PYRROLO[2,3-d]PYRIMIDINE COMPOUNDS

Background of the Invention

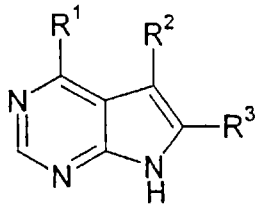
The present invention relates to pyrrolo[2,3-d]pyrimidine compounds which are inhibitors of protein tyrosine kinases, such as the enzyme Janus Kinase 3 (hereinafter also referred to as JAK3) and as such are useful therapy as immunosuppressive agents for organ transplants, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable

This invention also relates to a method of using such compounds in the treatment of the above indications in mammals, especially humans, and the phamaceutical compositions useful therefor.

JAK3 is a member of the Janus family of protein tyrosine kinases. Although the other members of this family are expressed by essentially all tissues, JAK3 expression is limited to hematopoetic cells. This is consistent with its essential role in signaling through the receptors for IL-2, IL-4, IL-7, IL-9 and IL-15 by non-covalent association of JAK3 with the gamma chain common to these multichain receptors XSCID patient populations have been identified with severely reduced levels of JAK3 protein or with genetic defects to the common gamma chain, suggesting that immunosuppression should result from blocking signaling through the JAK3 pathway. Animal studies have suggested that JAK3 not only plays a critical role in B and T lymphocyte maturation, but that JAK3 is constitutively required to maintain T cell function Modulation of immune activity through this novel mechanism can prove useful in the treatment of T cell proliferative disorders such as transplant rejection and autoimmune diseases.

Summary of the Invention

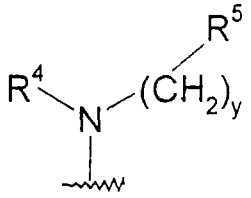
The present invention relates to a compound of the formula



I

or the pharmaceutically acceptable salt thereof, wherein

R^1 is a group of the formula



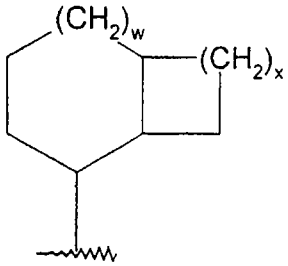
wherein y is 0, 1 or 2,

R^4 is selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_6)$acyloxy, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)alkyl)_2$amino, cyano, nitro, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl or $(C_1$-$C_6)$acylamino; or R^4 is $(C_3$-$C_{10})$cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1$-$C_6)$acyloxy, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)alkyl)_2$amino, cyano, cyano$(C_1$-$C_6)$alkyl, trifluoromethyl$(C_1$-$C_6)$alkyl, nitro, nitro$(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$acylamino;

R^5 is selected from the group consisting of trifluoromethyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkyl(difluoromethylene)$(C_1$-$C_3)$alkyl, $(C_3$-$C_{10})$cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo, $(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkylamino, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-CO-NH, $(C_1$-$C_6)$alkylamino-CO-, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_1$-$C_6)$alkylamino, amino$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_1$-$C_6)$alkyl, nitro, cyano$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, nitro$(C_1$-$C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$acylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$acylamino, amino$(C_1$-$C_6)$acyl, amino$(C_1$-$C_6)$acyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$acyl, $((C_1$-$C_6)alkyl)_2$amino$(C_1$-$C_6)$acyl, $R^{15}R^{16}$N-CO-O-, $R^{15}R^{16}$N-CO-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-S$(O)_m$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m$ $(C_1$-$C_6)$alkyl, $R^{15}S(O)_m$ R^{16}N, $R^{15}S(O)_mR^{16}N(C_1$-$C_6)$alkyl wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1$-$C_6)$alkyl; or R^5 is $(C_3$-$C_{10})$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, piperazinyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acylamino$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylthio$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylthio$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfinyl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfinyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfonyl$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, $((C_1$-$C_6)alkyl)_2$amino, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by one to five cyano, nitro, halo, deuterium, hydroxy, carboxy, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$acylamino, amino$(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$acyl or $((C_1$-$C_6)alkyl)_2$amino$(C_1$-$C_6)$acyl, or R^5 is $R^{13}CO(C_1$-$C_6)$alkyl or $R^{13}CO(C_3$-$C_{10})$cycloalkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}$N wherein R^{20} and

R^{21} are each independently selected from the group consisting of hydrogen, deuterium, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl(C_1-C_6)alkyl, or R^5 is R^{14}, R^{14}(C_1-C_6)alkyl or R^{14}(C_3-C_{10})cycloalkyl wherein R^{14} is (C_2-C_9)heterocycloalkyl, (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidinyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6)acylpiperidyl,

