, 1 H), 3.39 - 3.53 (m, 2 H), 3.53 - 3.69 (m, 2 H), 3.95 - 4.06 (m, 1 H), 6.65 (d, *J* = 5.6 Hz, 1 H), 7.73 (s, 1 H), 7.95 (br s, 1 H). LRMS m/z calcd. for $C_{19}H_{29}N_6O$ $[M+H]^+$ 357. Found: 357.

Table 21. Compounds **323-325** were prepared according to the method **P** as described above.

#	Structure	Compound Name	M+1	NMR Data
323		(1s,4s)-4-(4-(7-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexanol	357	1H NMR (400 MHz, CD_3OD) δ ppm 0.88 (d, J=6.82 Hz, 3 H) 1.05 (d, J=7.07 Hz, 2 H) 1.28 - 1.50 (m, 4 H) 1.93 - 2.04 (m, 2 H) 2.04 - 2.18 (m, 4 H) 2.39 - 2.51 (m, 1 H) 3.39 - 3.53 (m, 2 H) 3.53 - 3.69 (m, 2 H) 3.95 - 4.06 (m, 1 H) 6.65 (d, J=5.56 Hz, 1 H) 7.73 (s, 1 H) 7.95 (br. s., 1
324		(*trans*)-4-(4-(7-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexanol	357	1H NMR (400 MHz, CD_3OD) δ ppm 0.88 (d, J=6.82 Hz, 3 H) 1.05 (d, J=7.07 Hz, 2 H) 1.28 - 1.50 (m, 4 H) 1.93 - 2.04 (m, 2 H) 2.04 - 2.18 (m, 4 H) 2.39 - 2.51 (m, 1 H) 3.39 - 3.53 (m, 2 H) 3.53 - 3.69 (m, 2 H) 3.95 - 4.06 (m, 1 H) 6.65 (d, J=5.56 Hz, 1 H) 7.73 (s, 1 H) 7.95 (br. s., 1
325		(*trans*)-4-(4-(7-isopropyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-ylamino)cyclohexanol	355	1H NMR (400 MHz, CD_3OD) δ ppm 0.75 (d, J=6.57 Hz, 3 H) 0.95 (d, J=7.07 Hz, 3 H) 1.26 - 1.54 (m, 4 H) 1.94 - 2.05 (m, 2 H) 2.05 - 2.17 (m, 2 H) 2.38 - 2.52 (m, 1 H) 3.55 - 3.78 (m, 2 H) 4.57 - 4.66 (m, 2 H) 4.68 - 4.77 (m, 1 H) 6.51 (d, J=8.08 Hz, 1 H) 6.72 (d, J=5.56 Hz, 1 H) 7.87

Method Q



280b

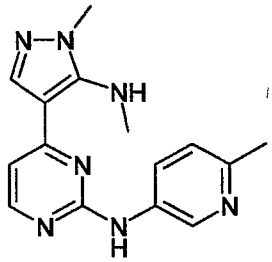
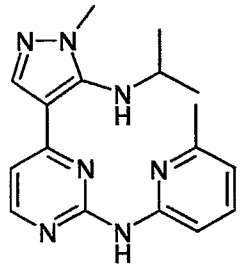
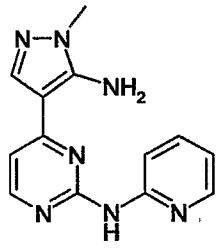
Prepared by method N

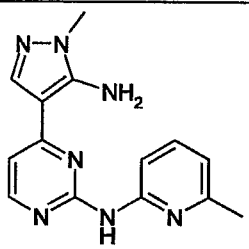
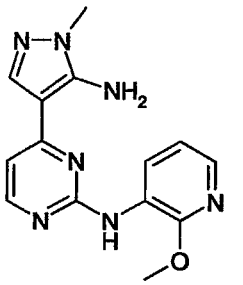
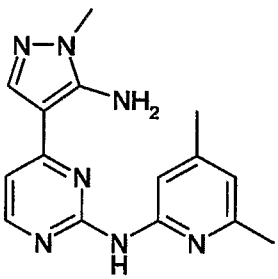
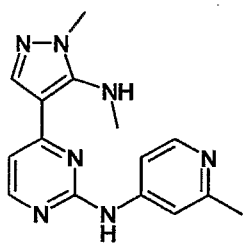
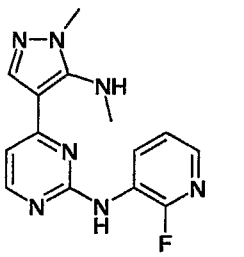
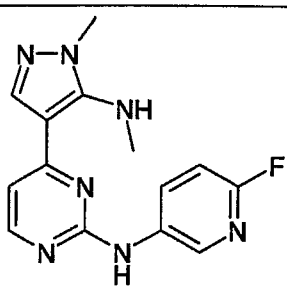
326

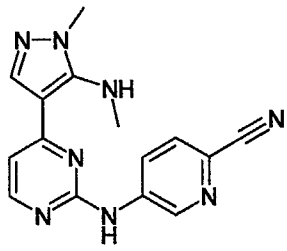
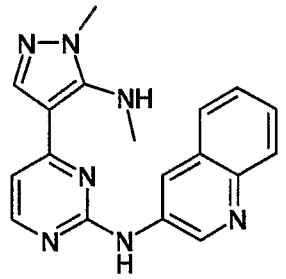
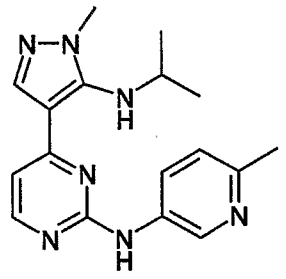
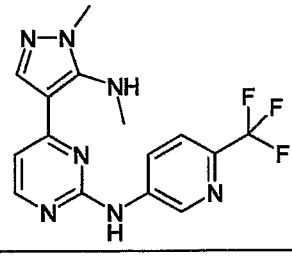
Preparation of 4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine (326):

In a scintillation vial, N,1-dimethyl-4-(2-(methylsulfonyl)pyrimidin-4-yl)-1H-pyrazol-5-amine (**280b**)(150mg, 0.56 mmol), 5-amino-2-methylpyridine (182mg, 1.68 mmol) and were dissolved in 5 mL of THF and cooled to 0 °C. The reaction was then treated with NaH (67 mg, 1.68 mmol). The reaction was removed from ice bath and allowed to warm to r.t. The reaction was diluted with 2-methyl THF and washed with water (1 X 20mL) & sat. NaCl(1 X 20mL). The organic layer was dried over $MgSO_4$, filtered and conc. The residue was taken up in DMSO and purified by HPLC (20-100% CH_3CN/H2O gradient) yielding 4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine (9.5 mg, 5%). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.43 (s, 3 H), 3.00 (d, *J* = 5.6 Hz, 3 H), 3.79 (s, 3 H), 6.96 (d, *J* = 5.6 Hz, 1 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 7.87 (s, 1 H), 8.03 (dd, *J* = 8.7, 1.4 Hz, 1 H), 8.24 (d, *J* = 5.6 Hz, 1 H), 8.65 (d, J = 2.0 Hz, 1 H), 9.49 (s, 1 H). LRMS m/z calcd. for $C_{15}H_{18}N_7$ $[M+H]^+$ 296. Found: 296.

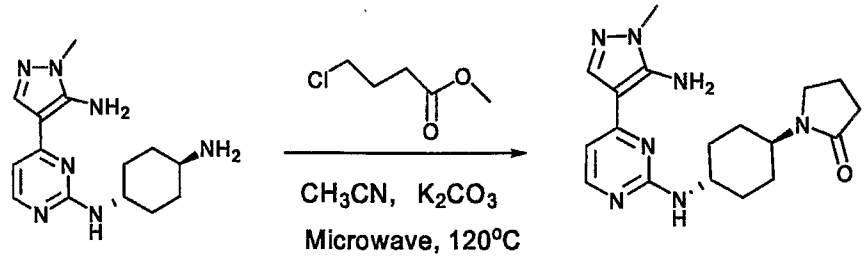
Table 22. Compounds **326-338** were prepared according to the method **Q** as described above.

#	Structure	Compound Name	M+1	NMR Data
326		4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine	296	1H NMR (400 MHz, DMSO-d6) δ ppm 2.43 (s, 3 H) 3.00 (d, J=5.56 Hz, 3 H) 3.79 (s, 3 H) 6.96 (d, J=5.56 Hz, 1 H) 7.22 (d, J=8.34 Hz, 2 H) 7.87 (s, 1 H) 8.03 (dd, J=8.72, 1.39 Hz, 1 H) 8.24 (d, J=5.56 Hz, 1 H) 8.65 (d, J=2.02 Hz, 1 H) 9.49 (s, 1 H)
327		4-[5-(isopropylamino)-1-methyl-1*H*-pyrazol-4-yl]-*N*-(6-methylpyridin-2-yl)pyrimidin-2-amine	324	1H NMR (400 MHz, CD_3OD) δ ppm 0.93 - 1.04 (m, 6 H) 2.31 - 2.39 (m, 3 H) 3.42 - 3.54 (m, 1 H) 3.61 - 3.68 (m, 3 H) 6.82 (d, J=7.33 Hz, 1 H) 6.95 (d, J=5.31 Hz, 1 H) 7.51 - 7.63 (m, 1 H) 7.76 - 7.86 (m, 2 H) 8.21 (d, J=5.56 Hz, 1 H)
328		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-pyridin-2-ylpyrimidin-2-amine	268	1H NMR (400 MHz, DMSO-d6) δ ppm 3.57 (s, 3 H) 6.91 - 6.98 (m, 2 H) 7.02 (s, 2 H) 7.68 - 7.75 (m, 1 H) 7.80 (s, 1 H) 8.12 (d, J=8.59 Hz, 1 H) 8.24 (d, J=5.30 Hz, 1 H) 8.26 (dd, J=4.80, 1.26 Hz, 1 H) 10.08 (s, 1 H)

#	Structure	Compound Name	M+1	NMR Data
329		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)pyrimidin-2-amine	282	1H NMR (400 MHz, DMSO-d6) δ ppm 2.40 (s, 3 H) 3.57 (s, 3 H) 6.80 (d, J=7.33 Hz, 1 H) 6.88 (s, 2 H) 6.95 (d, J=5.56 Hz, 1 H) 7.60 (t, J=7.96 Hz, 1 H) 7.79 (s, 1 H) 8.06 (d, J=8.34 Hz, 1 H) 8.23 (d, J=5.31 Hz, 1 H) 10.00 (s, 1 H)
330		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(2-methoxypyridin-3-yl)pyrimidin-2-amine	298	1H NMR (400 MHz, DMSO-d6) δ ppm 3.57 (s, 3 H) 3.95 (s, 3 H) 6.70 (s, 2 H) 6.91 (d, J=5.31 Hz, 1 H) 6.93 - 7.03 (m, 1 H) 7.68 - 7.85 (m, 2 H) 8.17 (d, J=5.31 Hz, 1 H) 8.39 (d, J=7.33 Hz, 1 H) 8.76 (s, 1 H)
331		4-(5-amino-1-methyl-1H-pyrazol-4-yl)-N-(4,6-dimethylpyridin-2-yl)pyrimidin-2-amine	296	1H NMR (400 MHz, DMSO-d6) δ ppm 2.26 (s, 3 H) 2.36 (s, 3 H) 3.57 (s, 3 H) 6.65 (s, 1 H) 6.87 (s, 2 H) 6.93 (s, 1 H) 7.79 (s, 1 H) 7.90 (s, 1 H) 8.24 (s, 1 H) 9.91 (s, 1 H)
332		4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]-N-(2-methylpyridin-4-yl)pyrimidin-2-amine	296	1H NMR (400 MHz, DMSO-d6) δ ppm 2.45 (s, 3 H) 3.05 (d, J=5.56 Hz, 3 H) 3.81 (s, 3 H) 7.10 (d, J=5.56 Hz, 1 H) 7.18 - 7.32 (m, 1 H) 7.60 (d, J=4.80 Hz, 1 H) 7.66 (s, 1 H) 7.91 (s, 1 H) 8.28 (d, J=6.06 Hz, 1 H) 8.35 (d, J=5.31 Hz, 1 H) 9.98 (s, 1 H)
333		N-(2-fluoropyridin-3-yl)-4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-amine	300	1H NMR (400 MHz, DMSO-d6) δ ppm 2.97 (d, J=5.81 Hz, 3 H) 3.78 (s, 3 H) 7.01 (d, J=5.56 Hz, 1 H) 7.22 (d, J=5.56 Hz, 1 H) 7.30 - 7.40 (m, 1 H) 7.85 - 7.92 (m, 2 H) 8.23 (d, J=5.56 Hz, 1 H) 8.52 (t, J=8.97 Hz, 1 H) 9.35 (s, 1 H)
334		N-(6-fluoropyridin-3-yl)-4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-amine	300	1H NMR (400 MHz, DMSO-d6) δ ppm 3.00 (d, J=5.56 Hz, 3 H) 3.79 (s, 3 H) 6.99 (d, J=5.56 Hz, 1 H) 7.17 (dd, J=8.72, 3.16 Hz, 2 H) 7.88 (s, 1 H) 8.25 (d, J=5.31 Hz, 2 H) 8.45 (s, 1 H) 9.63 (s, 1 H)

#	Structure	Compound Name	M+1	NMR Data
335		5-({4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)pyridine-2-carbonitrile	307	1H NMR (400 MHz, DMSO-d6) δ ppm 3.05 (s, 3 H) 3.75 - 3.86 (m, J=3.03 Hz, 3 H) 7.13 (d, J=3.79 Hz, 1 H) 7.22 (s, 1 H) 7.92 (d, J=3.03 Hz, 1 H) 7.96 (d, J=8.34 Hz, 1 H) 8.34 (s, 1 H) 8.49 (d, J=7.33 Hz, 1 H) 8.93 (s, 1 H) 10.19 (s, 1 H)
336		N-{4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]pyrimidin-2-yl}quinolin-3-amine	332	1H NMR (400 MHz, DMSO-d6) δ ppm 3.01 (s, 3 H) 3.80 (s, 3 H) 7.06 (s, 1 H) 7.29 (s, 1 H) 7.58 (s, 2 H) 7.87 (s, 3 H) 8.36 (s, 1 H) 8.75 (s, 1 H) 8.98 (s, 1 H) 9.88 (s, 1 H)
337		4-[5-(isopropylamino)-1-methyl-1*H*-pyrazol-4-yl]-*N*-(6-methylpyridin-3-yl)pyrimidin-2-amine	324	1H NMR (400 MHz, CD_3OD +D2O) δ ppm 0.96 - 1.02 (m, 6 H) 2.50 (s, 3 H) 3.34 (s, 1 H) 3.50 (dd, J=13.01, 6.44 Hz, 1 H) 3.70 - 3.75 (m, 3 H) 6.97 (d, J=5.31 Hz, 1 H) 7.28 (d, J=8.59 Hz, 1 H) 7.86 (s, 1 H) 7.96 (dd, J=8.34, 2.53 Hz, 1 H) 8.24 (d, J=5.31 Hz, 1 H) 8.61 (d, J=2.53 Hz, 1 H). Ms
338		4-[1-methyl-5-(methylamino)-1H-pyrazol-4-yl]-N-[6-(trifluoromethyl)pyridin-3-yl]pyrimidin-2-amine	350	1H NMR (400 MHz, DMSO-d6) δ ppm 3.05 (d, J=5.81 Hz, 3 H) 3.81 (s, 3 H) 7.10 (d, J=5.56 Hz, 1 H) 7.25 (d, J=3.54 Hz, 1 H) 7.85 (d, J=8.84 Hz, 1 H) 7.92 (s, 1 H) 8.33 (d, J=5.56 Hz, 1 H) 8.51 (dd, J=9.22, 1.89 Hz, 1 H) 8.94 (d, J=2.02 Hz, 1 H) 10.07 (s, 1 H)

Method R



108 trans **339**

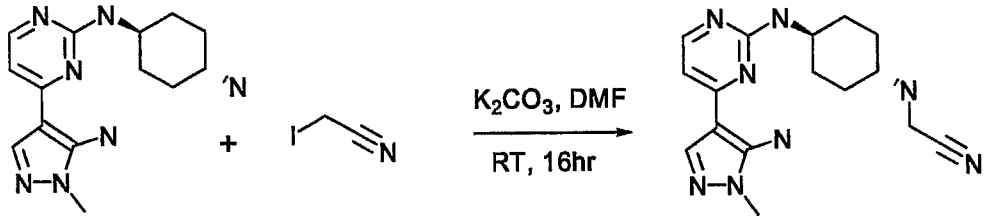
Preparation of 1-((*trans*)-4-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino) cyclohexyl)pyrrolidin-2-one (339)

In a 10mL microwave tube, (*trans*)-N1-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)cyclohexane-1,4-diamine **(108 trans)** (150mg, 0.52 mmol), methyl 4-chlorobutanoate (85mg, 0.62 mmol) and K_2CO_3 (216mg, 1.56 mmol) were suspended in acetonitrile (5 mL), sealed and heated to 120°C in the Biotage microwave for 30 minutes. The solution was filtrated and concentrated. The residue was purified by HPLC (10-50% acetonitrile-water) to give 15mg (8%) of the title compound **339.**

1H NMR (400 MHz, CD_3OD) δ ppm 1.57 - 1.72 (m, 2 H), 1.81 - 2.07 (m, 4 H), 2.17 - 2.29 (m, 2 H), 2.37 (d, *J* = 11.1 Hz, 2 H), 2.58 (t, *J* = 8.1 Hz, 2 H), 3.63 - 3.72 (m, 2 H), 3.81 (s, 3 H), 3.84 - 3.90 (m, 1 H), 4.02 - 4.19 (m, 1 H), 4.73 - 4.90 (m, 1 H), 6.87 (d, *J* = 5.6 Hz, 1 H), 7.92 (s, 1 H) 8.19 (d, *J* = 5.6 Hz, 1 H).

LRMS m/z calcd. for $C_{18}H_{26}N_7O$ $[M+H]^+$ 356. Found: 356

Preparation of [(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]acetonitrile (340)



108 trans **340**

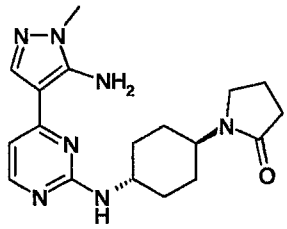
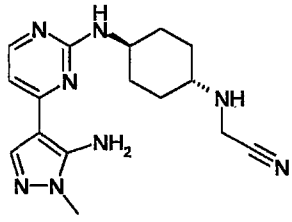
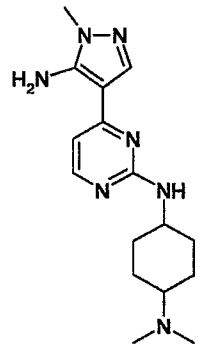
To a solution of (*trans*)-N1-(4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)cyclohexane-1,4-diamine (0.045 g, 0.16 mmol) in 5 mL of DMF was added K_2CO_3 (0.054 g, 0.39 mmol) and Iodoacetonitrile (0.039 g, 0.23 mmol) . The mixture was stirred at room temperature for 16 hr. The mixture was extracted with 2-methyl tetrahydrofuran (25 mL X 2), the combined organics were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by HPLC (20-100% CH_3CN/H2O gradient) to yield 10 mg (13%) the title compound **340.**

1H NMR (400 MHz, DMSO-d6) δ ppm 1.23 - 1.46 (m, 4 H), 1.95 - 2.22 (m, 4 H), 2.88 - 3.15 (m, 1 H), 3.35 - 3.52 (m, 2 H), 3.44 - 3.56 (m, 1 H), 3.59 (s, 3 H), 6.92 (d, 1 H), 7.17 (s, 1 H), 7.98 (d, *J* = 6.3 Hz, 1 H).

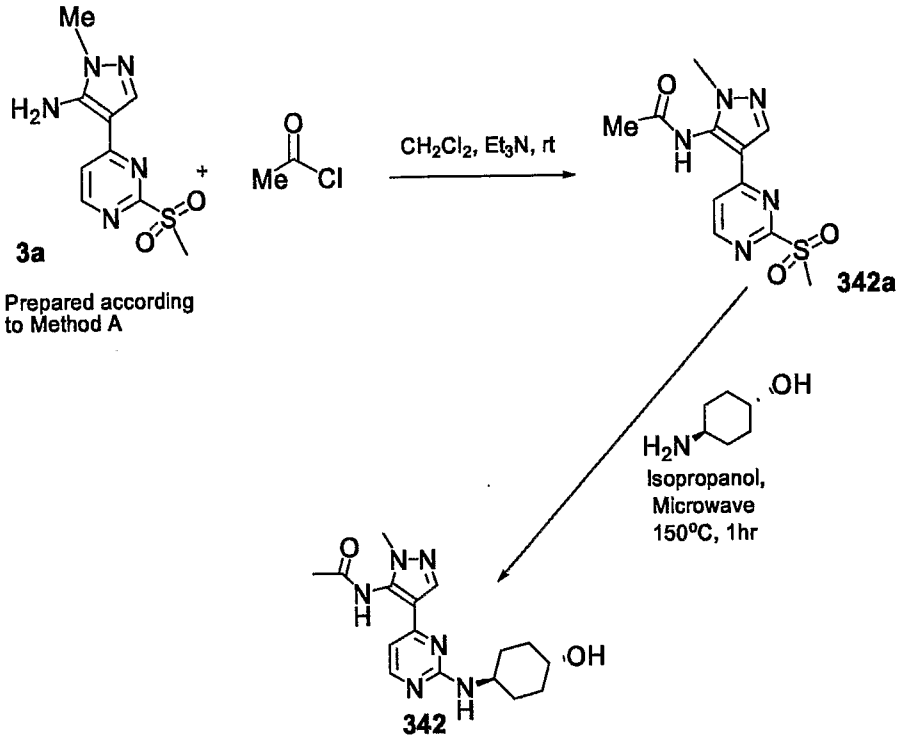
LRMS m/z calcd. for $C_{16}H_{23}N_8$ $[M+H]^+$ 327. Found: 327

LCMS $[M+H]^+$ = 327.2

Table 23. Compounds **339-341** were prepared according to the method **R** as described above.