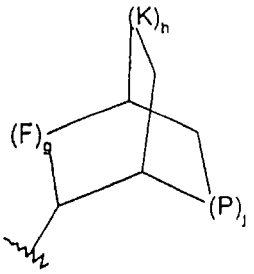
or R^5 is a group of the formula



wherein w is 0, 1 or 2;

x is 0, 1, 2 or 3;

or R^5 is a group of the formula



II

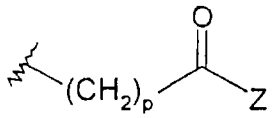
wherein g, h and j are each independently 0 to 3,

F, K and P are each independently oxygen, $S(O)_d$ wherein d is 0, 1 or 2, NR^6 or CR^7R^8,

R^6 is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkyl (difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_1-C_6)alkoxy(C_1-C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, hydroxy(C_2-C_6)alkyl, (C_1-C_6)acyloxy(C_2-C_6)alkyl, (C_1-C_6)alkoxy(C_2-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-

C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)alkyl, $R^{13}CO$(C_1-C_6)alkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl(C_1-C_6)alkyl, or R^{14}(C_2-C_6)alkyl wherein R^{14} is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)alkoxyacyl, (C_1-C_6)alkylaminoaryl, ((C_1-C_6)alkyl$_2$aminoacyl or (C_1-C_6)acylpiperidyl,

R^7 and R^8 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, amino, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)amino, (C_1-C_6)acylamino, (C_1-C_6)acyl(C_1-C_6)alkylamino, carboxy, (C_1-C_6)alkoxyacyl, (C_1-C_6)alkylaminoacyl, ((C_1-C_6)alkyl)$_2$aminoacyl, aminoacyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkyl (difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)alkyl, $R^{13}CO$(C_1-C_6)alkyl or $R^{13}CO$(C_3-C_{10})cycloalkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl(C_1-C_6)alkyl; R^{14}, R^{14}(C_1-C_6)alkyl or R^{14}(C_3-C_{10})cycloalkyl wherein R^{14} is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6)acylpiperidyl; or a group of the formula



III

wherein p is 0, 1, 2 or 3, and

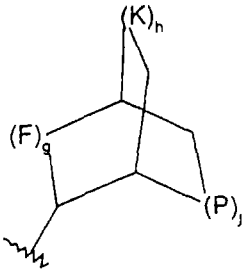
Z is hydroxy, (C_1-C_6)alkoxy or NR^1R^2 wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)acylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, R^5(C_1-C_6)alkyl, (C_1-C_5)alkyl(CHR^5)(C_1-C_6)alkyl wherein R^5 is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$ amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino, R^6(C_1-C_6)alkyl, (C_1-C_5)alkyl(CHR^6)(C_1-C_6)alkyl wherein R^6 is piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroarylpiperidyl or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl,

or R^1 is defined as OR^9 or $S(O)_qR^9$ wherein q is 0, 1 or 2, and

R^9 is selected from the group consisting of trifluoromethyl(C_1-C_6)alkyl, (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five carboxy, cyano, amino, hydroxy, (C_1-C_6) alkoxy, halo, (C_1-C_6)alkyl $S(O)_m$ wherein m is 0, 1 or 2; $R^{15}R^{16}NS(O)_m$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl, (C_1-C_6)acyl, (C_1-C_6)alkylamino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, $R^{15}R^{16}N$-CO-O-, $R^{15}R^{16}N$-CO-(C_1-C_6)alkyl wherein R^{15} and R^{16} are as defined above; (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, (C_1-C_6)alkylamino, amino(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, nitro, cyano(C_1-C_6)alkyl, nitro(C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)acylamino, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl or ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl; (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_{10})cycloalkyl(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, (C_2-C_6)alkoxy(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino, (C_1-C_6)alkyl wherein the alkyl group is optionally substituted by one to five cyano, nitro, hydroxy, carboxy, (C_1-C_6)acylamino, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl or ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, $R^{13}CO$(C_1-C_6)alkyl or $R^{13}CO$(C_3-C_{10})cycloalkyl wherein R^{13} is $R^{20}O$

or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl or $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, R^{14}, $R^{14}(C_1$-$C_6)$alkyl or $R^{14}(C_3$-$C_{10})$cycloalkyl wherein R^{14} is $(C_2$-$C_9)$heterocycloalkyl, $(C_1$-$C_6)$acylpiperazino, $(C_6$-$C_{10})$arylpiperazino, $(C_5$-$C_9)$heteroarylpiperazino, $(C_1$-$C_6)$alkylpiperazino, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkylpiperazino, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, $(C_1$-$C_6)$alkylpiperidinyl, $(C_6$-$C_{10})$arylpiperidyl, $(C_5$-$C_9)$heteroarylpiperidyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkylpiperidyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkylpiperidyl or $(C_1$-$C_6)$acylpiperidyl;

or R^9 is a group of the formula



II

wherein g, h and j are each independently 0 to 6;