#	Structure	Compound Name	M+1	NMR Data
339		1-(*trans*-4-{[4-(5-amino-1-methyl-1*H*-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)pyrrolidin-2-one	356	1H NMR (400 MHz, CD_3OD) δ ppm 1.57 - 1.72 (m, 2 H) 1.81 - 2.07 (m, 4 H) 2.17 - 2.29 (m, 2 H) 2.37 (d, J=11.12 Hz, 2 H) 2.58 (t, J=8.08 Hz, 2 H) 3.63 - 3.72 (m, 2 H) 3.81 (s, 3 H) 3.84 - 3.90 (m, 1 H) 4.02 - 4.19 (m, 1 H) 4.73 - 4.90 (m, 1 H) 6.87 (d, J=5.56 Hz, 1 H) 7.92 (s, 1 H) 8.19 (d
340		[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]acetonitrile	327	1H NMR (400 MHz, DMSO-d6) δ ppm 1.23 - 1.46 (m, 4 H) 1.95 - 2.22 (m, 4 H) 2.88 - 3.15 (m, 1 H) 3.35 - 3.52 (m, 2 H) 3.44 - 3.56 (m, 1 H) 3.59 (s, 3 H) 6.92 (d, 1 H) 7.17 (s, 1 H) 7.98 (d, J=6.32 Hz, 1 H)
341		N'-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N,N-dimethylcyclohexane-1,4-diamine	316	1H NMR (400 MHz, CD_3OD) δ ppm 1.33 - 1.51 (m, 1 H) 1.56 - 1.91 (m, 4 H) 2.05 - 2.20 (m, 2 H) 2.19 - 2.32 (m, 1 H) 2.77 (s, 3 H) 2.81 (s, 3 H) 3.08 - 3.25 (m, 1 H) 3.62 (s, 3 H) 3.64 - 3.74 (m, 1 H) 6.65 - 6.74 (m, 1 H) 7.73 (d, J=2.53 Hz, 1 H) 8.01 (t, 1 H)

Method S

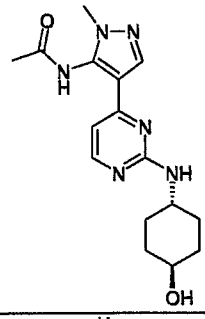
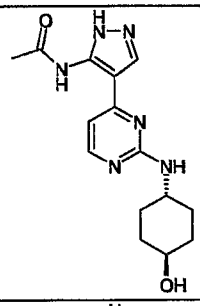
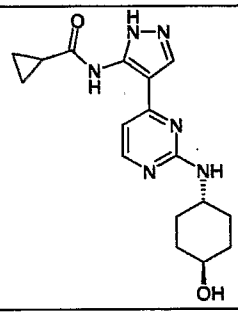
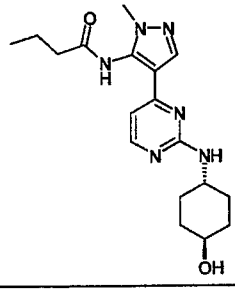
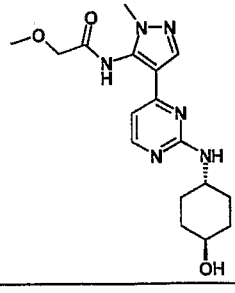


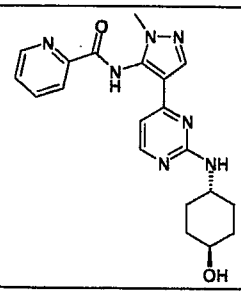
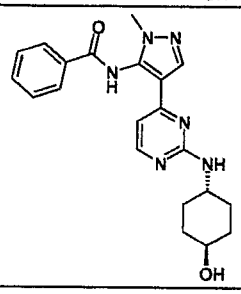
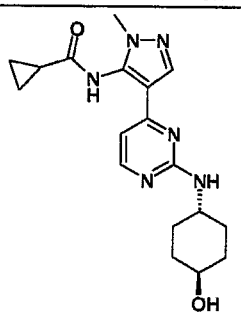
Preparation of N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1-methyl-1H-pyrazol-5-yl)acetamide (342):

Preparation of N-{1-methyl-4-[2-(methylsulfonyl)pyrimidin-4-yl]-1H-pyrazol-5-yl}acetamide 342a)
To a solution of 1-methyl-4-[2-(methylsulfonyl)pyrimidin-4-yl]-1H-pyrazol-5-amine (0.06 g, 0.23 mmol) in 5 mL of dichloromethane was added triethylamine (0.06 mL, 0.46 mmol) and acetyl chloride (0.05 mL , 0.46 mmol). The mixture was stirred at rt for 15 minutes. The solution was concentrated under vacuum. The residue was used in next step without purification.

Preparation of N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1-methyl-1H-pyrazol-5-yl)acetamide (342)
N-{1-methyl-4-[2-(methylsulfonyl)pyrimidin-4-yl]-1H-pyrazol-5-yl}acetamide (0.065 g crude, 0.22 mmol) and trans-4-aminocyclohexanol (0.075 g, 0.66 mmol) in 5 mL of isopropanol was heated in the automated Microwave Reactor for 1.5 h at 150°C . The solution was concentrated under vacuum. The residue was purified by HPLC (20-100% $CH_3CN/H2O$ gradient) to yield 21 mg (27%) the title compound.
1H NMR (400 MHz, CD_3OD) δ ppm 1.29 - 1.51 (m, 4 H), 1.94 - 2.02 (m, 2 H), 2.02 - 2.11 (m, 2 H), 2.27 (s, 3 H), 3.53 - 3.65 (m, 1 H), 3.69 - 3.76 (s, 3 H), 3.75 - 3.88 (m, 1 H), 6.77 (d, J = 5.3 Hz, 1 H), 7.99 (s, 1 H), 8.15 (d, J = 5.3 Hz, 1 H). LRMS m/z calcd. for $C_{16}H_{23}N_6O_2$ $[M+H]^+$ 331. Found: 331.

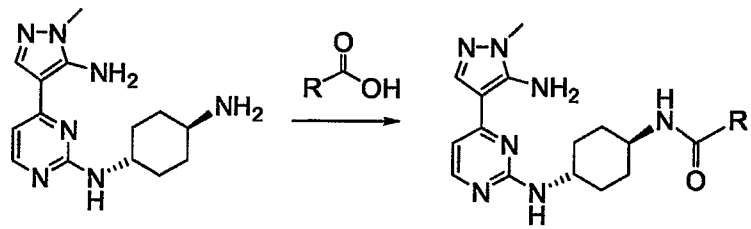
Table 24. Compounds **342-349** were prepared according to the method **S** as described above.

#	Structure	Compound Name	M+1	NMR Data
342		N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1-methyl-1H-pyrazol-5-yl)acetamide	331	1H NMR (400 MHz, CD_3OD) δ ppm 1.29 - 1.51 (m, 4 H) 1.94 - 2.02 (m, 2 H) 2.02 - 2.11 (m, 2 H) 2.27 (s, 3 H) 3.53 - 3.65 (m, 1 H) 3.69 - 3.76 (s, 3 H) 3.75 - 3.88 (m, 1 H) 6.77 (d, J=5.31 Hz, 1 H) 7.99 (s, 1 H) 8.15 (d, J=5.30 Hz, 1 H)
343		N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1H-pyrazol-5-yl)acetamide	317	1H NMR (400 MHz, CD_3OD) δ ppm 1.31 - 1.52 (m, 4 H) 1.93 - 2.05 (m, 2 H) 2.06 - 2.16 (m, 2 H) 2.35 (s, 3 H) 3.53 - 3.68 (m, 1 H) 3.68 - 3.88 (m, 1 H) 6.83 (d, J=5.31 Hz, 1 H) 8.00 (s, 1 H) 8.14 (d, J=5.30 Hz, 1 H)
344		N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1H-pyrazol-5-yl)cyclopropanecarboxamide	343	1H NMR (400 MHz, CD_3OD) δ ppm 0.90 - 1.15 (m, 4 H) 1.32 - 1.52 (m, 4 H) 1.93 - 2.04 (m, 2 H) 2.03 - 2.22 (m, 3 H) 3.51 - 3.67 (m, 1 H) 3.70 - 3.86 (m, 1 H) 6.84 (d, J=5.31 Hz, 1 H) 7.97 (s, 1 H) 8.15 (d, J=5.30 Hz, 1 H)
345		N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1-methyl-1H-pyrazol-5-yl)butanamide	359	1H NMR (400 MHz, CD_3OD) δ ppm 1.01 (t, J=7.20 Hz, 3 H) 1.24 - 1.48 (m, 4 H) 1.68 - 1.84 (m, 2 H) 1.92 - 2.10 (m, 4 H) 2.49 (t, J=7.07 Hz, 2 H) 3.50 - 3.64 (m, 1 H) 3.70 (s, 3 H) 3.71 - 3.83 (m, 1 H) 6.73 (d, J=5.31 Hz, 1 H) 7.95 (s, 1 H) 8.12 (d, J=5.30 Hz, 1 H)
346		N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1-methyl-1H-pyrazol-5-yl)-2-methoxyacetamide	361	1H NMR (400 MHz, CD_3OD) δ ppm 1.24 - 1.53 (m, 4 H) 1.94 - 2.12 (m, 4 H) 3.57 (s, 3 H) 3.57 - 3.64 (m, 1 H) 3.77 (s, 3 H) 3.79 - 3.86 (m, 1 H) 4.19 (s, 2 H) 6.78 (d, J=5.31 Hz, 1 H) 7.99 (s, 1 H) 8.16 (d, J=5.31 Hz, 1 H)

#	Structure	Compound Name	M+1	NMR Data
347		N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1-methyl-1H-pyrazol-5-yl)pyridine-2-carboxamide	394	1H NMR (400 MHz, CD_3OD) δ ppm 1.15 - 1.39 (m, 4 H) 1.82 - 1.96 (m, 2 H) 1.96 - 2.08 (m, 2 H) 3.49 - 3.62 (m, 1 H) 3.65 - 3.79 (m, 1 H) 3.86 (s, 3 H) 6.83 (d, J=5.31 Hz, 1 H) 7.70 (t, 1 H) 8.04 (s, 1 H) 8.07 (t, 1 H) 8.13 (d, J=5.31 Hz, 1 H) 8.24 (d, J=7.83 Hz, 1 H) 8.81 (d, J=4.5
348		N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1-methyl-1H-pyrazol-5-yl)benzamide	393	1H NMR (400 MHz, CD_3OD) δ ppm 1.03 - 1.35 (m, 4 H) 1.71 - 2.09 (m, 4 H) 3.44 - 3.57 (m, 1 H) 3.57 - 3.70 (m, 1 H) 3.81 (s, 3 H) 6.79 (d, J=5.31 Hz, 1 H) 7.60 (t, 2 H) 7.68 (t, 1 H) 8.04 (s, 1 H) 8.08 (d, J=7.33 Hz, 2 H) 8.12 (d, J=5.30 Hz, 1 H)
349		N-(4-{2-[(trans-4-hydroxycyclohexyl)amino]pyrimidin-4-yl}-1-methyl-1H-pyrazol-5-yl)cyclopropanecarboxamide	357	1H NMR (400 MHz, CD_3OD) δ ppm 0.90 - 1.09 (m, 4 H) 1.24 - 1.57 (m, 4 H) 1.89 - 2.01 (m, 3 H) 2.01 - 2.15 (m, 2 H) 3.49 - 3.65 (m, 1 H) 3.70 (s, 3 H) 3.77 - 3.90 (m, 1 H) 6.76 (d, J=5.31 Hz, 1 H) 7.97 (s, 1 H) 8.13 (d, J=5.31 Hz, 1 H)

OTHER COMPOUNDS OF THE INVENTION:

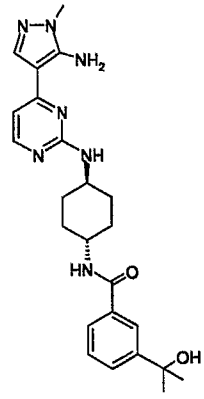
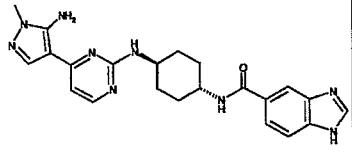
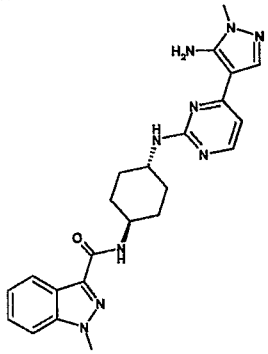
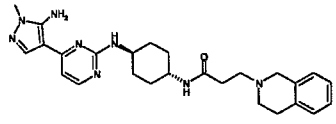
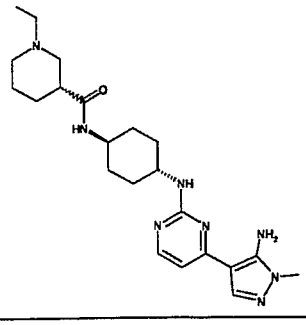
Method T

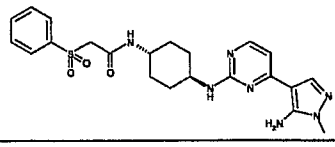
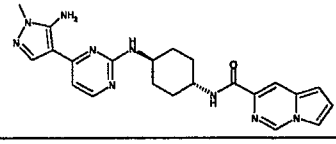
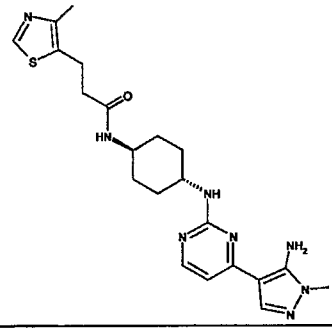
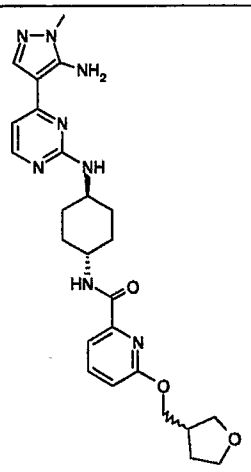
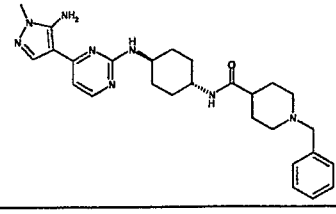


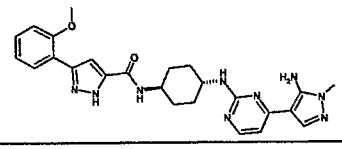
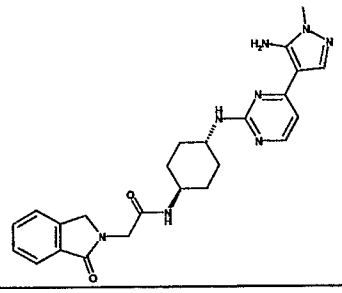
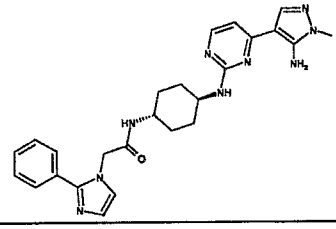
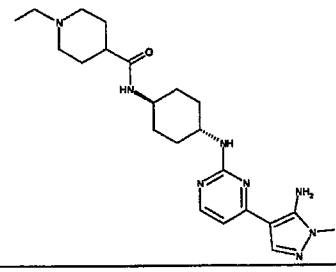
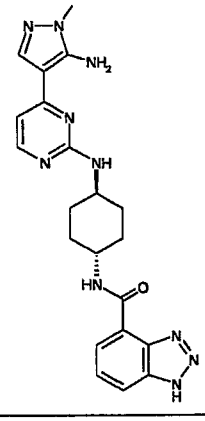
107 (trans)

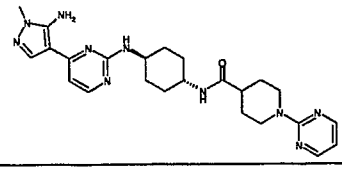
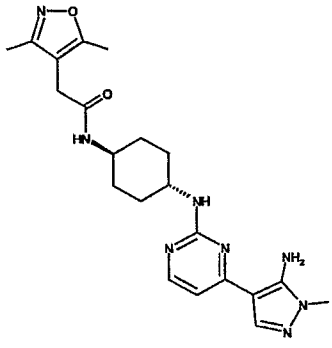
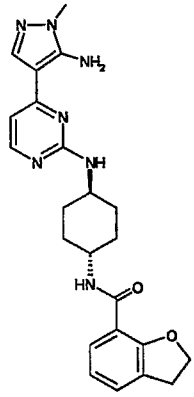
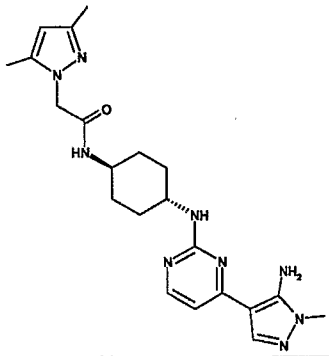
To a solution of equal stoichiometry of the **107 (trans)** (0.2M) and acids (0.2M) and triethylamine (0.5M) all in DMF stirred at room temperature, was added 1 eq. of *O*-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate (HATU) (0.5M) in DMF. The reaction was stirred at room temperature for 16 h. The crude was purified by preHPLC to afford the amide product (with yield 30-95% depending on the acid used).

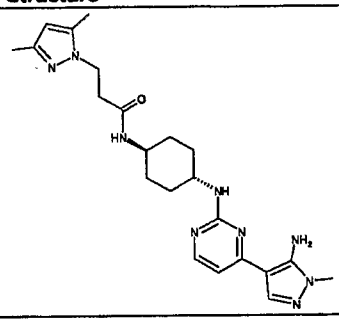
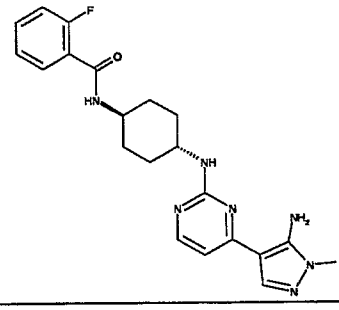
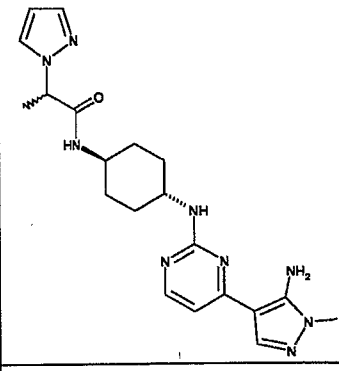
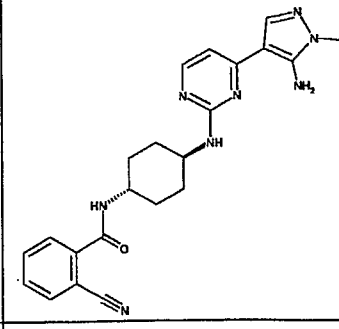
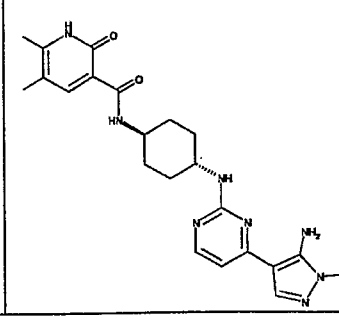
Table 25. Compounds **349-458** were prepared according to the methods **T** as described above.

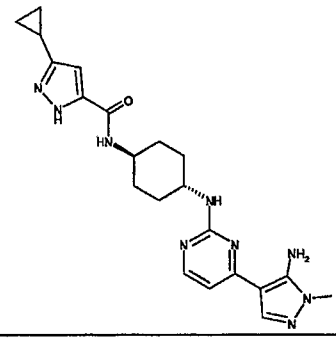
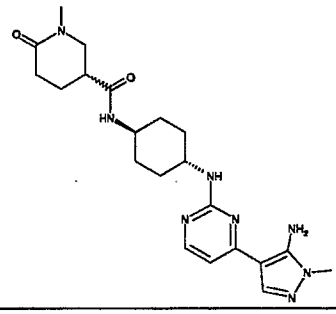
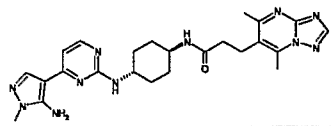
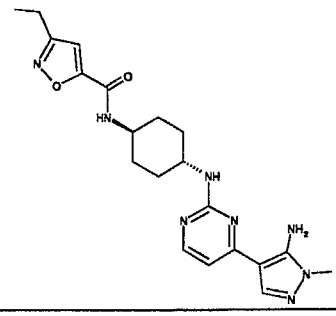
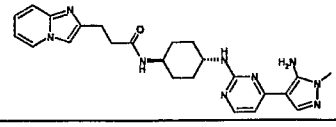
#	Structure	Compound Name	M+1
350		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(1-hydroxy-1-methylethyl)benzamide	451
351		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1H-benzimidazole-5-carboxamide	432
352		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-methyl-1H-indazole-3-carboxamide	447
353		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(34-dihydroisoquinolin-2(1H)-yl)propanamide	476
354		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-ethylpiperidine-3-carboxamide	428

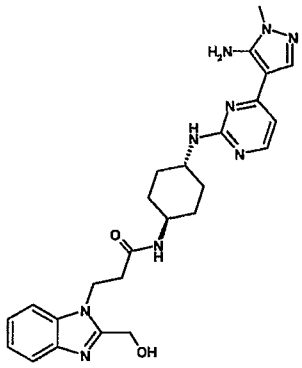
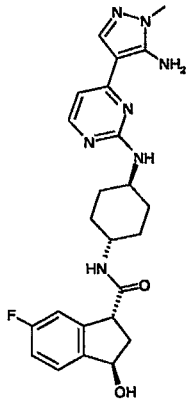
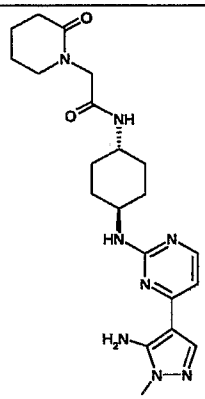
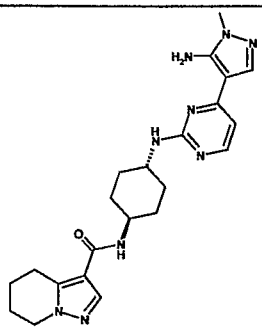
#	Structure	Compound Name	M+1
355		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(phenylsulfonyl)acetamide	471
356		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)pyrrolo[12-c]pyrimidine-3-carboxamide	432
357		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(4-methyl-13-thiazol-5-yl)propanamide	442
358		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-6-(tetrahydrofuran-3-ylmethoxy)pyridine-2-carboxamide	494
359		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-benzylpiperidine-4-carboxamide	490

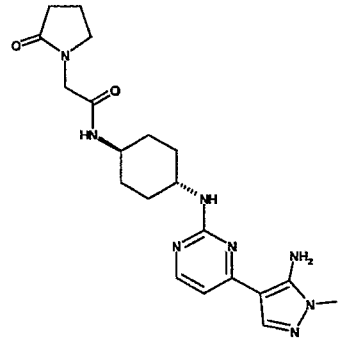
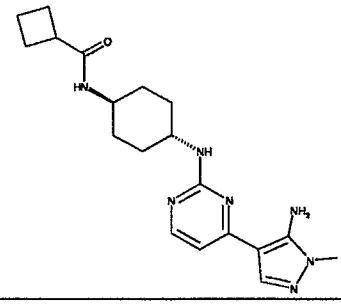
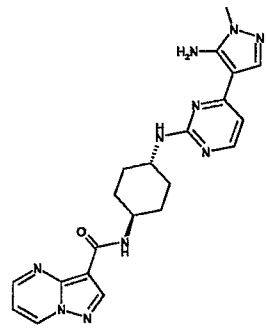
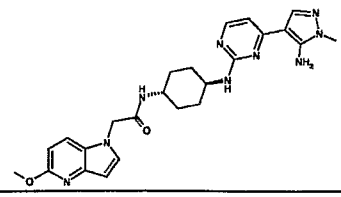
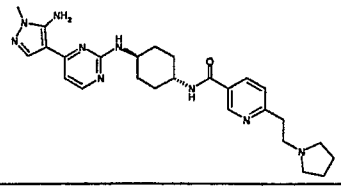
#	Structure	Compound Name	M+1
360		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(2-methoxyphenyl)-1H-pyrazole-5-carboxamide	489
361		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(1-oxo-13-dihydro-2H-isoindol-2-yl)acetamide	462
362		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(2-phenyl-1H-imidazol-1-yl)acetamide	473
363		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-ethylpiperidine-4-carboxamide	428
364		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1H-123-benzotriazole-4-carboxamide	433

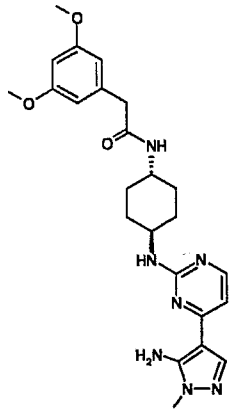
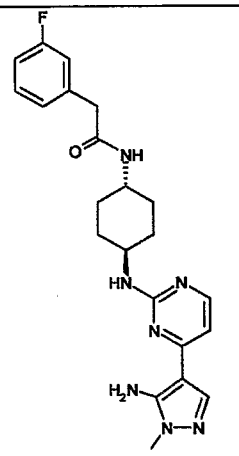
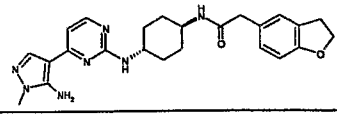
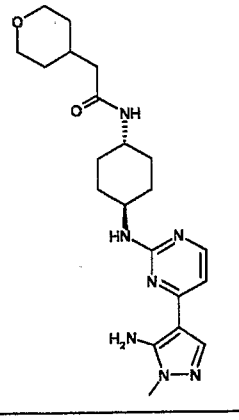
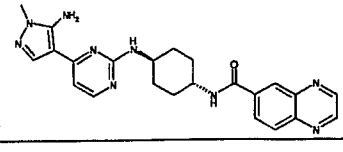
#	Structure	Compound Name	M+1
365		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-pyrimidin-2-ylpiperidine-4-carboxamide	478
366		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(35-dimethylisoxazol-4-yl)acetamide	425
367		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-23-dihydro-1-benzofuran-7-carboxamide	435
368		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(35-dimethyl-1H-pyrazol-1-yl)acetamide	425
369		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(35-dimethyl-1H-pyrazol-1-yl)propanamide	439

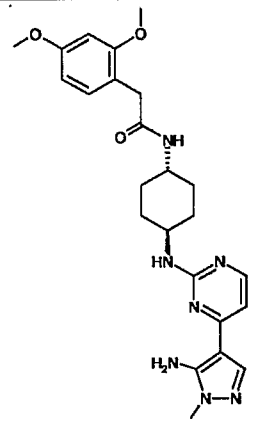
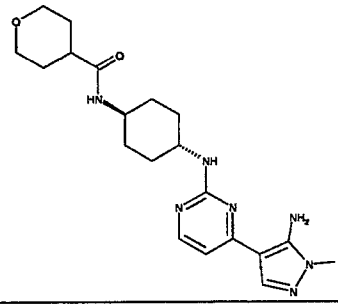
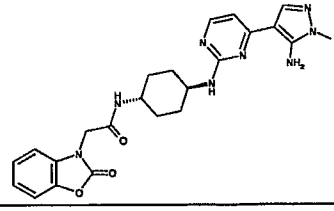
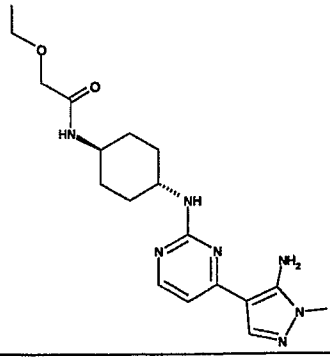
#	Structure	Compound Name	M+1
			
370		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-fluorobenzamide	410
371		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(1H-pyrazol-1-yl)propanamide	410
372		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-cyanobenzamide	417
373		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-56-dimethyl-2-oxo-12-dihydropyridine-3-carboxamide	438

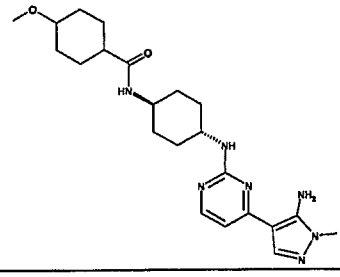
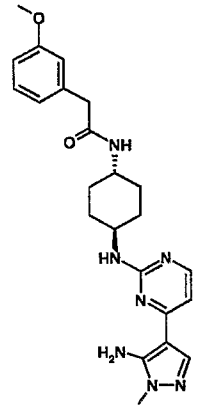
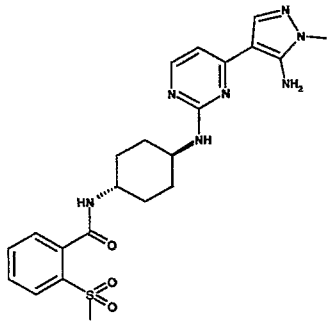
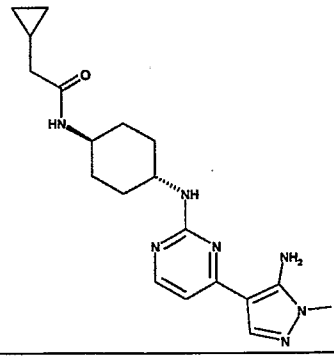
#	Structure	Compound Name	M+1
374		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-cyclopropyl-1H-pyrazole-5-carboxamide	422
375		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-methyl-6-oxopiperidine-3-carboxamide	428
376		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(57-dimethyl[124]triazolo[15-a]pyrimidin-6-yl)propanamide	491
377		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-ethylisoxazole-5-carboxamide	411
378		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-imidazo[12-a]pyridin-2-ylpropanamide	461

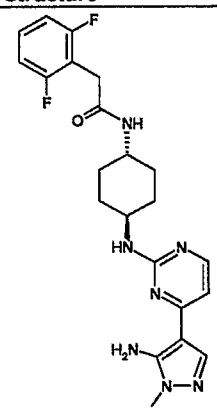
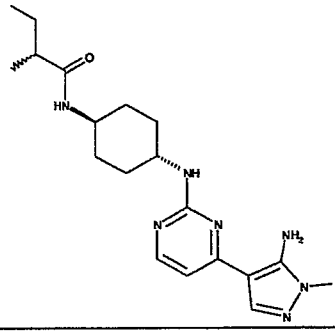
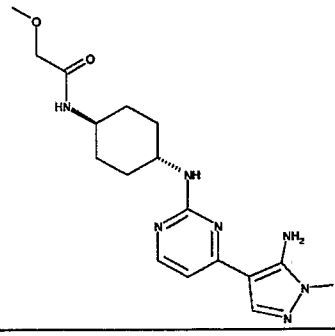
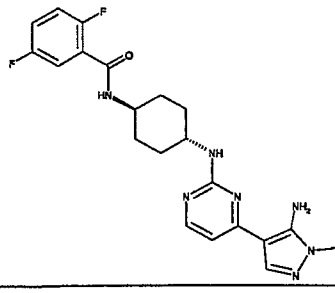
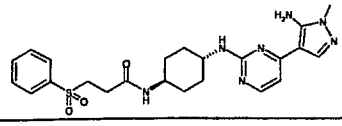
#	Structure	Compound Name	M+1
379		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-[2-(hydroxymethyl)-1H-benzimidazol-1-yl]propanamide	491
380		(1R3R)-N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-6-fluoro-3-hydroxyindane-1-carboxamide	467
381		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(2-oxopiperidin-1-yl)acetamide	428
382		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4567-tetrahydropyrazolo[15-a]pyridine-3-carboxamide	437

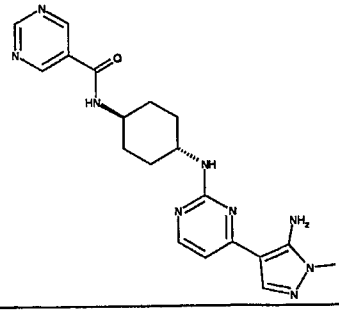
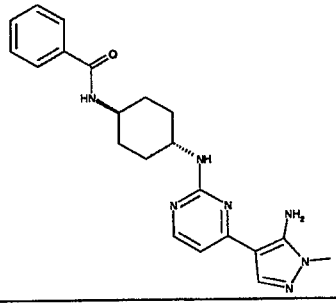
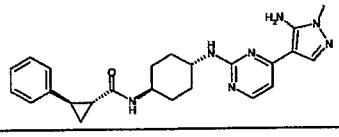
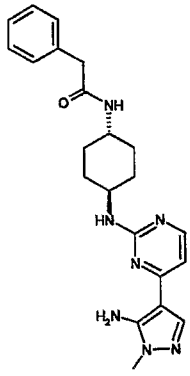
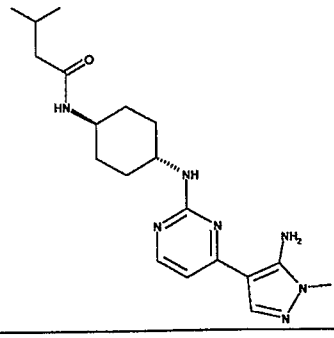
#	Structure	Compound Name	M+1
383		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(2-oxopyrrolidin-1-yl)acetamide	413
384		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)cyclobutanecarboxamide	370
385		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)pyrazolo[15-a]pyrimidine-3-carboxamide	433
386		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(5-methoxy-1H-pyrrolo[32-b]pyridin-1-yl)acetamide	477
387		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-6-(2-pyrrolidin-1-ylethyl)nicotinamide	491

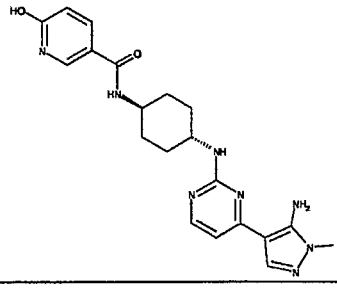
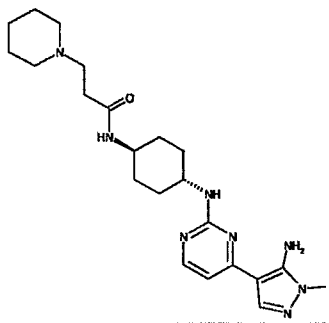
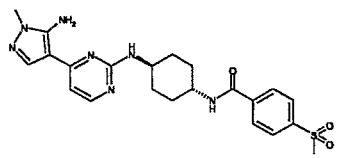
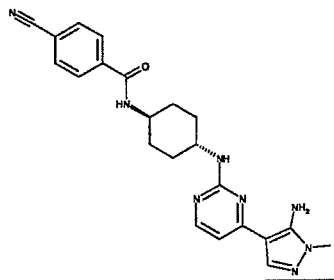
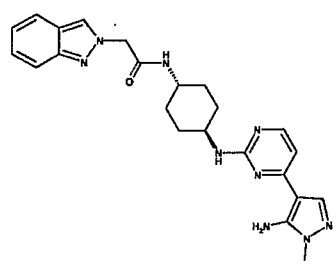
#	Structure	Compound Name	M+1
388		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(35-dimethoxyphenyl)acetamide	467
389		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(3-fluorophenyl)acetamide	424
390		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(23-dihydro-1-benzofuran-5-yl)acetamide	449
391		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(tetrahydro-2H-pyran-4-yl)acetamide	415
392		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)quinoxaline-6-carboxamide	445

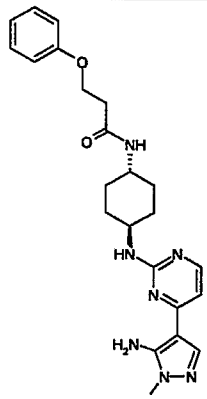
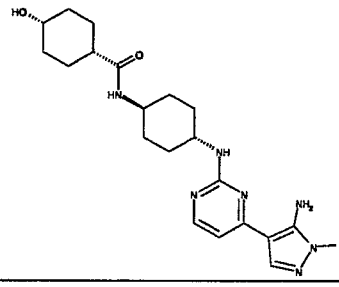
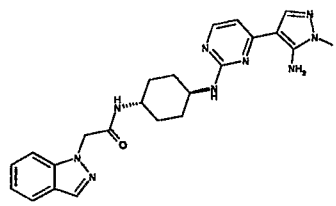
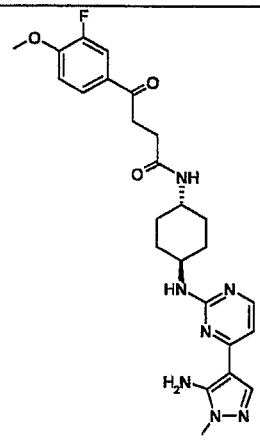
#	Structure	Compound Name	M+1
393		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(24-dimethoxyphenyl)acetamide	467
394		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)tetrahydro-2H-pyran-4-carboxamide	400
395		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(2-oxo-13-benzoxazol-3(2H)-yl)acetamide	464
396		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-ethoxyacetamide	374

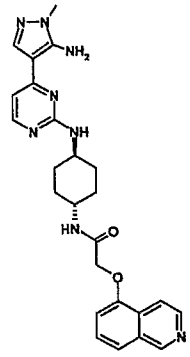
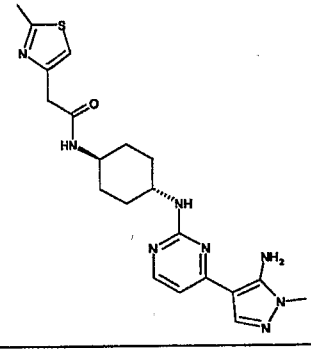
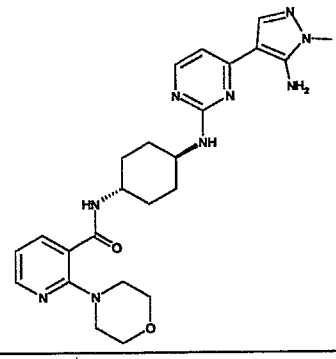
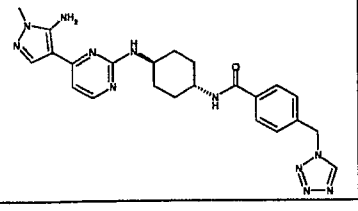
#	Structure	Compound Name	M+1
397		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-methoxycyclohexanecarboxamide	429
398		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(3-methoxyphenyl)acetamide	437
399		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(methylsulfonyl)benzamide	471
400		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-cyclopropylacetamide	370

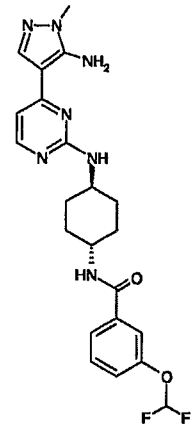
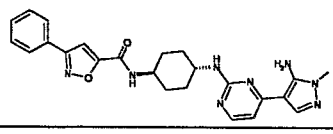
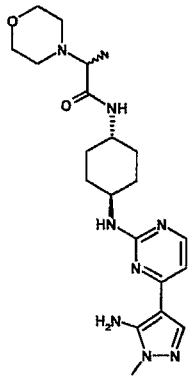
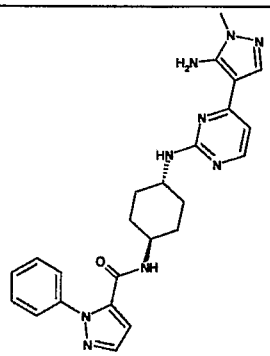
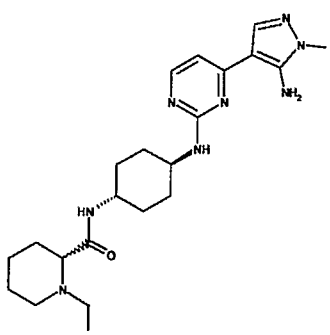
#	Structure	Compound Name	M+1
401		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(26-difluorophenyl)acetamide	442
402		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-methylbutanamide	372
403		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-methoxyacetamide	360
404		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-25-difluorobenzamide	428
405		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(phenylsulfonyl)propanamide	485

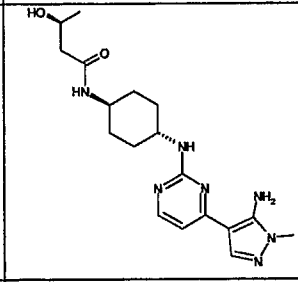
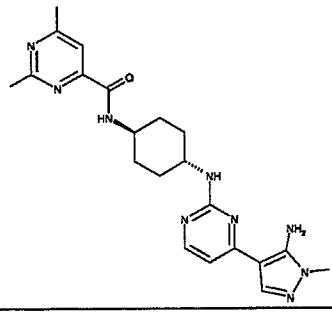
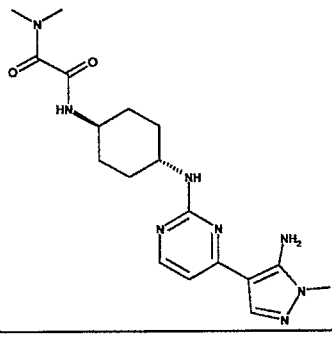
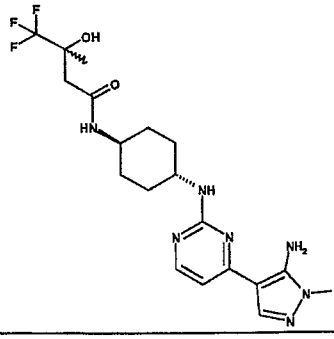
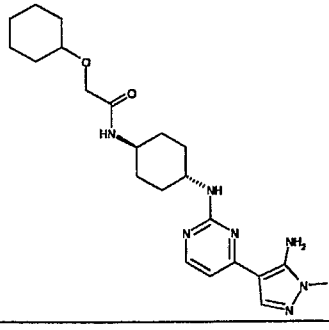
#	Structure	Compound Name	M+1
406		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)pyrimidine-5-carboxamide	394
407		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)benzamide	392
408		(1R2R)-N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-phenylcyclopropanecarboxamide	433
409		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-phenylacetamide	406
410		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-methylbutanamide	372

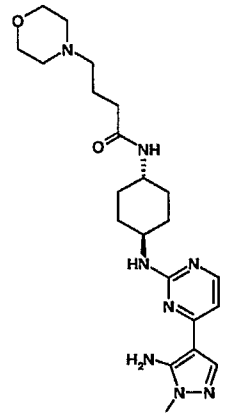
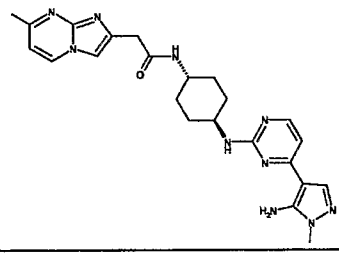
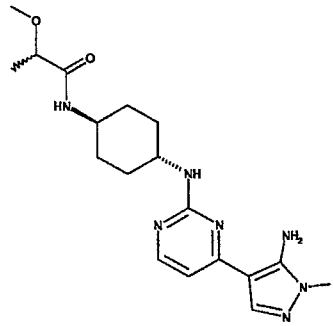
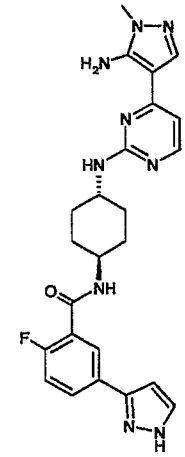
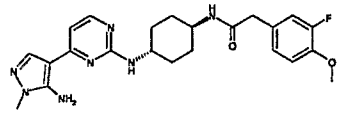
#	Structure	Compound Name	M+1
411		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-6-hydroxynicotinamide	409
412		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-piperidin-1-ylpropanamide	428
413		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-(methylsulfonyl)benzamide	471
414		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-cyanobenzamide	417
415		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(2H-indazol-2-yl)acetamide	447

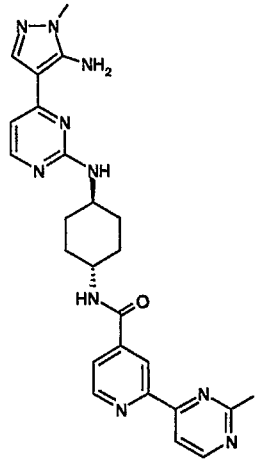
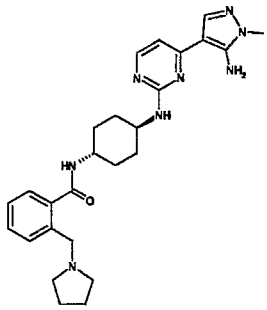
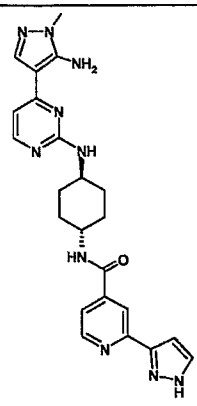
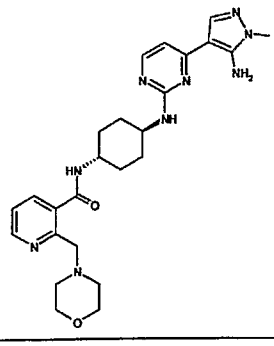
#	Structure	Compound Name	M+1
416		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-phenoxypropanamide	437
417		cis-N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-hydroxycyclohexanecarboxamide	415
418		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(1H-indazol-1-yl)acetamide	447
419		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-(3-fluoro-4-methoxyphenyl)-4-oxobutanamide	497