F, K and P are each independently oxygen, $S(O)_d$ wherein d is 0, 1 or 2, NR^6 or CR^7R^8 wherein R^6, R^7 and R^8 are as defined above,

R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydoxy, nitro, carboxy, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, trifluoromethyl, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy wherein the alkyl or alkoxy groups are optionally substittued by one to three groups selected from halo, hydroxy, carboxy, amino $(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, $(C_5$-$C_9)$heteroaryl, $(C_2$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$cycloalkyl or $(C_6$-$C_{10})$aryl; or R^2 and R^3 are each independently $(C_3$-$C_{10})$cycloalkyl, $(C_3$-$C_{10})$cycloalkoxy, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, $(C_6$-$C_{10})$arylamino, $(C_1$-$C_6)$alkylthio, $(C_6$-$C_{10})$arylthio, $(C_1$-$C_6)$alkylsulfinyl, $(C_6$-$C_{10})$arylsulfinyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_6$-$C_{10})$arylsulfonyl, $(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkoxy-CO-NH-, $(C_1$-$C_6)$alkyamino-CO-, $(C_5$-$C_9)$heteroaryl, $(C_2$-$C_9)$heterocycloalkyl or $(C_6$-$C_{10})$aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-CO-NH-, $(C_1$-$C_6)$alkoxy-CO-NH-, $(C_1$-$C_6)$alkyl-CO-NH-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-CO-NH-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-CO-NH-$(C_1$-$C_6)$alkoxy, carboxy, carboxy$(C_1$-$C_6)$alkyl, carboxy$(C_1$-$C_6)$alkoxy, benzyloxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryl, amino, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonylamino, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxycarbonylamino, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, $((C_1$-$C_6)$alkyl$)_2$amino$(C_1$-$C_6)$alkyl, hydroxy, $(C_1$-$C_6)$alkoxy, carboxy, carboxy$(C_1$-

C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyl-CO-NH-, cyano, (C_5-C_9)heterocycloalkyl, amino-CO-NH-, (C_1-C_6)alkylamino-CO-NH-, ((C_1-C_6)alkyl)$_2$amino-CO-NH-, (C_6-C_{10})arylamino-CO-NH-, (C_5-C_9)heteroarylamino-CO-NH-, (C_1-C_6)alkylamino-CO-NH-(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino-CO-NH-(C_1-C_6)alkyl, (C_6-C_{10})arylamino-CO-NH-(C_1-C_6)alkyl, (C_5-C_9)heteroarylamino-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonylamino, (C_6-C_{10})arylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_5-C_9)heteroaryl or (C_2-C_9)heterocycloalkyl,

with the proviso that when either R^4 and R^5 is hydrogen, the other of R^4 or R^5 cannot be (C_6-C_{10})aryl or (C_6-C_{10})aryl(C_1-C_6)alkyl;

with the proviso that when R^4 is hydrogen, unsubstituted (C_1-C_6)alkyl or unsubstituted (C_3-C_{10})cycloalkyl, R^5 cannot be (C_6-C_{10})aryl(C_1-C_6)alkyl, R^{20} and R^{21} cannot be (C_5-C_9)heteroaryl(C_1-C_6)alkyl, and R^{14} cannot be (C_2-C_9)heterocycloalkyl, morpholino, thiomorphlino, piperidino, pyrrolidino, piperidinyl or (C_1-C_6)alkylpiperidinyl,

with the proviso that the sp^2 and sp carbons of alkenyl or alkynyl cannot be substituted by hydroxy or amino;

with the proviso that when R^4 is hydrogen, R^5 cannot be amino (C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)alkyl, furanyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl or carboxy(C_1-C_6)alkyl,

with the proviso that both R^4 and R^5 cannot both be hydroxy (C_1-C_6)alkyl,

with the proviso that when R^4 is (C_1-C_6)alkyl, R^5 cannot be (C_1-C_6)alkoxy(C_1-C_6)alkyl or carboxy(C_1-C_6)alkyl; and

with the proviso that R^1 cannot be carboxy(C_1-C_6)alkylthio or (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkylthio.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene bis-(2-hydroxy-3-naphthoate)]salts

The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those

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

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof

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

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

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

Unless otherwise indicated, the alkyl and alkenyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched, and they may also be cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl) or be linear or branched and contain cyclic moieties Unless otherwise indicated, halogen includes fluorine, chlorine, bromine, and iodine

(C_3-C_{10})Cycloalkyl when used herein refers to cycloalkyl groups containing zero to two levels of unsaturation such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, 1,3-cyclohexadiene, cycloheptyl, cycloheptenyl, bicyclo[3 2 1]octane, norbornanyl etc.

(C_2-C_9)Heterocycloalkyl when used herein refers to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranyl, thiopyranyl, aziridinyl, oxiranyl, methylenedioxyl, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, chromanyl, etc One of ordinary skill in the art will understand that the connection of said (C_2-C_9)heterocycloalkyl rings is through a carbon or a sp^3 hybridized nitrogen heteroatom

(C_2-C_9)Heteroaryl when used herein refers to furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl,

pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzoxazinyl; etc. One of ordinary skill in the art will understand that the connection of said (C_2-C_9)heterocycloalkyl rings is through a carbon atom or a sp^3 hybridized nitrogen heteroatom

(C_6-C_{10})aryl when used herein refers to phenyl or naphthyl.

Compounds of formula (I) may be administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents These agents may include but are not limited to cyclosporin A (e.g. Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e g. Cellcept®), azathioprine (e.g. Imuran®), daclizumab (e.g Zenapax®. OKT3 (e.g Orthoclone®), AtGam, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam, and antiinflammatory steroids (e g prednisolone or dexamethasone) These agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

The compounds of this invention include all conformational isomers (e g., cis and trans isomers) and all optical isomers of compounds of the formula I (e.g., enantiomers and diastereomers), as well as racemic, diastereomeric and other mixtures of such isomers

Preferred compounds of formula I include those wherein R^1 is NR^4R^5.

Other preferred compounds of formula I include those wherein R^4 is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by hydroxy, amino, trifluoromethyl, (C_1-C_6)acyloxy, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino or (C_1-C_6)acylamino; or R^4 is (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by hydroxy, trifluoromethyl or (C_1-C_6)acyloxy.

Other preferred compounds of formula I include those wherein R^5 is (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five deuterium, hydroxy, trifluoromethyl, halo, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, (C_1-C_6)acylamino, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, halo(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, $R^{15}S(O)_m R^{16}N$, $R^{15}S(O)_m R^{16}N(C_1$-$C_6)$alkyl wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl.

Other preferred compounds of formula I include those wherein R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-

C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkoxy, (C_2-C_9)heterocycloalkyl, (C_5-C_9)heteroaryl or (C_6-C_{10})aryl

Specific preferred compounds of formula I include the following.

2-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohexyl}-propan-2-ol,

2-{3-[(2-Hydroxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-4-methyl-cyclohexyl}-propan-2-ol,

2-[(5-Isopropenyl-2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol,

(5-Isopropenyl-2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,2-trifluoro-ethyl)-amine;

2-{4-Methyl-3-[(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,2-trifluoro-ethyl)-amino]-cyclohexyl}-propan-2-ol,

2-{4-Methyl-5-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohex-3-enyl}-propan-2-ol;

2-[1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-azetidin-3-yl]-propan-2-ol,

2-[1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-azetidin-2-yl]-propan-2-ol,

(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(5-isopropenyl-2-methyl-cyclohexyl)-methyl-amine;

2-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-cyclohexyl}-propan-2-ol,

(2-Ethyl-4-isopropenyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

2-{3-Ethyl-4-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclopentyl}-propan-2-ol;

2-{3-Ethyl-4-[(2-hydroxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclopentyl}-propan-2-ol;

2-[(2-Ethyl-4-isopropenyl-cyclopentyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;

(5-(S)-Isopropenyl-2-methyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

3-Methyl-8-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-8-aza-bicyclo[3.2.1]octan-3-ol,

2-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;

2-[Cyclooctyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol,

Bicyclo[2.2.1]hept-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine; and

4-Piperidin-1-yl-5-m-tolyl-7H-pyrrolo[2,3-d]pyrimidine

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple

sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in such disorders or conditions and a pharmaceutically acceptable carrier