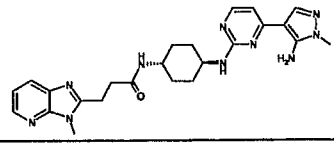
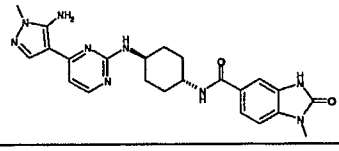
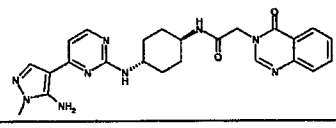
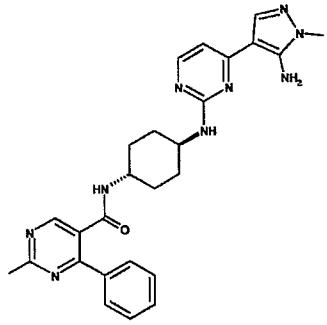
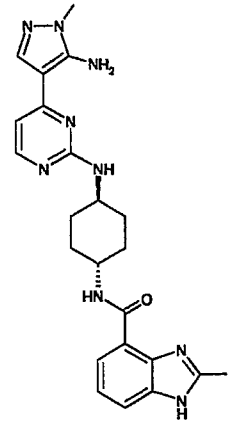
#	Structure	Compound Name	M+1
420		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(isoquinolin-5-yloxy)acetamide	474
421		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(2-methyl-13-thiazol-4-yl)acetamide	428
422		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-morpholin-4-ylnicotinamide	479
423		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-(1H-tetrazol-1-ylmethyl)benzamide	475

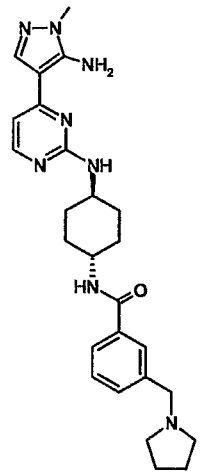
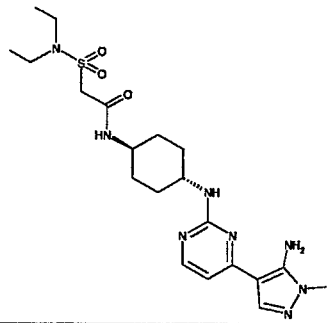
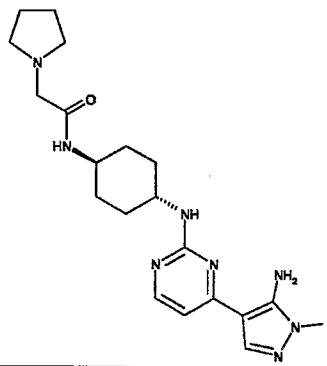
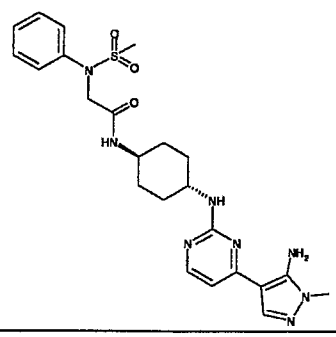
#	Structure	Compound Name	M+1
424		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(difluoromethoxy)benzamide	458
425		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-phenylisoxazole-5-carboxamide	460
426		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-morpholin-4-ylpropanamide	430
427		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-phenyl-1H-pyrazole-5-carboxamide	459
428		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-ethylpiperidine-2-carboxamide	428

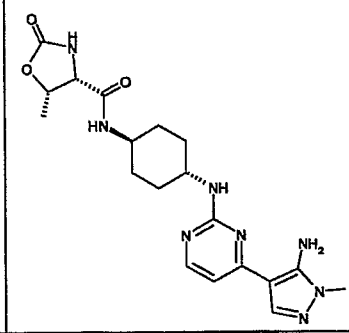
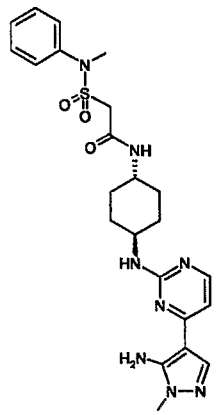
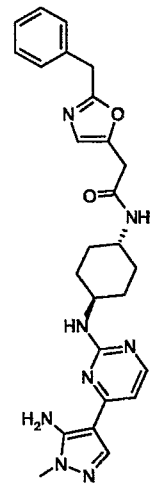
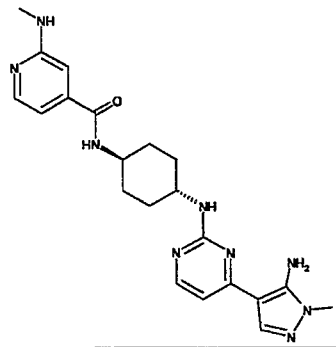
#	Structure	Compound Name	M+1
429		(3S)-N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-hydroxybutanamide	374
430		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-26-dimethylpyrimidine-4-carboxamide	422
431		N'-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-NN-dimethylethanediamide	387
432		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-444-trifluoro-3-hydroxy-3-methylbutanamide	442
433		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(cyclohexyloxy)acetamide	429

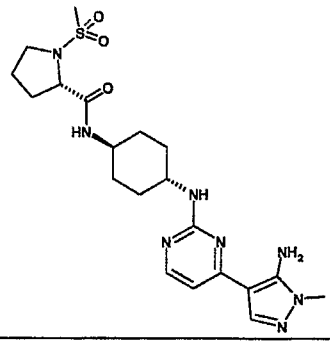
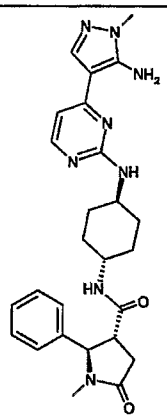
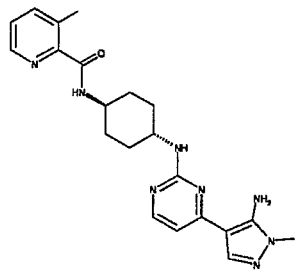
#	Structure	Compound Name	M+1
434		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-4-morpholin-4-ylbutanamide	444
435		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(7-methylimidazo[12-a]pyrimidin-2-yl)acetamide	462
436		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-methoxypropanamide	374
437		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-fluoro-5-(1H-pyrazol-3-yl)benzamide	477
438		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(3-fluoro-4-methoxyphenyl)acetamide	455

#	Structure	Compound Name	M+1
439		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(2-methylpyrimidin-4-yl)isonicotinamide	486
440		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(pyrrolidin-1-ylmethyl)benzamide	476
441		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(1H-pyrazol-3-yl)isonicotinamide	460
442		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(morpholin-4-ylmethyl)nicotinamide	493

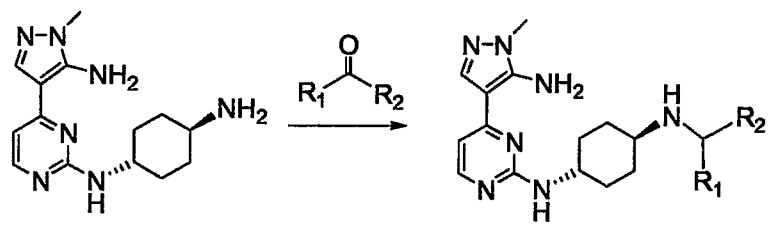
#	Structure	Compound Name	M+1
443		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(3-methyl-3H-imidazo[45-b]pyridin-2-yl)propanamide	476
444		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-methyl-2-oxo-23-dihydro-1H-benzimidazole-5-carboxamide	463
445		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(4-oxoquinazolin-3(4H)-yl)acetamide	475
446		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-methyl-4-phenylpyrimidine-5-carboxamide	485
447		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-methyl-1H-benzimidazole-4-carboxamide	447

#	Structure	Compound Name	M+1
448		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-(pyrrolidin-1-ylmethyl)benzamide	476
449		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-[(diethylamino)sulfonyl]acetamide	466
450		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-pyrrolidin-1-ylacetamide	400
451		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-N~2~-(methylsulfonyl)-N~2~-phenylglycinamide	500

#	Structure	Compound Name	M+1
452		(4S5S)-N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-5-methyl-2-oxo-13-oxazolidine-4-carboxamide	415
453		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-{[methyl(phenyl)amino]sulfonyl}acetamide	500
454		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(2-benzyl-13-oxazol-5-yl)acetamide	488
455		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-2-(methylamino)isonicotinamide	422

#	Structure	Compound Name	M+1
456		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-(methylsulfonyl)-L-prolinamide	464
457		(2R3R)-N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-1-methyl-5-oxo-2-phenylpyrrolidine-3-carboxamide	490
458		N-(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)-3-methylpyridine-2-carboxamide	407

Method U

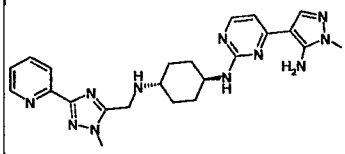
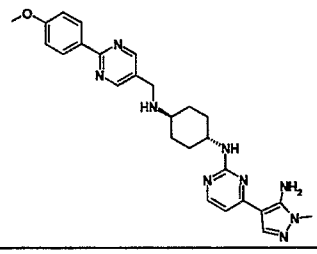
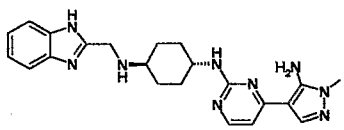
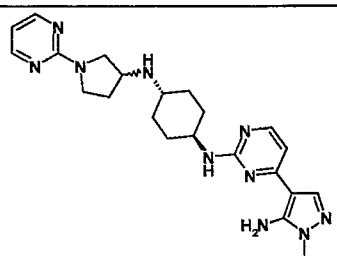
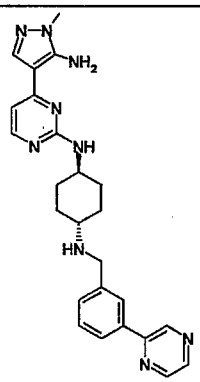


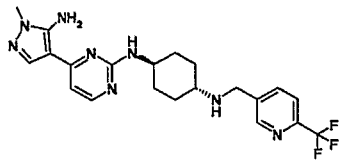
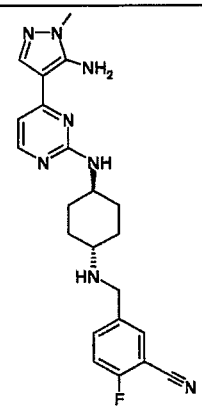
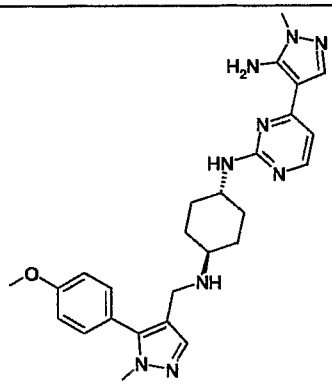
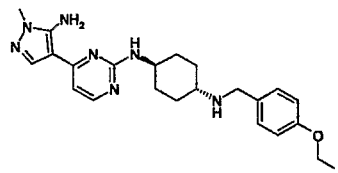
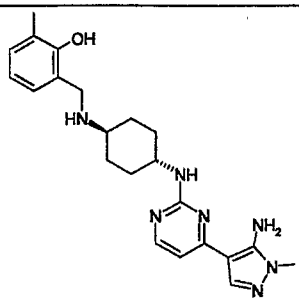
107 (trans)

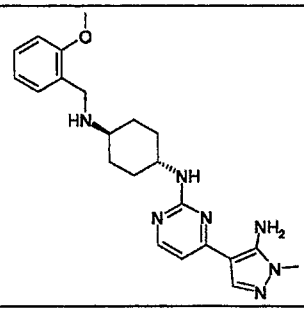
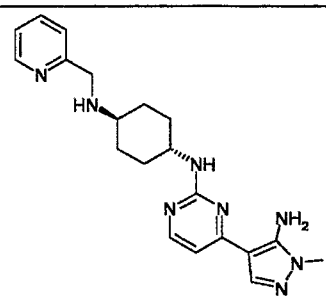
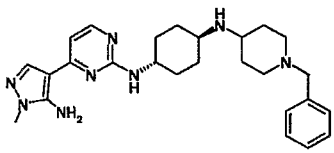
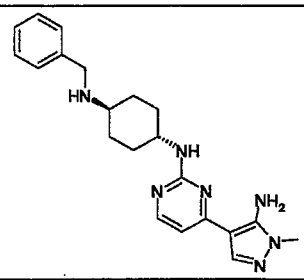
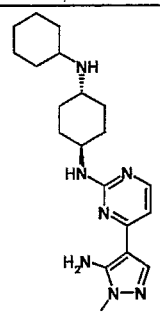
To a 0.4M solution of aldehyde or ketone (0.08 mmole) and **107 (trans)** (0.08 mmole) in a mixed solvent of anhydrous THF and anhydrous DMSO (1:1), was added a solution of 330 μL (0.2 mmole, or 2.5 equiv) of the sodium triacetoxyborohydride in THF/DMSO (1:1) and then 10 uL of glacial acetic acid. The mixture was stirred at room temperature for 24 h. The reaction was quenched with (3M) Na_2CO_3 aqueous and EtOH. Insoluble substance was filtered off and the filtrate was evaporated to give a crude product. The

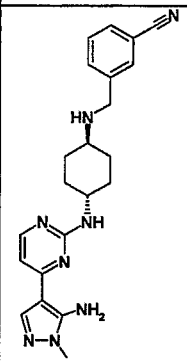
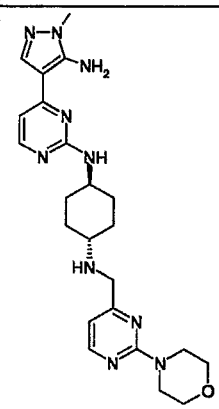
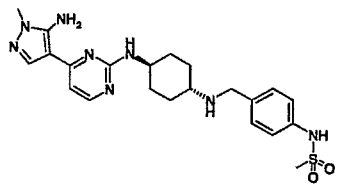
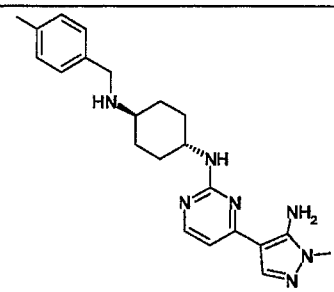
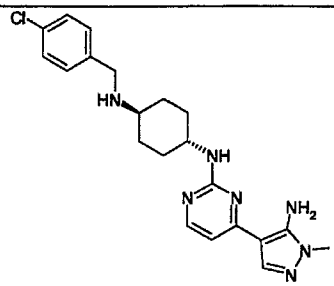
crude was dissolved in DMSO and purified using prepHPLC to afford the pure product (yield range from 30 to 70% depending on the aldehyde or ketone used).

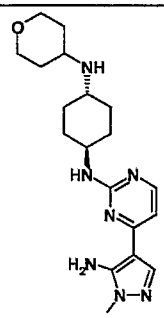
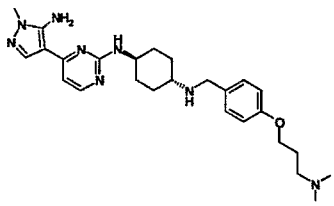
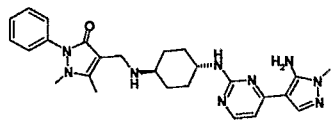
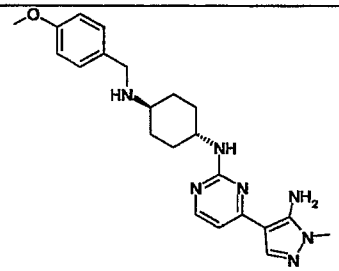
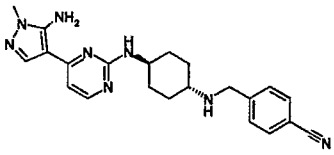
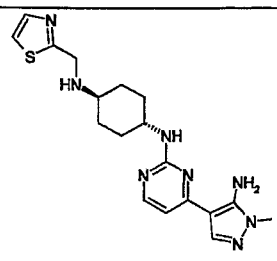
Table 26. Compounds **459-571** were prepared according to the method **U** as described above.

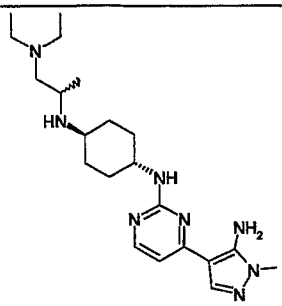
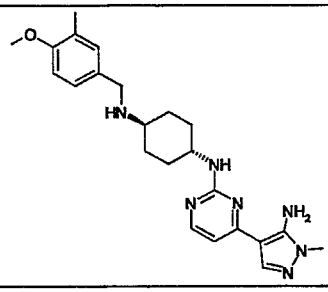
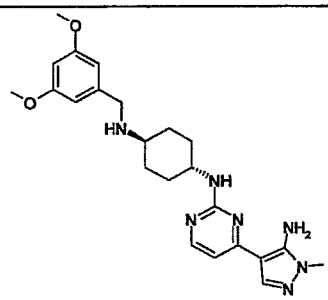
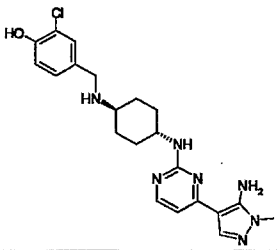
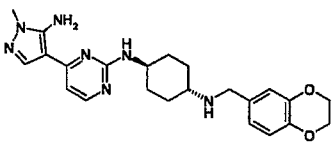
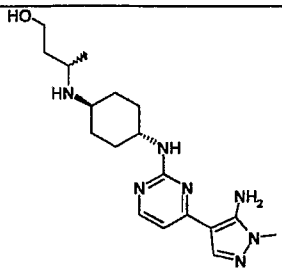
#	Structure	Compound Name	M+1
459		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(1-methyl-3-pyridin-2-yl-1H-1,2,4-triazol-5-yl)methyl]cyclohexane-1,4-diamine	461
460		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[2-(4-methoxyphenyl)pyrimidin-5-yl]methyl}cyclohexane-1,4-diamine	487
461		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1H-benzimidazol-2-ylmethyl)cyclohexane-1,4-diamine	419
462		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1-pyrimidin-2-ylpyrrolidin-3-yl)cyclohexane-1,4-diamine	436
463		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(3-pyrazin-2-ylbenzyl)cyclohexane-1,4-diamine	457

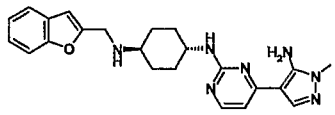
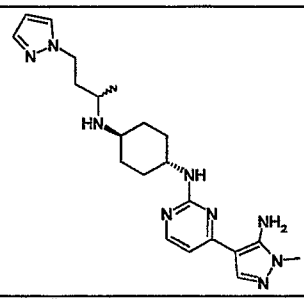
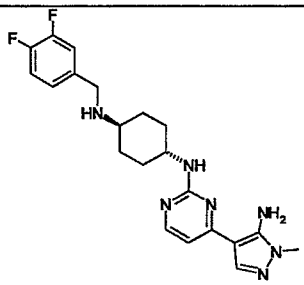
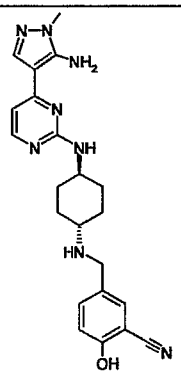
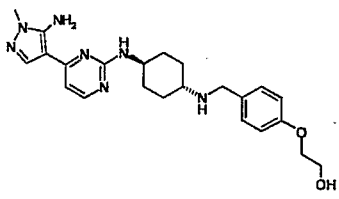
#	Structure	Compound Name	M+1
464		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[6-(trifluoromethyl)pyridin-3-yl]methyl}cyclohexane-1,4-diamine	447
465		5-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-2-fluorobenzonitrile	421
466		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-4-yl]methyl}cyclohexane-1,4-diamine	489
467		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(4-ethoxybenzyl)cyclohexane-1,4-diamine	423
468		2-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-6-methylphenol	409

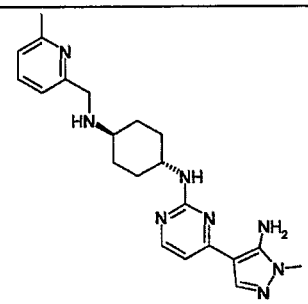
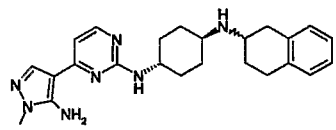
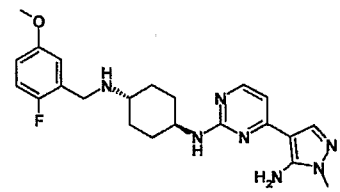
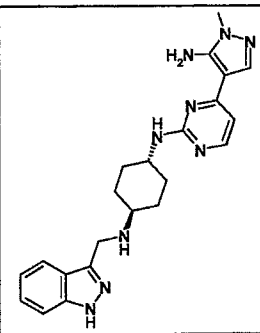
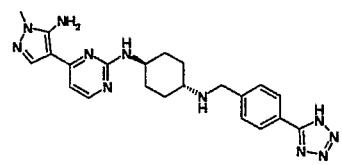
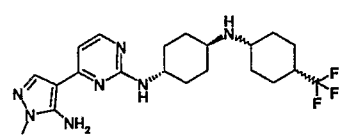
#	Structure	Compound Name	M+1
469		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(2-methoxybenzyl)cyclohexane-1,4-diamine	409
470		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(pyridin-2-ylmethyl)cyclohexane-1,4-diamine	379
471		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1-benzylpiperidin-4-yl)cyclohexane-1,4-diamine	462
472		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-benzylcyclohexane-1,4-diamine	378
473		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-cyclohexylcyclohexane-1,4-diamine	371

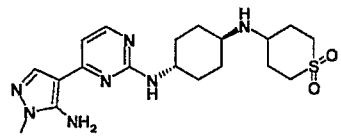
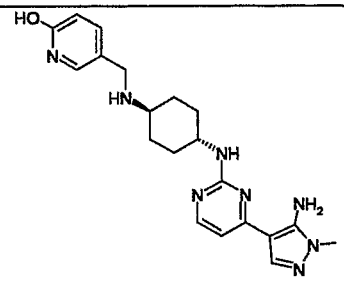
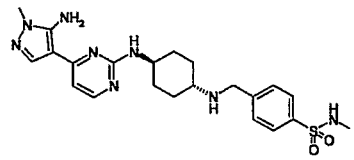
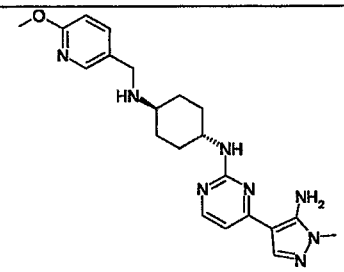
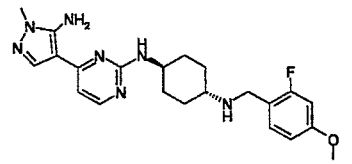
#	Structure	Compound Name	M+1
474		3-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}benzonitrile	404
475		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(2-morpholin-4-ylpyrimidin-4-yl)methyl]cyclohexane-1,4-diamine	466
476		N-(4-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}phenyl)methanesulfonamide	472
477		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(4-methylbenzyl)cyclohexane-1,4-diamine	393
478		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(4-chlorobenzyl)cyclohexane-1,4-diamine	413