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, alone or in combination with T-cell immunosuppressant or antiinflammatory agents, effective in such disorders or conditions and a pharmaceutically acceptable carrier

The present invention also relates to a method for the inhibition of protein typrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in treating such a condition

The present invention also relates to a method for the inhibition of protein typrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof, alone or in combination with T-cell immunosuppressant or antiinflammatory agents

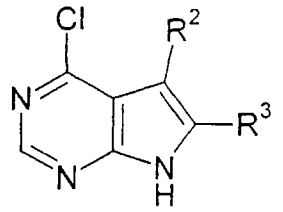
The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human,

comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, alone or in combination with T-cell immunosuppressant or antiinflammatory agents, effective in treating such a condition

Detailed Description of the Invention

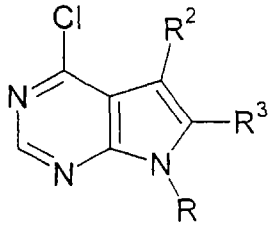
The following reaction Schemes illustrate the preparation of the compounds of the present invention Unless otherwise indicated R^1, R^2, R^3 and R^9 in the reaction Schemes and the discussion that follow are defined as above

SCHEME 1



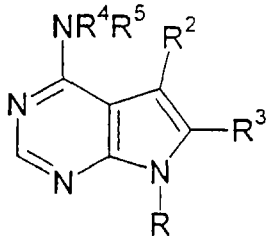
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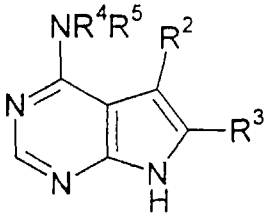
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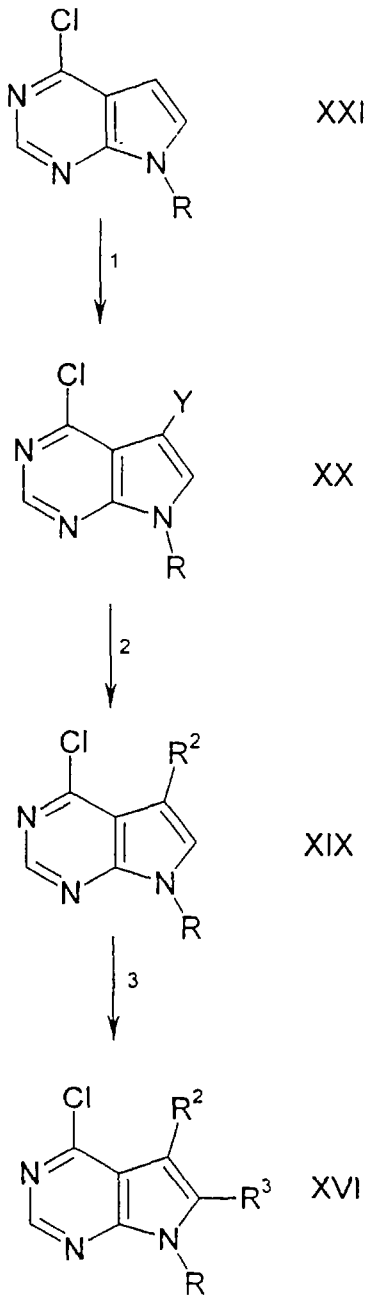
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I

SCHEME 2



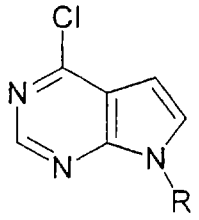
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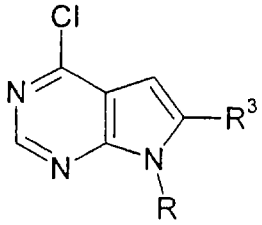
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SCHEME 3



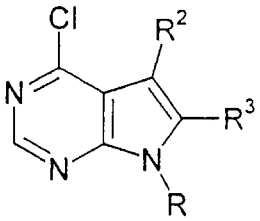
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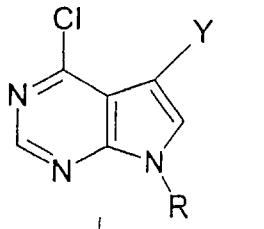
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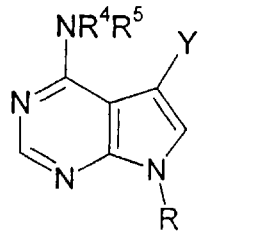
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SCHEME 4



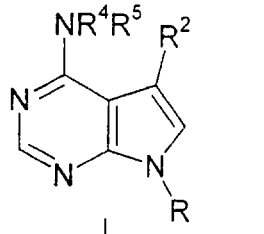
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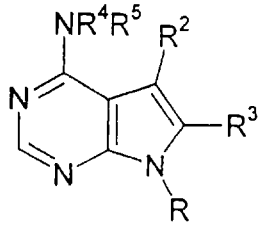
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XXIII

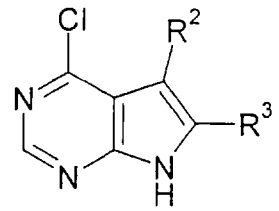
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XV

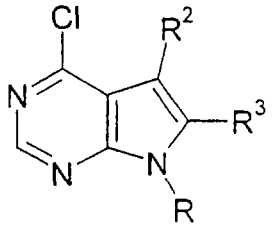
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SCHEME 5



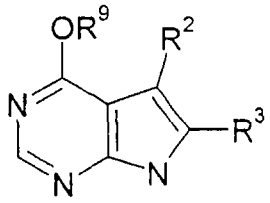
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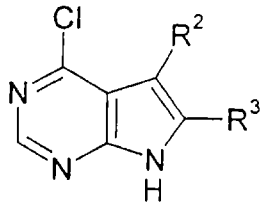
XVI

2



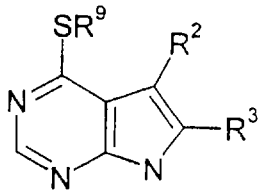
XXV

SCHEME 6



XVII

1



XXVI

In reaction 1 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVII** is converted to the corresponding compound of formula **XVI**, wherein R is benzenesulfonyl or benzyl, by treating **XVII** with benzenesulfonyl chloride, benzylchloride or benzylbromide in the presence of a base, such as sodium hydride or potassium carbonate, and a polar aprotic solvent, such as dimethylformamide or tetrahydrofuran The reaction mixture is stirred at a temperature between about 0°C to about 70°C, preferably about 30°C, for a time period between about 1 hour to about 3 hours, preferably about 2 hours

In reaction 2 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVI** is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula **XV** by coupling **XVI** with an amine of the formula HNR^4R^5. The reaction is carried out in an alcohol solvent, such as tert-butanol, methanol or ethanol, or other high boiling organic solvents, such as dimethylformamide, 1,4-dioxane or 1,2-dichloroethane, at a temperature between about 60°C to about 120°C, preferably about 80°C Typical reaction times are between about 2 hours to about 48 hours, preferably about 16 hours

In reaction 3 of Scheme 1, removal of the protecting group from the compound of formula **XV**, wherein R is benzenesulfonyl, to give the corresponding compound of formula **I**, is carried out by treating **XV** with an alkali base, such as sodium hydroxide or potassium hydroxide, in an alcohol solvent, such as methanol or ethanol, or mixed solvents, such as alcohol/tetrahydrofuran or alcohol/water The reaction is carried out at room temperature for a time period between about 15 minutes to about 1 hour, preferably 30 minutes Removal of the protecting group from the compound of formula **XV**, wherein R is benzyl, is conducted by treating **XV** with sodium in ammonia at a temperature of about -78°C for a time period between about 15 minutes to about 1 hour.

In reaction 1 of Scheme 2, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XXI**, wherein R is hydrogen or benzenesulfonate, is converted to the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula **XX**, wherein Y is chloro, bromo or iodo, by reacting **XXI** with N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide The reaction mixture is heated to reflux, in chloroform, for a time period between about 1 hour to about 3 hours, preferably about 1 hour Alternatively, in reaction 1 of Scheme 2, the 4-chloropyrrolo[2,3-d]pyrimidine of formula **XXI**, wherein R is hydrogen, is converted to the corresponding 4-chloro-5-nitropyrrolo[2,3-d]pyrimidine of formula **XX**, wherein Y is nitro, by reacting **XXI** with nitric acid in sulfuric acid at a temperature between about -10°C to about 10°C, preferably about 0°C, for a time period between about 5 minutes to about 15 minutes, preferably about 10 minutes. The compound of formula **XXI**, wherein Y is nitro, is converted to the corresponding 4-chloro-5-aminopyrrolo[2,3-d]pyrimidine of the formula **XX**, wherein Y is

amino, by reacting **XXI** under a variety of conditions known to one skilled in the art such as palladium hydrogenolysis or tin(IV)chloride and hydrochloric acid