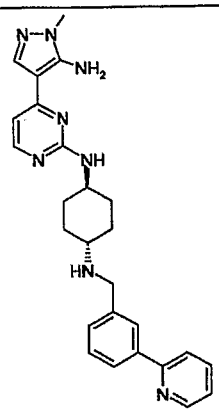
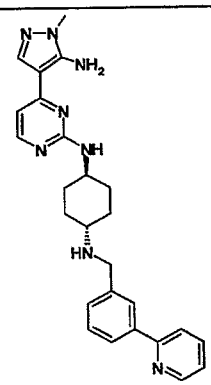
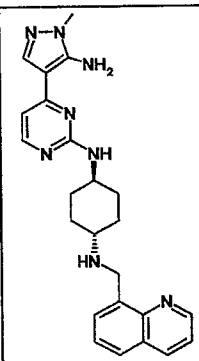
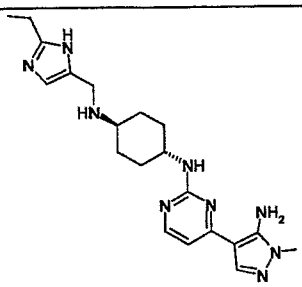
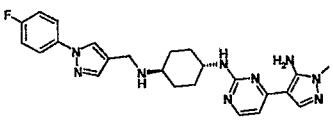
#	Structure	Compound Name	M+1
479		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(tetrahydro-2H-pyran-4-yl)cyclohexane-1,4-diamine	372
480		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{4-[3-(dimethylamino)propoxy]benzyl}cyclohexane-1,4-diamine	480
481		4-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one	489
482		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(4-methoxybenzyl)cyclohexane-1,4-diamine	409
483		4-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}benzonitrile	404
484		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1,3-thiazol-2-ylmethyl)cyclohexane-1,4-diamine	386

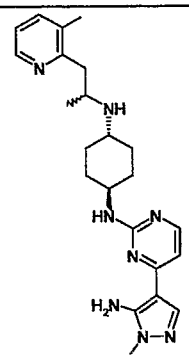
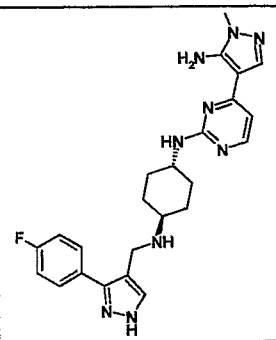
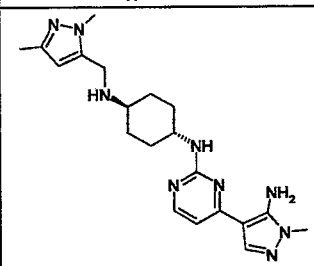
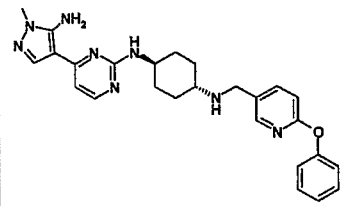
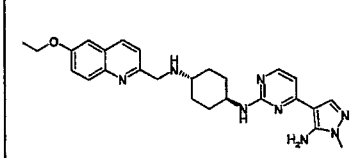
#	Structure	Compound Name	M+1
485		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[2-(diethylamino)-1-methylethyl]cyclohexane-1,4-diamine	402
486		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(4-methoxy-3-methylbenzyl)cyclohexane-1,4-diamine	423
487		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(3,5-dimethoxybenzyl)cyclohexane-1,4-diamine	439
488		4-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-2-chlorophenol	429
489		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)cyclohexane-1,4-diamine	437
490		3-[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]butan-1-ol	360

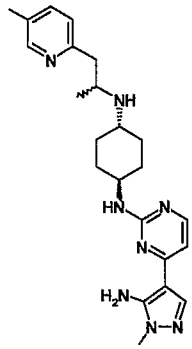
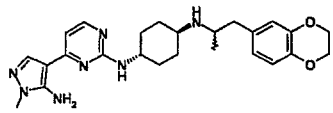
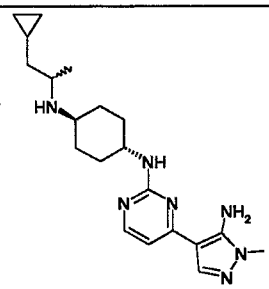
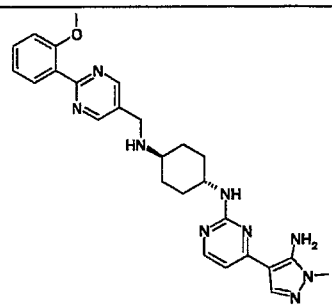
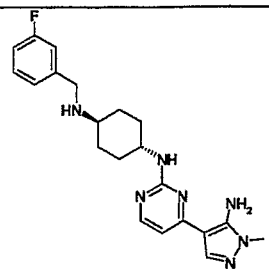
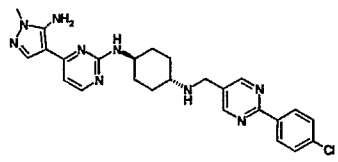
#	Structure	Compound Name	M+1
491		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1-benzofuran-2-ylmethyl)cyclohexane-1,4-diamine	419
492		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[1-methyl-3-(1H-pyrazol-1-yl)propyl]cyclohexane-1,4-diamine	411
493		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(3,4-difluorobenzyl)cyclohexane-1,4-diamine	414
494		5-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-2-hydroxybenzonitrile	420
495		2-(4-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}phenoxy)ethanol	439

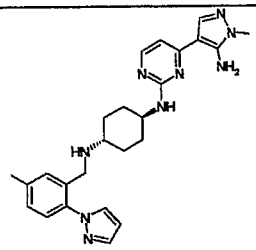
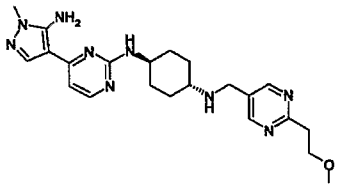
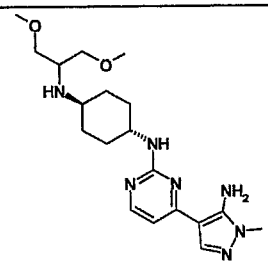
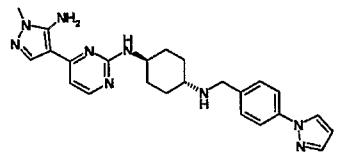
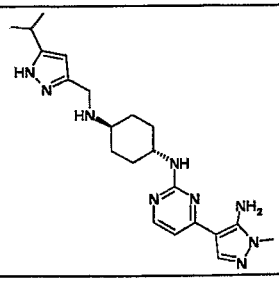
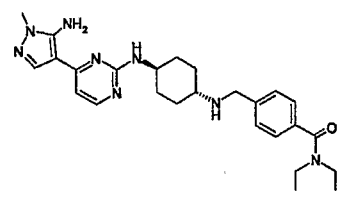
#	Structure	Compound Name	M+1
496		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(6-methylpyridin-2-yl)methyl]cyclohexane-1,4-diamine	394
497		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexane-1,4-diamine	419
498		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(2-fluoro-5-methoxybenzyl)cyclohexane-1,4-diamine	427
499		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1H-indazol-3-ylmethyl)cyclohexane-1,4-diamine	419
500		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[4-(1H-tetrazol-5-yl)benzyl]cyclohexane-1,4-diamine	447
501		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[4-(trifluoromethyl)cyclohexyl]cyclohexane-1,4-diamine	439

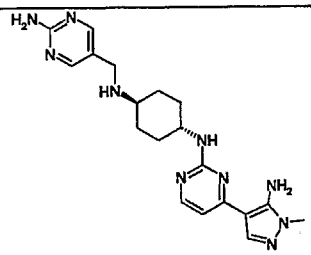
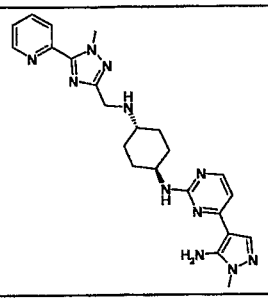
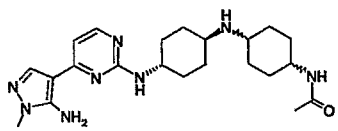
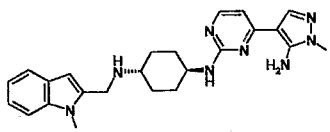
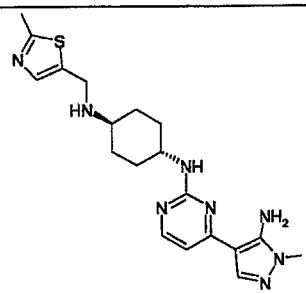
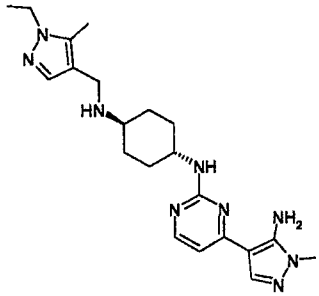
#	Structure	Compound Name	M+1
502		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)cyclohexane-1,4-diamine	421
503		5-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}pyridin-2-ol	395
504		4-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-N-methylbenzenesulfonamide	472
505		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(6-methoxypyridin-3-yl)methyl]cyclohexane-1,4-diamine	410
506		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(2-fluoro-4-methoxybenzyl)cyclohexane-1,4-diamine	427

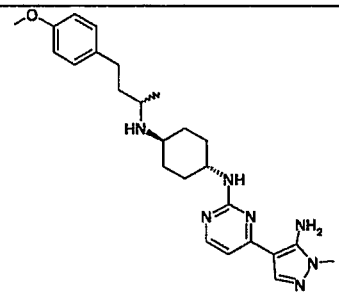
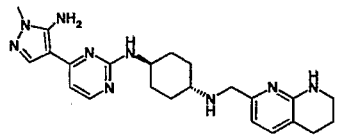
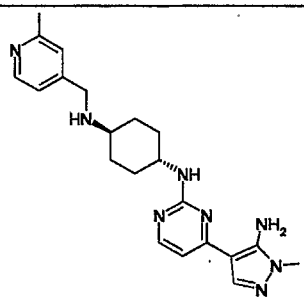
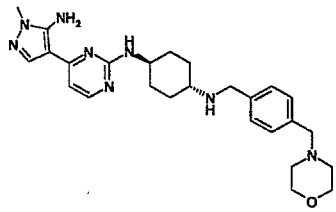
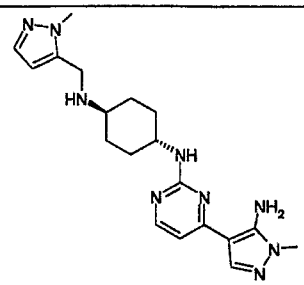
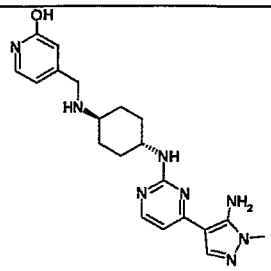
#	Structure	Compound Name	M+1
507		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(3-pyridin-2-ylbenzyl)cyclohexane-1,4-diamine	456
508		2-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}pyridin-3-ol	395
509		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(quinolin-8-ylmethyl)cyclohexane-1,4-diamine	430
510		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(2-ethyl-1H-imidazol-5-yl)methyl]cyclohexane-1,4-diamine	397
511		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[1-(4-fluorophenyl)-1H-pyrazol-4-yl]methyl}cyclohexane-1,4-diamine	463

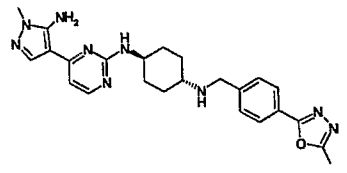
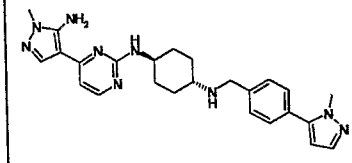
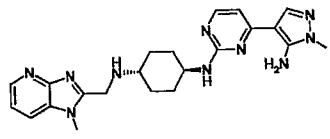
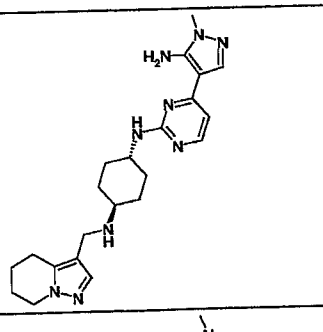
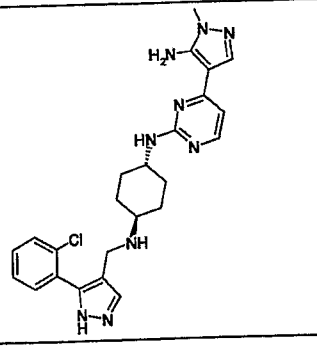
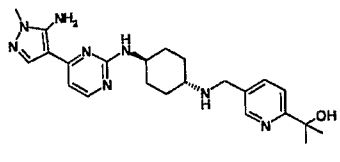
#	Structure	Compound Name	M+1
512		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[1-methyl-2-(3-methylpyridin-2-yl)ethyl]cyclohexane-1,4-diamine	422
513		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[3-(4-fluorophenyl)-1H-pyrazol-4-yl]methyl}cyclohexane-1,4-diamine	463
514		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]cyclohexane-1,4-diamine	397
515		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(6-phenoxypyridin-3-yl)methyl]cyclohexane-1,4-diamine	472
516		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(6-ethoxyquinolin-2-yl)methyl]cyclohexane-1,4-diamine	474

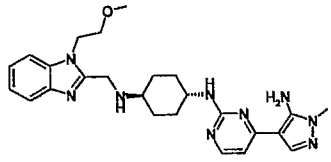
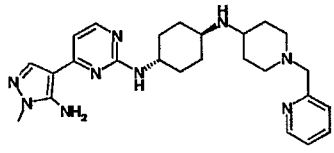
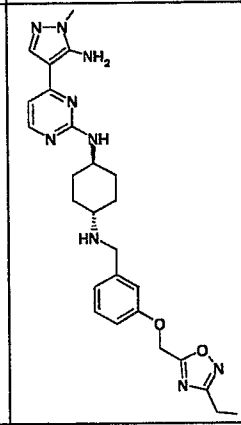
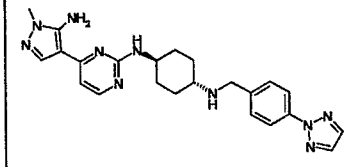
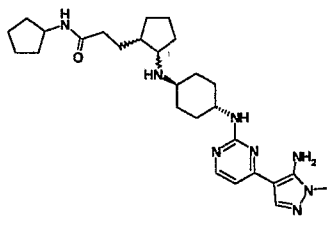
#	Structure	Compound Name	M+1
517		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[1-methyl-2-(5-methylpyridin-2-yl)ethyl]cyclohexane-1,4-diamine	422
518		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-methylethyl]cyclohexane-1,4-diamine	465
519		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(2-cyclopropyl-1-methylethyl)cyclohexane-1,4-diamine	371
520		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[2-(2-methoxyphenyl)pyrimidin-5-yl]methyl}cyclohexane-1,4-diamine	487
521		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(3-fluorobenzyl)cyclohexane-1,4-diamine	396
522		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[2-(4-chlorophenyl)pyrimidin-5-yl]methyl}cyclohexane-1,4-diamine	491

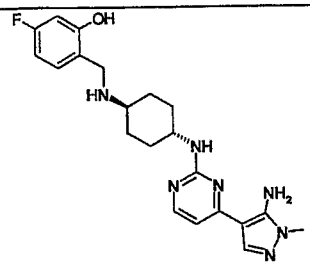
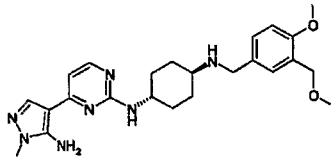
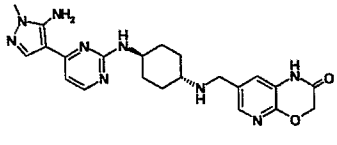
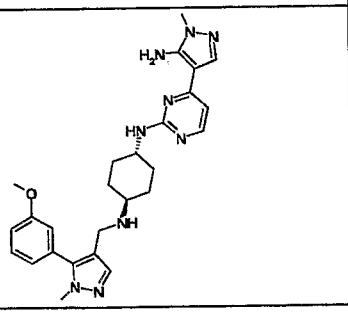
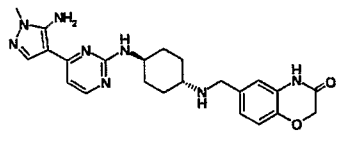
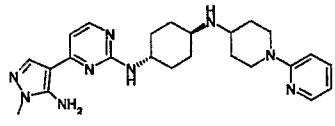
#	Structure	Compound Name	M+1
523		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[5-methyl-2-(1H-pyrazol-1-yl)benzyl]cyclohexane-1,4-diamine	459
524		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[2-(2-methoxyethyl)pyrimidin-5-yl]methyl}cyclohexane-1,4-diamine	439
525		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[2-methoxy-1-(methoxymethyl)ethyl]cyclohexane-1,4-diamine	391
526		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[4-(1H-pyrazol-1-yl)benzyl]cyclohexane-1,4-diamine	445
527		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(5-isopropyl-1H-pyrazol-3-yl)methyl]cyclohexane-1,4-diamine	411
528		4-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-N,N-diethylbenzamide	478

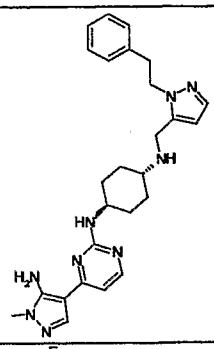
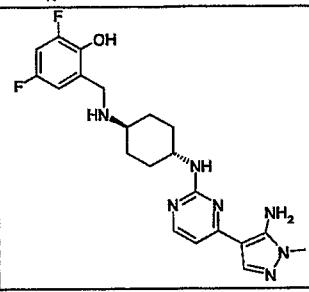
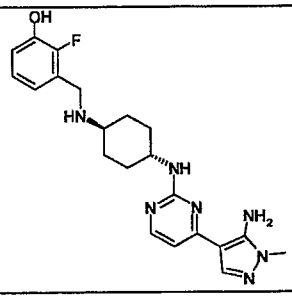
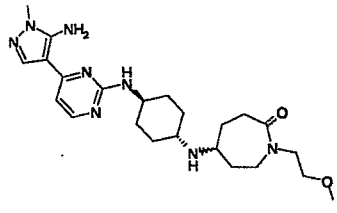
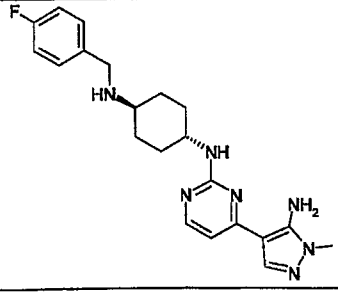
#	Structure	Compound Name	M+1
529		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(2-aminopyrimidin-5-yl)methyl]cyclohexane-1,4-diamine	395
530		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(1-methyl-5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)methyl]cyclohexane-1,4-diamine	461
531		N-{4-[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]cyclohexyl}acetamide	428
532		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(1-methyl-1H-indol-2-yl)methyl]cyclohexane-1,4-diamine	432
533		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(2-methyl-1,3-thiazol-5-yl)methyl]cyclohexane-1,4-diamine	400
534		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(1-ethyl-5-methyl-1H-pyrazol-4-yl)methyl]cyclohexane-1,4-diamine	411

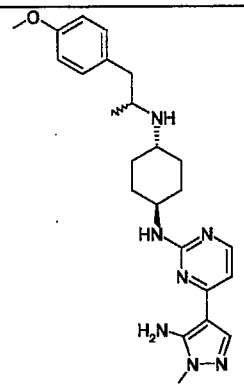
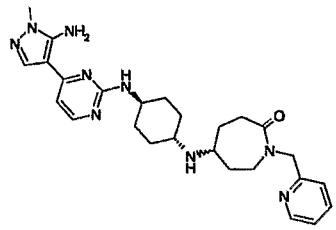
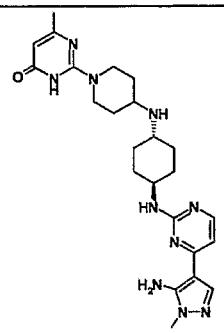
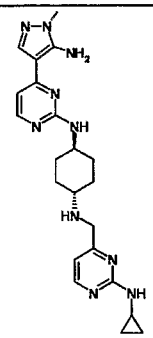
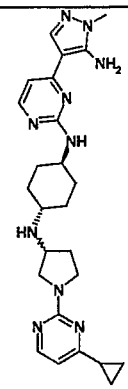
#	Structure	Compound Name	M+1
535		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[3-(4-methoxyphenyl)-1-methylpropyl]cyclohexane-1,4-diamine	451
536		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-ylmethyl)cyclohexane-1,4-diamine	435
537		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(2-methylpyridin-4-yl)methyl]cyclohexane-1,4-diamine	394
538		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[4-(morpholin-4-ylmethyl)benzyl]cyclohexane-1,4-diamine	478
539		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(1-methyl-1H-pyrazol-5-yl)methyl]cyclohexane-1,4-diamine	382
540		4-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}pyridin-2-ol	395

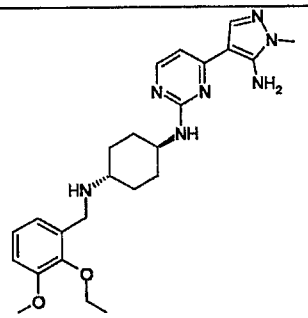
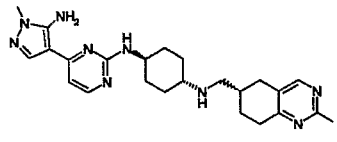
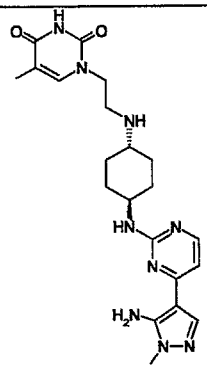
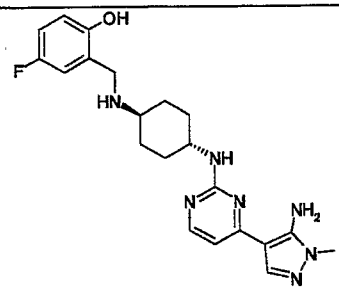
#	Structure	Compound Name	M+1
541		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl]cyclohexane-1,4-diamine	461
542		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[4-(1-methyl-1H-pyrazol-5-yl)benzyl]cyclohexane-1,4-diamine	459
543		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(1-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]cyclohexane-1,4-diamine	434
544		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-ylmethyl)cyclohexane-1,4-diamine	423
545		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[5-(2-chlorophenyl)-1H-pyrazol-4-yl]methyl}cyclohexane-1,4-diamine	479
546		2-(5-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}pyridin-2-yl)propan-2-ol	438