In reaction 2 of Scheme 2, the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula **XX**, wherein R is hydrogen, is converted to the corresponding compound of formula **XIX**, wherein R^2 is (C_1-C_6)alkyl or benzyl, by treating **XX** with N-butyllithium, at a temperature of about -78°C, and reacting the dianion intermediate so formed with an alkylhalide or benzylhalide at a temperature between about -78°C to room temperature, preferably room temperature Alternatively, the dianion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-5-hydroxypyrrolo[2,3-d]pyrimidine compound of formula **XIX**, wherein R^2 is hydroxy The compound of formula **XX**, wherein Y is bromine or iodine and R is benzenesulfonate, is converted to the compound of formula **XIX**, wherein R^2 is (C_6-C_{12})aryl or vinyl, by treating **XX** with N-butyllithium, at a temperature of about -78°C, followed by the addition of zinc chloride, at a temperature of about -78°C The corresponding organo zinc intermediate so formed is then reacted with aryliodide or vinyl iodide in the presence of a catalytic quantity of palladium. The reaction mixture is stirred at a temperature between about 50°C to about 80°C, preferably about 70°C, for a time period between about 1 hour to about 3 hours, preferably about 1 hour

In reaction 3 of Scheme 2, the compound of formula **XIX** is converted to the corresponding compound of formula **XVI** by treating **XIX** with N-butyllithium, lithium diisopropylamine or sodium hydride, at a temperature of about -78°C, in the presence of a polar aprotic solvent, such as tetrahydrofuran The anionic intermediate so formed is further reacted with (a) alkylhalide or benzylhalide, at a temperature between about -78°C to room temperature, preferably -78 °C, when R^3 is alkyl or benzyl, (b) an aldehyde or ketone, at a temperature between about -78°C to room temperature, preferably -78°C, when R^3 is alkoxy; and (c) zinc chloride, at a temperature between about -78°C to room temperature, preferably -78°C, and the corresponding organozinc intermediate so formed is then reacted with aryliodide or vinyl iodide in the presence of a catalytic quantity of palladium. The resulting reaction mixture is stirred at a temperature between about 50°C to about 80°C, preferably about 70°C, for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, the anion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-6-hydroxypyrrolo[2,3-d]pyrimidine compound of formula **XVI**, wherein R^3 is hydroxy

In reaction 1 of Scheme 3, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XXI** is converted to the corresponding compound of formula **XXII**, according to the procedure described above in reaction 3 of Scheme 2

In reaction 2 of Scheme 3, the compound of formula **XXII** is converted to the corresponding compound of formula **XVI**, according to the procedures described above in reactions 1 and 2 of Scheme 3

In reaction 1 of Scheme 4, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XX** is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula **XXIV**, according to the procedure described above in reaction 2 of Scheme 1

In reaction 2 of Scheme 4, the 4-amino-5-halopyrrolo[2,3-d]pyrimidine compound of formula **XXIV**, wherein R is benzenesulfonate and Z is bromine or iodine, is converted to the corresponding compound of formula **XXIII** by reacting **XXIV** with (a) arylboronic acid, when R^2 is aryl, in an aprotic solvent, such tetrahydrofuran or dioxane, in the presence of a catalytic quantity of palladium (0) at a temperature between about 50°C to about 100°C, preferably about 70°C, for a time period between about 2 hours to about 48 hours, preferably about 12 hours, (b) alkynes, when R^2 is alkynyl, in the presence of a catalytic quantity of copper (I) iodide and palladium (0), and a polar solvent, such as dimethylformamide, at room temperature, for a time period between about 1 hour to about 5 hours, preferably about 3 hours, and (c) alkenes or styrenes, when R^2 is vinyl or styrenyl, in the presence of a catalytic quantity of palladium in dimethylformamide, dioxane or tetrahydrofuran, at a temperature between about 80°C to about 100°C, preferably about 100°C, for a time period between about 2 hours to about 48 hours, preferably about 48 hours

In reaction 3 of Scheme 4, the compound of formula **XXIII** is converted to the corresponding compound of formula **XV**, according to the procedure described above in reaction 3 of Scheme 2.

In reaction 1 of Scheme 5, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVII** is converted to the corresponding compound of formula **XVI**, wherein R is defined as above, according to the procedure described above in reaction 1 of Scheme 1.