#	Structure	Compound Name	M+1
547		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[1-(2-methoxyethyl)-1H-benzimidazol-2-yl]methyl}cyclohexane-1,4-diamine	477
548		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[1-(pyridin-2-ylmethyl)piperidin-4-yl]cyclohexane-1,4-diamine	463
549		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{3-[(3-ethyl-1,2,4-oxadiazol-5-yl)methoxy]benzyl}cyclohexane-1,4-diamine	505
550		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[4-(2H-1,2,3-triazol-2-yl)benzyl]cyclohexane-1,4-diamine	446
551		3-{2-[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]cyclopentyl}-N-cyclopentylpropanamide	496

#	Structure	Compound Name	M+1
552		2-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-5-fluorophenol	412
553		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[4-methoxy-3-(methoxymethyl)benzyl]cyclohexane-1,4-diamine	453
554		7-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one	451
555		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[5-(3-methoxyphenyl)-1-methyl-1H-pyrazol-4-yl]methyl}cyclohexane-1,4-diamine	489
556		6-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-2H-1,4-benzoxazin-3(4H)-one	450
557		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(1-pyridin-2-ylpiperidin-4-yl)cyclohexane-1,4-diamine	449

#	Structure	Compound Name	M+1
558		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[1-(2-phenylethyl)-1H-pyrazol-5-yl]methyl}cyclohexane-1,4-diamine	473
559		2-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-4,6-difluorophenol	430
560		3-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-2-fluorophenol	412
561		5-[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]-1-(2-methoxyethyl)azepan-2-one	458
562		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(4-fluorobenzyl)cyclohexane-1,4-diamine	396

#	Structure	Compound Name	M+1
563		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[2-(4-methoxyphenyl)-1-methylethyl]cyclohexane-1,4-diamine	437
564		5-[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]-1-(pyridin-2-ylmethyl)azepan-2-one	491
565		2-{4-[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]piperidin-1-yl}-6-methylpyrimidin-4(3H)-one	480
566		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-{[2-(cyclopropylamino)pyrimidin-4-yl]methyl}cyclohexane-1,4-diamine	436
567		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[1-(4-cyclopropylpyrimidin-2-yl)pyrrolidin-3-yl]cyclohexane-1,4-diamine	476

#	Structure	Compound Name	M+1
568		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-(2-ethoxy-3-methoxybenzyl)cyclohexane-1,4-diamine	453
569		trans-N-[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-N'-[(2-methyl-5,6,7,8-tetrahydroquinazolin-6-yl)methyl]cyclohexane-1,4-diamine	449
570		1-{2-[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]ethyl}-5-methylpyrimidine-2,4(1H,3H)-dione	441
571		2-{[(trans-4-{[4-(5-amino-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]amino}cyclohexyl)amino]methyl}-4-fluorophenol	412

Biological activity

The percentage of inhibition (at 1 and 10 μM unless otherwise stated) and/or the Ki (in nM unless otherwise stated) for the compounds exemplified in the present application were obtained according to the protocol below:

% Inhibition and K_i Determination

A coupled spectrophotometric assay, coupling JNK1α1 activity to to the oxidation of β-NADH to NAD+ through the action of of pyruvate kinase (PK) and lactic dehydrogenase (LDH), was used to determine the potency (percent inhibition at 1 or 10 μM or K_i) of compounds against JNK1α1 (Genbank Accession Number: L26318). The final reaction conditions were as follows: 20 mM HEPES pH 7.6, 10 mM $MgCl_2$, 1 mM DTT, 200 μM peptide substrate (KRELVEPLTPSGEAPNQALLR), 300 μM NADH, 500 μM PEP (phophoenolpyruvate), 9-10 units/mL LDH, 8-12 units/mL PK, 40 nM JNK1α1_364nHis (catalytic domain containing amino acids 1-364 and N-terminal hexahistidine tag, previously activated by MKK4 and MKK7beta *in vitro*), 0-100 μM test compound, 2.5% DMSO, and 50 μM ATP (2.5X Km). The reaction was monitored by following the decrease in absorbance at 340 nm. The initial reaction rate was determined by the slope of the change in absorbance. To calculate percent inhibition the rate of the reaction in the presence of 1 or 10 μM compound was compared to the rate of the reaction with only DMSO multiplied by 100 percent. Note, the background rate of the above reaction in the presence of 10 μM PHA-00738186 was subtracted from all rates. To calculate the K_i, the reaction rates (with the background subtracted) were plotted vs. the compound concentration (0-100 μM) and fit to the tight binding for competitive inhibitors (Morrison) equation (see below).

Formula: Y=(-X+Eo-(Ki*(1+A/Km))+((X-
Eo+(Ki*(1+A/Km)))^2+4*Eo*(Ki*(1+A/Km)))^0.5)*(Vm*A/(Km+A)/(2*Eo))

Parameters: Eo, Ki, A, Km, Vo

Y is initial reaction velocity;

X is inhibitor concentration;

A is [ATP];

Ki is inhibition constant;

Vm is Vmax;

Eo is total (initial) enzyme concentration;

Km is ATP Km;

The compounds were prepared in 100% DMSO at a 40X concentration. For percent inhibition experiments this would be 400 or 40 μM for 10 and 1 μM final concentration, respectively. For the Ki determination 3X serial dilutions were made starting at 4 mM (100 μM at 1X) in DMSO. A total of 11 concentrations were used for the analysis. The compounds were added to the reaction plate first. Next, a solution containing the HEPES, $MgCl_2$, DTT, peptide substrate, NADH, PEP, PK/LDH enzyme, and JNK1α1_364nHis enzyme was added to the assay plate. The plate was incubated at room temperature for 15 minutes. Then the plate was warmed to 30 °C for 5 minutes. The reaction was initiated with the addition of ATP. The reaction was run in a plate reader at 30 °C for 20 minutes with absorbance readings made about every 10 seconds.

JNK1a1_364nHis purification procedure

Growth and induction conditions

BL21 (DE3) cells containing JNK1a1_364nHis vector were grown at 37°C until optical density (OD_{600}) was between 0.6 to 0.8. Expression was induced by addition of isopropylthiogalactoside (IPTG) to a

final concentration of 0.1-0.2mM and incubated at 23°C overnight. The cells were harvested at 5000 rpm for 15 minutes at 4°C. The cell pellet can be stored at –80°C for future purification.

Purification procedure

1. Cell pellet (1L culture) was resuspended with lysis buffer at 5-10mL/wet cell pellet. The maximum and minimum volumes were 350 mL and 60 mL.

Lysis Buffer	1L
25mM Tris-HCl, pH8.0	25mL of 1M
300mM NaCl	60mL of 5M
14mM β-ME (add fresh)	1mL of 14M stock
20mM Imidazole	5mL of 4M
dH_2O	909mL

   The lysis buffer was filtered before use.
2. The cell were lyzed with microfluidizer (three times) and ultracentrifuged at 40,000rpm for 45 minutes at 4°C. The supernatant was transferred to a chilled flask. A 20ul aliquot was saved for gel analysis.
3. Ni-NTA column (23mL) lines were rinsed with lysis buffer. The column (23mL) was washed with 160mL of lysis buffer at 5mL/min.
4. The supernatant was loaded onto Ni-NTA column at 4mL/min.
5. The unbound was washed with 160mL of lysis buffer at 5mL/min.
6. The protein was eluted with imidazole gradient (from 20mM to 0.5M). The elution buffer was prepared as follows:

Elution Buffer	250mL
25mM Tris-HCl, pH7.5	6.25mL of 1M
300mM NaCl	15mL of 5M
14mM β-ME (add fresh)	0.25mL of 14M stock
0.5M Imidazole	31.25mL of 4M
dH_2O	197.25mL

   The elution buffer was filtered before use
7. The elution settings were as follows. The record speed was set @1.0 mm/min.

BP	%B	FR	FS
0	0	3	8
200	100	3	8
250	100	3	8

   At the end of the elution the record speed was returned to 0.1 mm/min. Referring to the template above, BP means break point, %B means % buffer grading, FR means flow rate, and FS means fraction size.
8. The peak fractions were pooled. A 40ul aliquot was saved for gel analysis.
9. The sample was concentrated down to 4-6mL with ultrafiltration cell under nitrogen.

10. While sample was being concentrated, the Superdex 200 column was washed with 450mL Superdex buffer at 2 mL/min. The Superdex buffer was prepared as follows:

Superdex buffer	1L
25mM Hepes pH 7.5,	25mL
5% Glycerol	100mL
10mM DTT	1.54g
50mM NaCl	10mL
dH_2O	865mL

To prepare the protein that was used for the assay, Dundee buffer was used for Superdex column. The Dundee buffer was prepared as follows:

Dundee Buffer	1L
50mM Tris Cl pH 7.5,	50mL
270mM Sucrose	92.4g
150mM NaCl	30mL
0.1mM EGTA	1mL
0.1% bMe	1mL
0.03% Brij-35	1mL
1mM Benzamidine	1mL
0.2mM PMSF	1mL
dH_2O	to 1L

11. The concentrated sample was transferred to pre-chilled 1.5mL tubes and spinned at max for 10 minutes in cold room. The supernatant was transferred to 50mL chilled tube.
12. The sample was injected (total volume equals total sample loop volume plus 0.3mL) to pre-washed loop (4-6mL). A 5ul aliquat was saved of the remaining sample for SDS-PAGE (a detergent).
13. The protein was eluted overnight according to the following settings. The record speed was set at 0.2 mm/min.

BP	FR	FS	Injection valve
0	0.5	5	I
20	0.5	5	I
20.1	0.5	5	L
400	0.5	5	L

At the completion of the elution, the record speed was returned to 0.1 mm/min. Referring to the template above, BP means break point, FR means flow rate, FS means fraction size, I means inject, and L means load.

14. The peak fractions were pooled and the pool concentration was measured. The protein was concentrated down to 7-8mg/mL in hepes buffer protein. Aliquots of the protein were placed into chilled 0.5mL tubes at 100ul/tube, which were then snapped frozen in liquid nitrogen and stored at –80°C.

The following procedure to regenerate the Ni-NTA and the Superdex 200 columns was used:

Ni-NTA Column

The Ni-NTA column was washed with 80mL of dH_2O at 5mL/min. Next it was washed with 80mL of 0.1M EDTA, pH8.0 at 5mL/min. The flow was collected through in flask for proper disposal. The column was further washed with 150mL of dH_2O at 5mL/min. and charged with 60mL of 100mM $NiCl_2$ at 5mL/min. The flow was collected through in the same waste flask. The column was then washed with 60mL of dH_2O at 5mL/min and the flow was again collected through in the same waste flask. The column was then washed with 160mL of dH_2O at 5mL/min.

Superdex 200 Column

The Superdex 200 column was washed with 700mL of filtered dH_2O at 2 mL/min.

The data obtained from the compounds of the invention according to the above protocol are tabulated below. The column with "#" heading refers to compound number as exemplified in the Examples section. The column with "Ki" heading refers to Ki (in nM). The column with "% Inhibition" heading refers to percent inhibition at 1 μM (in %).

#	*JNK1 Ki*	*% Inhibition JNK-1*	*% Inhibition JNK-2 Ki*	*% Inhibition JNK-3 Ki*
1	7	ND	40	ND
2	14	ND	20	ND
3	83	ND	126	ND
4	21	ND	34	ND
5	125	ND	376	ND
6	84	ND	179	ND
7	336	ND	597	ND
8	48	ND	153	ND
9	1050	ND	ND	ND
10	758	ND	ND	ND
11	110	ND	ND	ND
12	324	ND	ND	ND
13	920	ND	ND	ND
14	25	ND	40	15
15	2720	ND	ND	ND
16	76	ND	ND	ND
17	3870	ND	ND	ND
18	503	ND	ND	ND
19	672	ND	ND	ND
20	94	ND	ND	ND
21	762	ND	ND	ND
22	1400	ND	ND	ND
23	2820	ND	ND	ND
24	72	ND	ND	ND
25	134	ND	ND	ND
26	269	ND	ND	ND
27	270	ND	ND	ND
28	336	ND	ND	ND
29	378	ND	ND	ND

#	*JNK1 Ki*	*% Inhibition JNK-1*	*% Inhibition JNK-2 Ki*	*% Inhibition JNK-3 Ki*
30	398	ND	ND	ND
31	415	ND	ND	ND
32	512	ND	ND	ND
33	568	ND	ND	ND
34	586	ND	ND	ND
35	857	ND	ND	ND
36	899	ND	ND	ND
37	982	ND	ND	ND
38	1020	ND	ND	ND
39	1350	ND	ND	ND
40	1350	ND	ND	ND
41	1400	ND	ND	ND
42	1530	ND	ND	ND
43	1590	ND	ND	ND
44	1640	ND	ND	ND
45	1860	ND	ND	ND
46	2170	ND	ND	ND
47	2230	ND	ND	ND
48	2450	ND	ND	ND
49	2450	ND	ND	ND
50	2710	ND	ND	ND
51	2740	ND	ND	ND
52	2840	ND	ND	ND
53	2850	ND	ND	ND
54	3100	ND	ND	ND
55	3480	ND	ND	ND
56	3550	ND	ND	ND
57	3650	ND	ND	ND
58	6000	ND	ND	ND
59	6610	ND	ND	ND
60	8090	ND	ND	ND
61	ND	2%@1uM	ND	ND
62	ND	13%@1uM	ND	ND
63	ND	6%@1uM	ND	ND
64	ND	17%@10uM	ND	ND
65	ND	9%@1uM	ND	ND
66	ND	49%@10uM	ND	ND
67	ND	34%@10uM	ND	ND
68	ND	21%@10uM	ND	ND
69	ND	2%@10uM	ND	ND
70	ND	43%@10 uM	ND	ND
71	ND	17%@1 uM	ND	ND
72	ND	16%@1 uM	ND	ND
73	ND	2%@1uM	ND	ND
74	ND	11%@10uM	ND	ND
75	ND	15%@1 uM	ND	ND
76	ND	10%@1uM	ND	ND
77	ND	12%@1uM	ND	ND
78	ND	25%@10uM	ND	ND

#	JNK1 Ki	% Inhibition JNK-1	% Inhibition JNK-2 Ki	% Inhibition JNK-3 Ki
79	ND	31%@10uM	ND	ND
80	ND	16%@1uM	ND	ND
81	ND	18%@1uM	ND	ND
82	ND	19%@10uM	ND	ND
83	ND	34%@10uM	ND	ND
84	ND	25%@10uM	ND	ND
85	ND	49%@10uM	ND	ND
86	ND	33%@10uM	ND	ND
87	ND	43%@10uM	ND	ND
88	ND	10%@1uM	ND	ND
89	ND	1%@10uM	ND	ND
90	ND	22%@1uM	ND	ND
91	ND	20%@10uM	ND	ND
92	ND	3%@1uM	ND	ND
93	ND	37%@10uM	ND	ND
94	ND	17%@1uM	ND	ND
95	ND	17%@10uM	ND	ND
96	ND	6%@1uM	ND	ND
97	ND	36%@10uM	ND	ND
98	ND	12%@1uM	ND	ND
99	ND	11%@1uM	ND	ND
100	ND	13%@10uM	ND	ND
101	ND	37%@10uM	ND	ND
102	ND	29%@10uM	ND	ND
103	ND	23%@10uM	ND	ND
104	ND	29%@10uM	ND	ND
105	ND	7%@1uM	ND	ND
106	ND	11%@10uM	ND	ND
107	593	ND	ND	ND
108	ND	11%@10 uM	>10000	ND
109	ND	21%@10uM	ND	ND
110	11	ND	44	ND
111	55	ND	82	ND
112	10.8	ND	45	ND
113	215	ND	933	ND
114	97	ND	386	ND
115	283	ND	59	ND
116	139	ND	443	ND
117	346	ND	ND	ND
118	338	ND	152	ND
119	537	ND	ND	ND
120	106	ND	319	ND
121	110	ND	ND	ND
122	69	ND	557	ND
123	132	ND	ND	ND
124	141	ND	376	ND
125	30	ND	ND	ND
126	4320	ND	ND	ND
127	235	ND	ND	ND

#	*JNK1 Ki*	*% Inhibition JNK-1*	*% Inhibition JNK-2 Ki*	*% Inhibition JNK-3 Ki*
128	98	ND	182	140
129	542	ND	ND	ND
130	342	ND	ND	ND
131	831	ND	ND	ND
132	67	ND	138	81
133	42	ND	ND	ND
134	33	ND	29	24
135	19	ND	ND	ND
136	24	ND	29	18
137	65	ND	91	40
138	62	ND	62	37
139	30	ND	47	29
140	10	ND	ND	18
141	4	ND	ND	ND
142	2	ND	ND	ND
143	1000	ND	ND	ND
144	641	ND	ND	ND
145	4500	ND	ND	ND
146	9800	ND	ND	ND
147	848	ND	ND	ND
148	233	ND	ND	ND
149	298	ND	ND	ND
150	113	ND	268	159
151	255	ND	ND	ND
152	6	ND	8	7
153	4	ND	ND	ND
154	10	ND	ND	ND
155	24	ND	ND	ND
156	10	ND	ND	ND
157	6	ND	ND	ND
158	6	ND	ND	ND
159	7	ND	ND	ND
160	16	ND	ND	ND
161	8	ND	ND	ND
162	10	ND	ND	ND
163	10	ND	ND	ND
164	16	ND	ND	ND
165	10	ND	ND	ND
166	10	ND	ND	ND
167	11	ND	ND	ND
168	12	ND	ND	ND
169	12	ND	ND	ND
170	12	ND	ND	ND
171	13	ND	ND	ND
172	13	ND	ND	ND
173	14	ND	ND	ND
174	15	ND	ND	ND
175	15	ND	ND	ND
176	16	ND	ND	ND

#	JNK1 Ki	% Inhibition JNK-1	% Inhibition JNK-2 Ki	% Inhibition JNK-3 Ki
177	16	ND	ND	ND
178	16	ND	ND	ND
179	16	ND	ND	ND
180	17	ND	ND	ND
181	17	ND	ND	ND
182	20	ND	ND	ND
183	20	ND	ND	ND
184	20	ND	ND	ND
185	20	ND	ND	ND
186	21	ND	ND	ND
187	22	ND	ND	ND
188	22	ND	ND	ND
189	23	ND	ND	ND
190	24	ND	ND	ND
191	24	ND	ND	ND
192	28	ND	20	9
193	40	ND	50	22
194	46	ND	44	14
195	51	ND	22	9
196	52	ND	28	11
197	707	ND	ND	ND
198	ND	39%@0.1uM	ND	ND
199	ND	31%@0.1uM	ND	ND
200	ND	43%@0.1uM	ND	ND
201	ND	33%@0.1uM	ND	ND
202	ND	32%@0.1uM	ND	ND
203	185	ND	ND	ND
204	47	ND	ND	ND
205	16	ND	ND	ND
206	28	ND	55	ND
207	87	ND	ND	ND
208	8	ND	ND	ND
209	10	ND	ND	ND
210	16	ND	ND	ND
211	20	ND	ND	ND
212	9	ND	ND	ND
213	43	ND	ND	ND
214	15	ND	ND	ND
215	41	ND	52	17
216	16	ND	ND	ND
217	18	ND	ND	ND
218	36	ND	53	11
219	21	ND	ND	ND
220	21	ND	ND	ND
221	22	ND	ND	ND
222	22	ND	ND	ND
223	33	ND	38	11
224	22	ND	43	11

#	JNK1 Ki	% Inhibition JNK-1	% Inhibition JNK-2 Ki	% Inhibition JNK-3 Ki
225	26	ND	ND	ND
226	28	ND	ND	ND
227	29	ND	ND	ND
228	32	ND	47	24
229	33	ND	ND	ND
230	45	ND	133	23
231	46	ND	ND	ND
232	49	ND	99	25
233	49	ND	62	24
234	52	ND	54	19
235	56	ND	76	31
236	63	ND	ND	ND
237	70	ND	ND	ND
238	76	ND	236	136
239	77	ND	141	50
240	89	ND	81	30
241	91	ND	184	55
242	200	ND	169	56
243	ND	14%@0.1uM	ND	ND
244	ND	35%@0.1uM	ND	ND
245	ND	32%@1uM	ND	ND
246	ND	34%@1uM	ND	ND
247	ND	43%@0.1uM	ND	ND
248	ND	28%@0.1uM	ND	ND
249	ND	23%@0.1uM	ND	ND
250	ND	45%@0.1uM	ND	ND
251	ND	27%@0.1uM	ND	ND
252	ND	22%@0.1uM	ND	ND
253	ND	32%@0.1uM	ND	ND
254	ND	42%@0.1uM	ND	ND
255	ND	49%@0.1uM	ND	ND
256	ND	38%@0.1uM	ND	ND
257	ND	36%@0.1uM	ND	ND
258	ND	35%@0.1uM	ND	ND
259	ND	24%@0.1uM	ND	ND
260	ND	44%@0.1uM	ND	ND
261	ND	31%@0.1uM	ND	ND
262	ND	44%@0.1uM	ND	ND
263	ND	22%@0.1uM	ND	ND
264	ND	12%@0.1uM	ND	ND
265	ND	27%@0.1uM	ND	ND
266	ND	49%@0.1uM	ND	ND
267	ND	37%@0.1uM	ND	ND
268	ND	67%@1uM	ND	ND
269	ND	48%@0.1uM	ND	ND
270	ND	30%@0.1uM	ND	ND
271	ND	14%@0.1uM	ND	ND
272	ND	32%@0.1uM	ND	ND
273	102	ND	ND	ND

#	JNK1 Ki	% Inhibition JNK-1	% Inhibition JNK-2 Ki	% Inhibition JNK-3 Ki
274	116	ND	ND	ND
275	82	ND	215	ND
276	30	ND	91	ND
277	66	ND	67	46
278	65	ND	59	46
279	1340	ND	ND	ND
280	28	ND	ND	ND
281	11	ND	ND	ND
282	82	ND	ND	ND
283	111	ND	ND	ND
284	99	ND	ND	ND
285	36	ND	ND	ND
286	19	ND	ND	ND
287	27	ND	61	44
288	13	ND	ND	ND
289	170	ND	ND	ND
290	30	ND	ND	ND
291	51	ND	ND	ND
292	6	ND	32	14
293	20	ND	ND	ND
294	2	ND	3	4
295	2	ND	6	3
296	24	ND	55	ND
297	24	ND	34	27
298	22	ND	24	17
299	16	ND	160	14
300	18	ND	33	19
301	68	ND	87	41
302	32	ND	ND	ND
303	22	ND	ND	ND
304	620	ND	ND	ND
305	143	ND	ND	ND
306	24	ND	ND	ND
307	69	ND	ND	ND
308	31	ND	ND	ND
309	27	ND	ND	ND
310	3	ND	6	5
311	3	ND	8	5
312	15	ND	ND	ND
313	76	ND	137	ND
314	2090	ND	4990	ND
315	3790	ND	9470	ND
316	60	ND	272	ND
317	107	ND	231	ND
318	165	ND	537	ND
319	63	ND	100	ND
320	16	ND	68	ND
321	4060	ND	ND	ND
322	15	ND	63	ND

#	JNK1 Ki	% Inhibition JNK-1	% Inhibition JNK-2 Ki	% Inhibition JNK-3 Ki
323	25	ND	ND	ND
324	65	ND	192	ND
325	43	ND	152	ND
326	9	ND	ND	ND
327	650	ND	ND	ND
328	294	ND	ND	ND
329	488	ND	ND	ND
330	162	ND	ND	ND
331	1300	ND	ND	ND
332	205	ND	ND	ND
333	106	ND	ND	ND
334	99	ND	ND	ND
335	155	ND	ND	ND
336	37	ND	ND	ND
337	388	ND	619	455
338	149	ND	ND	ND
339	38	ND	ND	ND
340	105	ND	234	182
341	720	ND	1470	ND
342	274	ND	>4000	ND
343	411	ND	885	ND
344	310	ND	499	ND
345	2450	ND	ND	ND
346	4640	ND	ND	ND
347	4770	ND	ND	ND
348	3540	ND	ND	ND
349	4440	ND	ND	ND
350	ND	65.5%@0.1uM	ND	ND
351	ND	72.5%@0.1uM	ND	ND
352	ND	50.2%@0.1uM	ND	ND
353	ND	43%@0.1uM	ND	ND
354	ND	35.7%@0.1uM	ND	ND
355	ND	54.9%@0.1uM	ND	ND
356	ND	74.5%@0.1uM	ND	ND
357	ND	48.6%@0.1uM	ND	ND
358	ND	60%@0.1uM	ND	ND
359	ND	55.9%@0.1uM	ND	ND
360	ND	82%@0.1uM	ND	ND
361	ND	94.4%@0.1uM	ND	ND
362	ND	61.1%@0.1uM	ND	ND
363	ND	33.4%@0.1uM	ND	ND
364	ND	76.7%@0.1uM	ND	ND
365	ND	91.5%@0.1uM	ND	ND
366	ND	63.6%@0.1uM	ND	ND
367	ND	80.7%@0.1uM	ND	ND
368	ND	67.5%@0.1uM	ND	ND
369	ND	52.3%@0.1uM	ND	ND
370	ND	67.4%@0.1uM	ND	ND
371	ND	56.7%@0.1uM	ND	ND

#	JNK1 Ki	% Inhibition JNK-1	% Inhibition JNK-2 Ki	% Inhibition JNK-3 Ki
372	ND	54.7%@0.1uM	ND	ND
373	ND	57.8%@0.1uM	ND	ND
374	ND	41.1%@0.1uM	ND	ND
375	ND	45.5%@0.1uM	ND	ND
376	ND	43.3%@0.1uM	ND	ND
377	ND	71.8%@0.1uM	ND	ND
378	ND	62.1%@0.1uM	ND	ND
379	ND	62.3%@0.1uM	ND	ND
380	ND	ND	ND	ND
381	ND	49.1%@0.1uM	ND	ND
382	ND	ND	ND	ND
383	ND	49.9%@0.1uM	ND	ND
384	ND	59.8%@0.1uM	ND	ND
385	ND	52%@0.1uM	ND	ND
386	ND	88.7%@0.1uM	ND	ND
387	ND	74.6%@0.1uM	ND	ND
388	ND	78.7%@0.1uM	ND	ND
389	ND	82.4%@0.1uM	ND	ND
390	ND	83.1%@0.1uM	ND	ND
391	ND	31.7%@0.1uM	ND	ND
392	ND	61%@1uM	ND	ND
393	ND	88.1%@0.1uM	ND	ND
394	ND	61.8%@0.1uM	ND	ND
395	ND	24.7%@0.1uM	ND	ND
396	ND	28.9%@0.1uM	ND	ND
397	ND	60.9%@0.1uM	ND	ND
398	ND	80.7%@0.1uM	ND	ND
399	ND	45.7%@0.1uM	ND	ND
400	ND	49.6%@0.1uM	ND	ND
401	ND	79.7%@0.1uM	ND	ND
402	ND	47.6%@0.1uM	ND	ND
403	ND	50.2%@0.1uM	ND	ND
404	ND	54.5%@0.1uM	ND	ND
405	ND	66.6%@0.1uM	ND	ND
406	ND	74.8%@0.1uM	ND	ND
407	ND	61%@0.1uM	ND	ND
408	ND	55%@0.1uM	ND	ND
409	ND	75.3%@0.1uM	ND	ND
410	ND	46.8%@0.1uM	ND	ND
411	ND	57.6%@0.1uM	ND	ND
412	ND	38.6%@0.1uM	ND	ND
413	ND	47.7%@0.1uM	ND	ND
414	ND	60.3%@0.1uM	ND	ND
415	ND	80.1%@0.1uM	ND	ND
416	ND	71.4%@0.1uM	ND	ND
417	ND	11.3%@0.1uM	ND	ND
418	ND	6.79%@0.1uM	ND	ND
419	ND	85.9%@0.1uM	ND	ND
420	ND	72.1%@0.1uM	ND	ND

#	JNK1 Ki	% Inhibition JNK-1	% Inhibition JNK-2 Ki	% Inhibition JNK-3 Ki
421	ND	51.5%@0.1uM	ND	ND
422	ND	61.8%@0.1uM	ND	ND
423	ND	83.7%@0.1uM	ND	ND
424	ND	86.9%@0.1uM	ND	ND
425	ND	83.3%@0.1uM	ND	ND
426	ND	60.5%@0.1uM	ND	ND
427	ND	61.3%@0.1uM	ND	ND
428	ND	40.4%@0.1uM	ND	ND
429	ND	26.5%@0.1uM	ND	ND
430	ND	71.3%@0.1uM	ND	ND
431	ND	55.5%@0.1uM	ND	ND
432	ND	51.4%@0.1uM	ND	ND
433	ND	55.4%@0.1uM	ND	ND
434	ND	40.3%@0.1uM	ND	ND
435	ND	59.5%@0.1uM	ND	ND
436	ND	54%@0.1uM	ND	ND
437	ND	84.3%@0.1uM	ND	ND
438	ND	83%@0.1uM	ND	ND
439	ND	76.1%@0.1uM	ND	ND
440	ND	57.3%@0.1uM	ND	ND
441	ND	74.4%@0.1uM	ND	ND
442	ND	45.2%@0.1uM	ND	ND
443	ND	60%@0.1uM	ND	ND
444	ND	86.6%@0.1uM	ND	ND
445	ND	54.6%@0.1uM	ND	ND
446	ND	78.4%@0.1uM	ND	ND
447	ND	54.1%@0.1uM	ND	ND
448	ND	61.2%@0.1uM	ND	ND
449	ND	40.4%@0.1uM	ND	ND
450	ND	71.6%@0.1uM	ND	ND
451	ND	53.8%@0.1uM	ND	ND
452	ND	35.5%@0.1uM	ND	ND
453	ND	36.9%@0.1uM	ND	ND
454	ND	54%@0.1uM	ND	ND
455	ND	53%@0.1uM	ND	ND
456	ND	65.6%@0.1uM	ND	ND
457	ND	58.5%@0.1uM	ND	ND
458	ND	42.1%@0.1uM	ND	ND
459	60	ND	ND	ND
460	84	ND	ND	ND
461	120	ND	ND	ND
462	132	ND	ND	ND
463	136	ND	ND	ND
464	145	ND	ND	ND
465	146	ND	ND	ND
466	170	ND	ND	ND
467	177	ND	ND	ND
468	234	ND	ND	ND
469	ND	64%@1uM	ND	ND

#	JNK1 Ki	% Inhibition JNK-1	% Inhibition JNK-2 Ki	% Inhibition JNK-3 Ki
470	ND	57%@1uM	ND	ND
471	ND	52%@1uM	ND	ND
472	ND	55%@1uM	ND	ND
473	ND	29%@1uM	ND	ND
474	ND	68%@1uM	ND	ND
475	ND	60%@1uM	ND	ND
476	ND	60%@1uM	ND	ND
477	ND	55%@1uM	ND	ND
478	ND	60%@1uM	ND	ND
479	ND	28%@1uM	ND	ND
480	ND	55%@1uM	ND	ND
481	ND	52%@1uM	ND	ND
482	ND	63%@1uM	ND	ND
483	ND	59%@1uM	ND	ND
484	ND	40%@0.1uM	ND	ND
485	ND	57%@1uM	ND	ND
486	ND	79%21uM	ND	ND
487	ND	71%@1uM	ND	ND
488	ND	72%@1uM	ND	ND
489	ND	66%@1uM	ND	ND
490	ND	30%@0.1uM	ND	ND
491	ND	73%@1uM	ND	ND
492	ND	33%@1uM	ND	ND
493	ND	58%@1uM	ND	ND
494	ND	65%@1uM	ND	ND
495	ND	65%@1uM	ND	ND
496	ND	62%@1uM	ND	ND
497	ND	51%@1uM	ND	ND
498	ND	66%@1uM	ND	ND
499	ND	74%@1uM	ND	ND
500	ND	68%@1uM	ND	ND
501	ND	48%@1uM	ND	ND
502	ND	62%@1uM	ND	ND
503	ND	53%@1uM	ND	ND
504	ND	41%@0.1uM	ND	ND
505	ND	55%@1uM	ND	ND
506	ND	58%@1uM	ND	ND
507	ND	41%@0.1uM	ND	ND
508	ND	64%@1uM	ND	ND
509	ND	65%@1uM	ND	ND
510	ND	48%@1uM	ND	ND
511	ND	69%@1uM	ND	ND
512	ND	55%@1uM	ND	ND
513	ND	83%@1uM	ND	ND
514	ND	61%@1uM	ND	ND
515	ND	72%@1uM	ND	ND
516	ND	76%@1uM	ND	ND
517	ND	50%@1uM	ND	ND
518	ND	59%@1uM	ND	ND

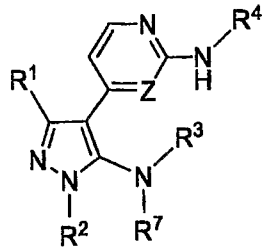
#	*JNK1 Ki*	*% Inhibition JNK-1*	*% Inhibition JNK-2 Ki*	*% Inhibition JNK-3 Ki*
519	ND	34%@1uM	ND	ND
520	ND	78%@1uM	ND	ND
521	ND	61%@1uM	ND	ND
522	ND	30%@0.1uM	ND	ND
523	ND	63%@1uM	ND	ND
524	ND	59%@1uM	ND	ND
525	ND	29%@1uM	ND	ND
526	ND	56%@1uM	ND	ND
527	ND	23%@1uM	ND	ND
528	ND	58%@1uM	ND	ND
529	ND	54%@1uM	ND	ND
530	ND	55%@1uM	ND	ND
531	ND	22%@1uM	ND	ND
532	ND	43%@1uM	ND	ND
533	ND	44%@1uM	ND	ND
534	ND	37%@1uM	ND	ND
535	ND	43%@1uM	ND	ND
536	ND	69%@1uM	ND	ND
537	ND	52%@1uM	ND	ND
538	ND	48%@1uM	ND	ND
539	ND	61%@1uM	ND	ND
540	ND	52%@1uM	ND	ND
541	ND	69%@1uM	ND	ND
542	ND	51%@1uM	ND	ND
543	ND	64%@1uM	ND	ND
544	ND	34%@1uM	ND	ND
545	ND	63%@1uM	ND	ND
546	ND	46%@1uM	ND	ND
547	ND	69%@1uM	ND	ND
548	ND	34%@1uM	ND	ND
549	ND	69%@1uM	ND	ND
550	ND	14%@0.1uM	ND	ND
551	ND	53%@1uM	ND	ND
552	ND	61%@1uM	ND	ND
553	ND	46%@1uM	ND	ND
554	ND	54%@1uM	ND	ND
555	ND	56%@1uM	ND	ND
556	ND	32%@1uM	ND	ND
557	ND	44%@1uM	ND	ND
558	ND	65%@1uM	ND	ND
559	ND	57%@1uM	ND	ND
560	ND	56%@1uM	ND	ND
561	ND	24%@1uM	ND	ND
562	ND	55%@1uM	ND	ND
563	ND	45%@1uM	ND	ND
564	ND	32%@1uM	ND	ND
565	ND	26%@1uM	ND	ND
566	ND	67%@1uM	ND	ND
567	ND	55%@1uM	ND	ND

#	*JNK1 Ki*	*% Inhibition JNK-1*	*% Inhibition JNK-2 Ki*	*% Inhibition JNK-3 Ki*
568	ND	35%@1uM	ND	ND
569	ND	61%@1uM	ND	ND
570	ND	81%@1uM	ND	ND
571	ND	60%@1uM	ND	ND

Various embodiments of the present invention have been described above but a person skilled in the art realizes further minor alterations that would fall into the scope of the present invention. The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.

We Claim:

1. A compound of formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

-Z- is -C- or -N-;

R^1 is H or halo;

R^2 is H, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$amino$(CR^5R^6)_v$, $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

R^3 is H, $(C_1\text{-}C_6)$alkyl, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$amino$(CR^5R^6)_v$, $-(C{=}O)\text{-}O\text{-}R^5$, $-(C{=}O)\text{-}NR^5R^6$, $-S(O)_kNR^5R^6$, $-S(O)_j(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10}$aryl), $-(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_q(C{=}O)(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, $-(CR^5R^6)_q(C{=}O)(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_qS(O)_j(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v$(4-12)-membered heterocyclyl;

Or optionally, R^2 together with the –N- to which R^3 and R^7 are attached to form a ring A, which is a (5-8)-membered heterocyclyl;

Provided that when R^2 together with the –N- to which R^3 and R^7 are attached to said ring A (5-8)-membered heterocyclyl, R^7 is a bond, and R^3 may be absent;

Or optionally, R^3 together with R^7 and the –C- to which R^3 and R^7 are attached to form a ring B, which is a (3-8)-membered heterocyclyl;

R^4 is $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

each of R^5 and R^6 are independently selected from H, $(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6\text{-}C_{10})$aryl, and $-(CR^8R^9)_p$(4-12)-membered heterocyclyl;

R^7 is H or $(C_1\text{-}C_6)$alkyl;

any carbon atoms of said ring A, ring B, and the $(C_1\text{-}C_6)$alkyl, the (3-10)-membered cycloalkyl, the $(C_6\text{-}C_{10})$aryl and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^3, R^4, R^5, and R^6 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, R^{9a}, $-(CR^8R^9)_q\text{-}(C{=}O)\text{-}R^8$, $-(CR^8R^9)_q\text{-}(C{=}O)\text{-}R^{9a}$, $-(CR^8R^9)_q\text{-}(C{=}O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_q\text{-}(C{=}O)\text{-}O\text{-}R^{9a}$, $-O\text{-}(C{=}O)\text{-}R^8$, $-O\text{-}(C{=}O)\text{-}R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C{=}O)\text{-}R^9$, $-NR^8\text{-}(CR^8R^9)_q(C{=}O)R^{9a}$, $-NR^8\text{-}(CR^8R^9)_q(C{=}O)\text{-}O(C_1\text{-}C_6)$alkyl,

$-NR^8-(CR^8R^9)_q(C=O)-OR^9$, $-NR^8-(C=O)NR^8R^9$, $-NR^8-(C=O)NR^8R^{9a}$, $-NR^8-(C=O)-(C=O)-NR^8R^9$, $-NR^8-(C=O)-(C=O)-NR^8R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)-NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{9a}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8-S(O)_k(C_1-C_6)$alkyl, $-NR^8-S(O)_kR^{9a}$, $-NR^8-S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any carbon atoms of each of the foregoing R^{10} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O-CF_3$, $-O-CHF_2$, $-O-CH_2F$, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{14}, $-O-R^{14}$, $-(C=O)-R^8$, $-(C=O)-R^{14}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-O-R^{14}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{14}$, $-NR^8(C=O)-R^9$, $-NR^8(C=O)-R^{14}$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, $-NR^8OR^{14}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{14}$, $NR^8-S(O)_k(C_1-C_6)$alkyl, $NR^{14}-S(O)_k(C_1-C_6)$alkyl, and $-NR^8-S(O)_kR^{14}$;

any nitrogen atoms of said ring A, ring B, and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{10}, R^{11} and R^{14} are optionally substituted with R^{12} substituents each independently selected from (C_1-C_6)alkyl, $-(C=O)-R^8$, $-(C=O)-R^{14a}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14a}$, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14a}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6-C_{10}$aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(C=O)-R^8$, $-(C=O)-O-(C_1-C_6)$alkyl, $-O-(C=O)-R^8$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, and $-NR^8-S(O)_k(C_1-C_6)$alkyl;

each R^8 and R^9 are independently H or (C_1-C_6)alkyl;

each R^{9a}, R^{14}, and R^{14a} are independently $-(CR^8R^9)_v$(3-10)-membered cycloalkyl, $-(CR^8R^9)_v(C_6-C_{10})$aryl, or $-(CR^8R^9)_v$(4-12)-membered heterocyclyl;

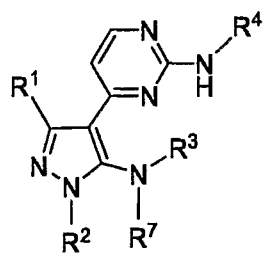
p, q, and v are each independently 0, 1, 2, 3, 4, or 5;

n and j are each independently 0, 1, or 2;

w is 0, 1, 2, or 3, and

k is 1 or 2.

2. A compound of formula (Ia):



(Ia);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or halo;

R^2 is H, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, (C_1-C_6)alkoxy, (C_1-C_6)amino$(CR^5R^6)_v$, (C_1-C_6)alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

R^3 is H, (C_1-C_6)alkyl, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, (C_1-C_6)alkoxy, (C_1-C_6)amino$(CR^5R^6)_v$, $-(C=O)-O-R^5$, $-(C=O)-NR^5R^6$, $-S(O)_kNR^5R^6$, $-S(O)_j(C_1-C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10}$aryl), $-(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_q(C=O)(C_1-C_6)$alkyl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v(C_6-C_{10})$aryl, $-(CR^5R^6)_q(C=O)(CR^5R^6)_v$(4-12)-membered heterocyclyl, $-(CR^5R^6)_qS(O)_j(C_1-C_6)$alkyl, $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_qS(O)_j(CR^5R^6)_v$(4-12)-membered heterocyclyl;

R^4 is (C_1-C_6)alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6-C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

each of R^5 and R^6 are independently selected from H, (C_1-C_6)alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6-C_{10})$aryl, and $-(CR^8R^9)_p$(4-12)-membered heterocyclyl;

R^7 is H or (C_1-C_6)alkyl;

any carbon atoms of the (C_1-C_6)alkyl, the (3-10)-membered cycloalkyl, the (C_6-C_{10})aryl and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^3, R^4, R^5, and R^6 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, $-(CR^8R^9)_q-(C=O)-R^8$, $-(CR^8R^9)_q-(C=O)-R^{9a}$, $-(CR^8R^9)_q-(C=O)-O-(C_1-C_6)$alkyl, $-(CR^8R^9)_q-(C=O)-O-R^{9a}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-R^9$, $-NR^8-(CR^8R^9)_q(C=O)R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-O(C_1-C_6)$alkyl, $-NR^8-(CR^8R^9)_q(C=O)-OR^9$, $-NR^8-(C=O)NR^8R^9$, $-NR^8-(C=O)NR^8R^{9a}$, $-NR^8-(C=O)-(C=O)-NR^8R^9$, $-NR^8-(C=O)-(C=O)-NR^8R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)-NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_k$ NR^8R^{9a}, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8-S(O)_k(C_1-C_6)$alkyl, $-NR^8-S(O)_kR^{9a}$, $-NR^8-S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any carbon atoms of each of the foregoing R^{10} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O-CF_3$, $-O-CHF_2$, $-O-CH_2F$, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{14}, $-O-R^{14}$, $-(C=O)-R^8$, $-(C=O)-R^{14}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-O-R^{14}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{14}$, $-NR^8(C=O)-R^9$, $-NR^8(C=O)-R^{14}$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, $-NR^8OR^{14}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{14}$, $NR^8-S(O)_k(C_1-C_6)$alkyl, $NR^{14}-S(O)_k(C_1-C_6)$alkyl, and $-NR^8-S(O)_kR^{14}$;

any nitrogen atoms of the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{10}, R^{11} and R^{14} are optionally substituted with R^{12} substituents each independently selected

from $(C_1\text{-}C_6)$alkyl, -(C=O)-R^8, -(C=O)-R^{14a}, -(C=O)-O-$(C_1\text{-}C_6)$alkyl, -(C=O)-NR^8R^9, -(C=O)-NR^8R^{14a}, R^{14a}, -$(CR^8R^9)_q$(C=O)R^{14a}, and -$(CR^8R^9)_qS(O)_jR^{14a}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} $(C_1\text{-}C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6\text{-}C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, -$(CR^8R^9)_p$(3-10)-membered cycloalkyl, -$(CR^8R^9)_p(C_6\text{-}C_{10}$aryl), -$(CR^8R^9)_p$(4-12)-membered heterocyclyl, -(C=O)-R^8, -(C=O)-O-$(C_1\text{-}C_6)$alkyl, -O-(C=O)-R^8, -NR^8(C=O)-R^9, -(C=O)-NR^8R^9, -(C=O)-NR^8R^{14}, -NR^8R^9, -NR^8OR^9, -$S(O)_kNR^8R^9$, -$S(O)_j(C_1\text{-}C_6)$alkyl, and -NR^8-$S(O)_k(C_1\text{-}C_6)$alkyl;

each R^8 and R^9 are independently H or $(C_1\text{-}C_6)$alkyl;

each R^{9a}, R^{14}, and R^{14a} are independently -$(CR^8R^9)_v$(3-10)-membered cycloalkyl, -$(CR^8R^9)_v(C_6\text{-}C_{10})$aryl, or -$(CR^8R^9)_v$(4-12)-membered heterocyclyl;

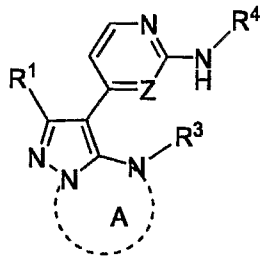
p, q, and v are each independently 0, 1, 2, 3, 4, or 5;

n and j are each independently 0, 1, or 2;

w is 0, 1, 2, or 3, and

k is 1 or 2.

3. A compound of formula (Ib):



(Ib);

wherein ring A is a (5-8)-membered heterocyclyl;

-Z- is -C- or -N-;

R^1 is H or halo,

R^3 is H, $(C_1\text{-}C_6)$alkyl, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$amino$(CR^5R^6)_v$, -(C=O)-O-R^5, -(C=O)-NR^5R^6, -$S(O)_kNR^5R^6$, -$S(O)_j(C_1\text{-}C_6)$alkyl, -$(CR^5R^6)_v$(3-10)-membered cycloalkyl, -$(CR^5R^6)_v(C_6\text{-}C_{10}$aryl), -$(CR^5R^6)_v$(4-12)-membered heterocyclyl, -$(CR^5R^6)_q$(C=O)$(C_1\text{-}C_6)$alkyl, -$(CR^5R^6)_q$(C=O)$(CR^5R^6)_v$(3-10)-membered cycloalkyl, -$(CR^5R^6)_q$(C=O)$(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, -$(CR^5R^6)_q$(C=O)$(CR^5R^6)_v$(4-12)-membered heterocyclyl, -$(CR^5R^6)_qS(O)_j(C_1\text{-}C_6)$alkyl, -$(CR^5R^6)_qS(O)_j(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or -$(CR^5R^6)_qS(O)_j(CR^5R^6)_v$(4-12)-membered heterocyclyl;

Or R^3 may be absent;

R^4 is $(C_1\text{-}C_6)$alkyl, -$(CR^5R^6)_v$(3-10)-membered cycloalkyl, -$(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or -$(CR^5R^6)_v$(4-12)-membered heterocyclyl;

each of R^5 and R^6 are independently selected from H, $(C_1\text{-}C_6)$alkyl, -$(CR^8R^9)_p$(3-10)-membered cycloalkyl, -$(CR^8R^9)_p(C_6\text{-}C_{10})$aryl, and -$(CR^8R^9)_p$(4-12)-membered heterocyclyl;

any carbon atoms of said ring A and the $(C_1$-$C_6)$alkyl, the (3-10)-membered cycloalkyl, the $(C_6$-$C_{10})$aryl and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^3, R^4, R^5, and R^6 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, R^{9a}, $-(CR^8R^9)_q$-(C=O)-R^8, $-(CR^8R^9)_q$-(C=O)-R^{9a}, $-(CR^8R^9)_q$-(C=O)-O-$(C_1$-$C_6)$alkyl, $-(CR^8R^9)_q$-(C=O)-O-R^{9a}, -O-(C=O)-R^8, -O-(C=O)-R^{9a}, $-NR^8$-$(CR^8R^9)_q$(C=O)-R^9, $-NR^8$-$(CR^8R^9)_q$(C=O)R^{9a}, $-NR^8$-$(CR^8R^9)_q$(C=O)-O$(C_1$-$C_6)$alkyl, $-NR^8$-$(CR^8R^9)_q$(C=O)-OR^9, $-NR^8$-(C=O)NR^8R^9, $-NR^8$-(C=O)NR^8R^{9a}, $-NR^8$-(C=O)-(C=O)-NR^8R^9, $-NR^8$-(C=O)-(C=O)-NR^8R^{9a}, $-NR^8$-$(CR^8R^9)_q$(C=O)OR^{9a}, -(C=O)-NR^8R^9, -(C=O)NR^8R^{9a}, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_k$ NR^8R^{9a}, $-S(O)_j(C_1$-$C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8$-$S(O)_k(C_1$-$C_6)$alkyl, $-NR^8$-$S(O)_kR^{9a}$, $-NR^8$-$S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any carbon atoms of each of the foregoing R^{10} $(C_1$-$C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6$-C_{10}aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O-CF_3$, $-O-CHF_2$, $-O-CH_2F$, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, R^{14}, $-O-R^{14}$, -(C=O)-R^8, -(C=O)-R^{14}, -(C=O)-O-$(C_1$-$C_6)$alkyl, -(C=O)-O-R^{14}, -O-(C=O)-R^8, -O-(C=O)-R^{14}, $-NR^8$(C=O)-R^9, $-NR^8$(C=O)-R^{14}, -(C=O)-NR^8R^9, -(C=O)-NR^8R^{14}, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, $-NR^8OR^{14}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1$-$C_6)$alkyl, $-S(O)_jR^{14}$, NR^8-$S(O)_k(C_1$-$C_6)$alkyl, NR^{14}-$S(O)_k(C_1$-$C_6)$alkyl, and $-NR^8$-$S(O)_kR^{14}$;

any nitrogen atoms of said ring A and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^3, R^4, R^5, R^6, R^{9a}, R^{10}, R^{11} and R^{14} are optionally substituted with R^{12} substituents each independently selected from $(C_1$-$C_6)$alkyl, -(C=O)-R^8, -(C=O)-R^{14a}, -(C=O)-O-$(C_1$-$C_6)$alkyl, -(C=O)-NR^8R^9, -(C=O)-NR^8R^{14a}, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14a}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} $(C_1$-$C_6)$alkyl, (3-10)-membered cycloalkyl, $(C_6$-C_{10}aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6$-C_{10}aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, -(C=O)-R^8, -(C=O)-O-$(C_1$-$C_6)$alkyl, -O-(C=O)-R^8, $-NR^8$(C=O)-R^9, -(C=O)-NR^8R^9, -(C=O)-NR^8R^{14}, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1$-$C_6)$alkyl, and $-NR^8$-$S(O)_k(C_1$-$C_6)$alkyl;

each R^8 and R^9 are independently H or $(C_1$-$C_6)$alkyl;

each R^{9a}, R^{14}, and R^{14a} are independently $-(CR^8R^9)_v$(3-10)-membered cycloalkyl, $-(CR^8R^9)_v(C_6$-$C_{10})$aryl, or $-(CR^8R^9)_v$(4-12)-membered heterocyclyl;

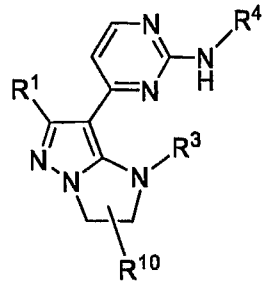
p, q, and v are each independently 0, 1, 2, 3, 4, or 5;

n and j are each independently 0, 1, or 2;

w is 0, 1, 2, or 3, and

k is 1 or 2.

4. The compound according to claim 3 selected from the group consisting of: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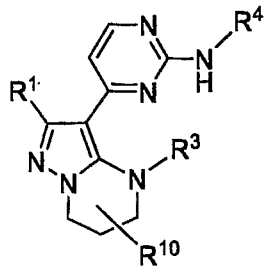
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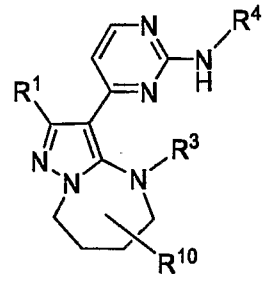
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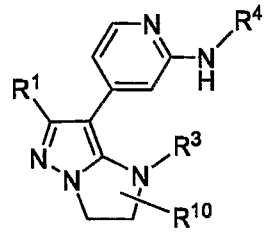
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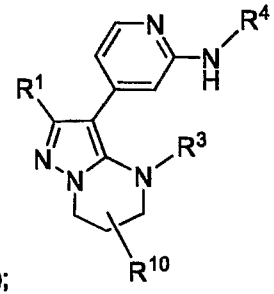
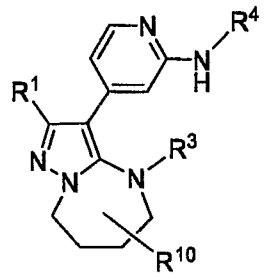
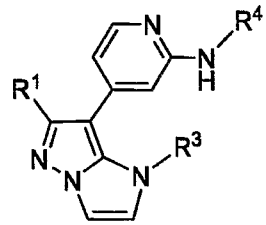
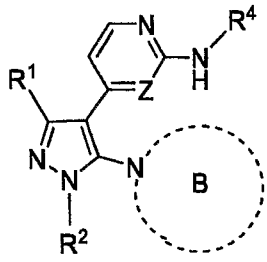

(Ib5);

(Ib6); and

(Ib7).

4. A compound of formula (Ic):


(Ic);

wherein ring B is a (3-8)-membered heterocyclyl;

-Z- is -C- or -N-;

R^1 is H or halo;

R^2 is H, CF_3, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$amino$(CR^5R^6)_v$, $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

R^4 is $(C_1\text{-}C_6)$alkyl, $-(CR^5R^6)_v$(3-10)-membered cycloalkyl, $-(CR^5R^6)_v(C_6\text{-}C_{10})$aryl, or $-(CR^5R^6)_v$(4-12)-membered heterocyclyl;

each of R^5 and R^6 are independently selected from H, $(C_1\text{-}C_6)$alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6\text{-}C_{10})$aryl, and $-(CR^8R^9)_p$(4-12)-membered heterocyclyl;

any carbon atoms of said ring B, and the $(C_1\text{-}C_6)$alkyl, the (3-10)-membered cycloalkyl, the $(C_6\text{-}C_{10})$aryl and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^4, R^5, and R^6 are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, $-CF_3$,

$-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, $-(CR^8R^9)_q-(C=O)-R^8$, $-(CR^8R^9)_q-(C=O)-R^{9a}$, $-(CR^8R^9)_q-(C=O)-O-(C_1-C_6)$alkyl, $-(CR^8R^9)_q-(C=O)-O-R^{9a}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-R^9$, $-NR^8-(CR^8R^9)_q(C=O)R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-O(C_1-C_6)$alkyl, $-NR^8-(CR^8R^9)_q(C=O)-OR^9$, $-NR^8-(C=O)NR^8R^9$, $-NR^8-(C=O)NR^8R^{9a}$, $-NR^8-(C=O)-(C=O)-NR^8R^9$, $-NR^8-(C=O)-(C=O)-NR^8R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)-NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_k NR^8R^{9a}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8-S(O)_k(C_1-C_6)$alkyl, $-NR^8-S(O)_kR^{9a}$, $-NR^8-S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any carbon atoms of each of the foregoing R^{10} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{11} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $-O-CF_3$, $-O-CHF_2$, $-O-CH_2F$, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{14}, $-O-R^{14}$, $-(C=O)-R^8$, $-(C=O)-R^{14}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-O-R^{14}$, $-O-(C=O)-R^8$, $-O-(C=O)-R^{14}$, $-NR^8(C=O)-R^9$, $-NR^8(C=O)-R^{14}$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8R^{14}$, $-NR^8OR^9$, $-NR^8OR^{14}$, $-S(O)_kNR^8R^9$, $-S(O)_kNR^8R^{14}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{14}$, $NR^8-S(O)_k(C_1-C_6)$alkyl, $NR^{14}-S(O)_k(C_1-C_6)$alkyl, and $-NR^8-S(O)_kR^{14}$;

any nitrogen atoms of said ring B, and the (4-12)-membered heterocyclyl moieties of the foregoing R^1, R^2, R^4, R^5, R^6, R^{9a}, R^{10}, R^{11} and R^{14} are optionally substituted with R^{12} substituents each independently selected from (C_1-C_6)alkyl, $-(C=O)-R^8$, $-(C=O)-R^{14a}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14a}$, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14a}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6-C_{10}$aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(C=O)-R^8$, $-(C=O)-O-(C_1-C_6)$alkyl, $-O-(C=O)-R^8$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, and $-NR^8-S(O)_k(C_1-C_6)$alkyl;

each R^8 and R^9 are independently H or (C_1-C_6)alkyl;

each R^{9a}, R^{14}, and R^{14a} are independently $-(CR^8R^9)_v$(3-10)-membered cycloalkyl, $-(CR^8R^9)_v(C_6-C_{10})$aryl, or $-(CR^8R^9)_v$(4-12)-membered heterocyclyl;

p, q, and v are each independently 0, 1, 2, 3, 4, or 5;

n and j are each independently 0, 1, or 2;

w is 0, 1, 2, or 3, and

k is 1 or 2.

5. The compound according to any one of claims 1, 2, 3, or 4, wherein –Z- is –N-.

6. The compound according to any one of claims 1, 2, 3, or 4, wherein R^1 is H or F.

7. The compound according to any one of claims 1, 2, or 4, wherein R^2 is H, (C_1-C_6)alkyl, benzyl, phenyl, or (4-12)-membered heterocyclyl, wherein any carbon atoms of the said $(C_1-$

C_6)alkyl, benzyl, phenyl, or (4-12)-membered heterocyclyl are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, -(C=O)-R^8, -(C=O)-R^{9a}, -(C=O)-O-(C_1-C_6)alkyl, -O-(C=O)-R^8, -(C=O)-NR^8R^9, -NR^8R^9, -NR^8R^{9a},,-$S(O)_kNR^8R^9$, -$S(O)_j$(C_1-C_6)alkyl, and -NR^8-$S(O)_k$(C_1-C_6)alkyl.

8. The compound according to any one of claims 1, 2, or 3, wherein R^3 is H, (C_1-C_6)alkyl, -$(CR^5R^6)_v$(3-10)-membered cycloalkyl, -$(CR^5R^6)_v$(C_6-C_{10}aryl), -$(CR^5R^6)_v$(4-7)-membered heterocyclyl, -$(CR^5R^6)_q$(C=O)(C_1-C_6)alkyl, -$(CR^5R^6)_q$(C=O)$(CR^5R^6)_v$(3-10)-membered cycloalkyl, -$(CR^5R^6)_q$(C=O)$(CR^5R^6)_v$(C_6-C_{10})aryl, -$(CR^5R^6)_q$(C=O)$(CR^5R^6)_v$(4-12)-membered heterocyclyl, -$(CR^5R^6)_qS(O)_2$(C_1-C_6)alkyl, -$(CR^5R^6)_qS(O)_2(CR^5R^6)_v$($C_6$-$C_{10}$)aryl, or -$(CR^5R^6)_qS(O)_2(CR^5R^6)_v$(4-7)-membered heterocyclyl;

wherein any carbon atoms of said R^3 (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, (C_6-C_{10}aryl), or (4-7)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{10} substituents each independently selected from halo, cyano, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, -$(CR^8R^9)_q$-(C=O)-R^8, -$(CR^8R^9)_q$-(C=O)-R^{9a}, -$(CR^8R^9)_q$-(C=O)-O-(C_1-C_6)alkyl, -$(CR^8R^9)_q$-(C=O)-O-R^{9a}, -O-(C=O)-R^8, -O-(C=O)-R^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)-R^9, -NR^8-$(CR^8R^9)_q$(C=O)R^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)-O(C_1-C_6)alkyl, -NR^8-$(CR^8R^9)_q$(C=O)-OR^9, -NR^8-(C=O)NR^9, -NR^8-(C=O)NR^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)OR^{9a}, -(C=O)-NR^8R^9, -(C=O)NR^8R^{9a}, -NR^8R^9, -NR^8R^{9a}, -NR^8OR^9, -NR^8OR^{9a}, -$S(O)_kNR^8R^9$, -$S(O)_k$ NR^8R^{9a}, -$S(O)_j$(C_1-C_6)alkyl, -$S(O)_jR^{9a}$, -NR^8-$S(O)_k$(C_1-C_6)alkyl, -NR^8-$S(O)_kR^{9a}$, -NR^8-$S(O)_kNR^{9a}$, and -$(CR^8R^9)_qS(O)_jR^{9a}$.

9. The compound according to any one of claims 1, 2, 3, or 4, wherein R^4 is (C_1-C_6)alkyl; wherein any carbon atoms of said R^4 are optionally substituted with with 1 to 3 R^{10} substituents each independently selected from halo, cyano, -CF_3, -CHF_2, -CH_2F, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, -$(CR^8R^9)_q$-(C=O)-R^8, -$(CR^8R^9)_q$-(C=O)-R^{9a}, -$(CR^8R^9)_q$-(C=O)-O-(C_1-C_6)alkyl, -$(CR^8R^9)_q$-(C=O)-O-R^{9a}, -O-(C=O)-R^8, -O-(C=O)-R^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)-R^9, -NR^8-$(CR^8R^9)_q$(C=O)R^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)-O(C_1-C_6)alkyl, -NR^8-$(CR^8R^9)_q$(C=O)-OR^9, -NR^8-(C=O)NR^9, -NR^8-(C=O)NR^{9a}, -NR^8-$(CR^8R^9)_q$(C=O)OR^{9a}, -(C=O)-NR^8R^9, -(C=O)NR^8R^{9a}, -NR^8R^9, -NR^8R^{9a}, -NR^8OR^9, -NR^8OR^{9a}, -$S(O)_kNR^8R^9$, -$S(O)_k$ NR^8R^{9a}, -$S(O)_j$(C_1-C_6)alkyl, -$S(O)_jR^{9a}$, -NR^8-$S(O)_k$(C_1-C_6)alkyl, -NR^8-$S(O)_kR^{9a}$, -NR^8-$S(O)_kNR^{9a}$, and -$(CR^8R^9)_qS(O)_jR^{9a}$.

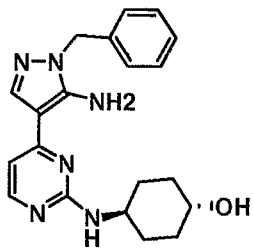
10. The compound according to any one of claims 1, 2, 3, or 4, wherein R^4 is -$(CR^5R^6)_v$(3-10)-membered cycloalkyl, -$(CR^5R^6)_v$(C_6-C_{10})aryl, or -$(CR^5R^6)_v$(4-12)-membered heterocyclyl; wherein any carbon atoms of said R^4 (3-10)-membered cycloalkyl, (C_6-C_{10}aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with with 1 to 3 R^{10} substituents each independently selected from halo, cyano, -CF_3, -CHF_2, -CH_2F, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, R^{9a}, -$(CR^8R^9)_q$-(C=O)-R^8, -$(CR^8R^9)_q$-(C=O)-R^{9a}, -$(CR^8R^9)_q$-(C=O)-O-(C_1-C_6)alkyl, -$(CR^8R^9)_q$-(C=O)-O-R^{9a}, -O-(C=O)-R^8, -O-(C=O)-R^{9a},

$-NR^8-(CR^8R^9)_q(C=O)-R^9$, $-NR^8-(CR^8R^9)_q(C=O)R^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)-O(C_1-C_6)$alkyl, $-NR^8-(CR^8R^9)_q(C=O)-OR^9$, $-NR^8-(C=O)NR^9$, $-NR^8-(C=O)NR^{9a}$, $-NR^8-(CR^8R^9)_q(C=O)OR^{9a}$, $-(C=O)-NR^8R^9$, $-(C=O)NR^8R^{9a}$, $-NR^8R^9$, $-NR^8R^{9a}$, $-NR^8OR^9$, $-NR^8OR^{9a}$, $-S(O)_kNR^8R^9$, $-S(O)_k NR^8R^{9a}$, $-S(O)_j(C_1-C_6)$alkyl, $-S(O)_jR^{9a}$, $-NR^8-S(O)_k(C_1-C_6)$alkyl, $-NR^8-S(O)_kR^{9a}$, $-NR^8-S(O)_kNR^{9a}$, and $-(CR^8R^9)_qS(O)_jR^{9a}$;

wherein any nitrogen atoms of said R^4 (4-12)-membered heterocyclyl moeieties are optionally substituted with R^{12} substituents each independently selected from (C_1-C_6)alkyl, $-(C=O)-R^8$, $-(C=O)-R^{14a}$, $-(C=O)-O-(C_1-C_6)$alkyl, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14a}$, R^{14a}, $-(CR^8R^9)_q(C=O)R^{14a}$, and $-(CR^8R^9)_qS(O)_jR^{14}$;

wherein any carbon atoms of each of the foregoing R^{11} and R^{12} (C_1-C_6)alkyl, (3-10)-membered cycloalkyl, $(C_6-C_{10}$aryl), or (4-12)-membered heterocyclyl moieties are optionally substituted with 1 to 3 R^{13} substituents each independently selected from halo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, $-(CR^8R^9)_p$(3-10)-membered cycloalkyl, $-(CR^8R^9)_p(C_6-C_{10}$aryl), $-(CR^8R^9)_p$(4-12)-membered heterocyclyl, $-(C=O)-R^8$, $-(C=O)-O-(C_1-C_6)$alkyl, $-O-(C=O)-R^8$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-(C=O)-NR^8R^{14}$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, and $-NR^8-S(O)_k(C_1-C_6)$alkyl;

11. The compound according to claim 1, selected from the group consisting of: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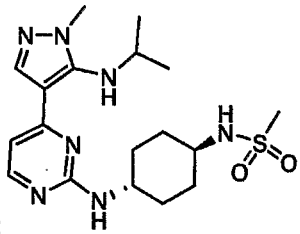
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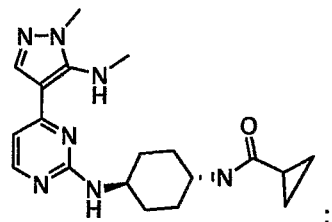
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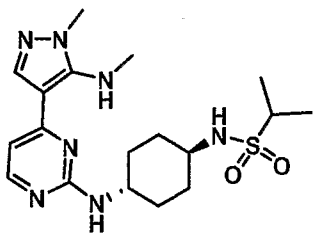
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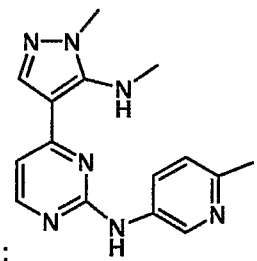
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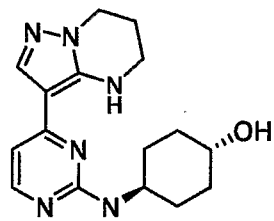
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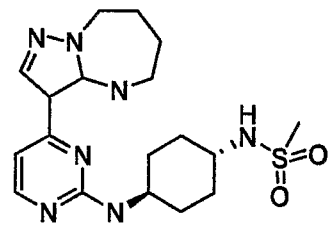
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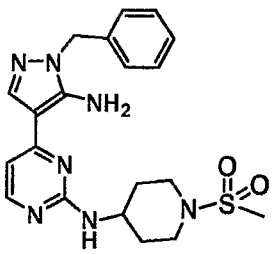
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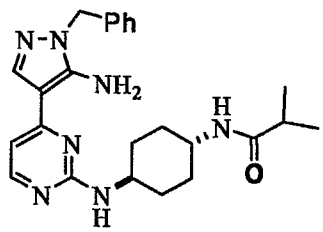
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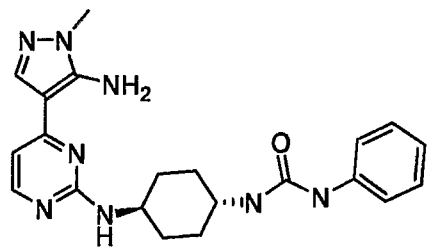
; or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. A method of treating a condition that is mediated by the modulation of JNK, the method comprising administering to a mammal an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

14. A method of treating diabetes, metabolic syndrome, insulin resistance syndrome, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, atherosclerosis, dementia, depression, virus diseases, inflammatory disorders, or diseases in which the liver is a target organ, the method comprising administering to a mammal an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.