In reaction 2 of Scheme 5, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVI** is converted the to the corresponding compound of formula **XXV** by coupling **XVI** with a compound of the formula, R^9OH, in the presence of sodium hydroxide. The reaction is carried out in a polar aprotic solvent, such as tetrahydrofuran, and heated to reflux for a time period between about 2 hours to about 4 hours, preferably about 3 hours. Removal of the protecting group is carried out according to the procedure described above in reaction 3 of Scheme 1.

In reaction 1 of Scheme 6, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVII** is converted to the corresponding compound of formula **XXVI** by coupling **XVII** with a compound of the formula, SR^9, in the presence of potassium tert-butoxide and a polar aprotic solvent, such as tetrahydrofuran The resulting reaction mixture is heated to reflux for a time period between about 2 5 hours to about 5 hours, preferably about 3.5 hours The compound

of formula **XXVI** may be further reacted with an oxidizing agent known to one of ordinary skill in the art, such as hydrogen peroxide, oxone, 3-chloroperoxybenzoic acid or tert-butylperoxide to generate the corresponding 4- R^9 sulfinylpyrrolo[2,3-d]pyrimidine or 4- R^9 sulfonylpyrrolo compounds

The compounds of the present invention 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 the present invention 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 the present invention 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 the present invention. 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 compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration

by inhalation or insufflation. The active compounds of the invention may also be formulated for sustained delivery

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e g , pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose), fillers (e.g , lactose, microcrystalline cellulose or calcium phosphate), lubricants (e g , magnesium stearate, talc or silica), disintegrants (e.g , potato starch or sodium starch glycolate), or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e g , sorbitol syrup, methyl cellulose or hydrogenated edible fats), emulsifying agents (e g , lecithin or acacia); non-aqueous vehicles (e.g , almond oil, oily esters or ethyl alcohol), and preservatives (e g , methyl or propyl p-hydroxybenzoates or sorbic acid)

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion Formulations for injection may be presented in unit dosage form, e g., in ampules or in multi-dose containers, with an added preservative The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e g , sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e g , containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount The pressurized container or

nebulizer may contain a solution or suspension of the active compound Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e g., rheumatoid arthritis) is 0 1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day

Aerosol formulations for treatment of the conditions referred to above (e g , asthma) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 µg to 1000 µg of the compound of the invention The overall daily dose with an aerosol will be within the range 0 1 mg to 1000 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time

A compound of formula (I) administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammlian immune system or with antiinflammatory agents, agents which may include but are not limited to cyclosporin A (e g Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept®, azathioprine (e g Imuran®), daclizumab (e g Zenapax®), OKT3 (e.g Orthocolone®), AtGam, aspirin, acctaminophen, ibuprofen, naproxen, piroxicam, and antiinflimmatory steroids (e g prednisolone or dexamethasone), and such agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice

FK506 (Tacrolimus) is given orally at 0.10-0 15 mg/kg body weight, every 12 hours, within first 48 hours postoperative. Does is monitored by serum Tacrolimus trough levels.

Cyclosporin A (Sandimmune oral or intravenous formulation, or Neoral®, oral solution or capsules) is given orally at 5 mg/kg body weight, every 12 hours within 48 hours postoperative Dose is monitored by blood Cyclosporin A trough levels

The active agents can be formulated for sustained delivery according to methods well known to those of ordinary skill in the art Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397

The ability of the compounds of formula I or their pharmaceutically acceptable salts to inhibit Janus Kinase 3 and, consequently, demonstrate their effectiveness for treating disorders or conditions characterized by Janus Kinase 3 is shown by the following in vitro assay tests

Biological Assay

JAK3 (JH1 GST) Enzymatic Assay

The JAK3 kinase assay utilizes a protein expressed in baculovirus-infected SF9 cells (a fusion protein of GST and the catalytic domain of human JAK3) purified by affinity chromatography on glutathione-Sepaharose The substrate for the reaction is poly-Glutamic acid-Tyrosine (PGT (4 1), Sigma catalog # P0275), coated onto Nunc Maxi Sorp plates at 100 µg/ml overnight at 37°C The morning after coating, the plates are washed three times and JAK3 is added to the wells containing 100 µl of kinase buffer (50 mM HEPES, pH 7.3, 125 mM NaCl, 24 mM MgCl2)+ 0 2 uM ATP + 1 mM Na orthovanadate) The reaction proceeds for 30 minutes at room temperature and the plates is washed three more times. The level of phosphorylated tyrosine in a given well is quantitated by standard ELISA assay utilizing an anti-phosphotyrosine antibody (ICN PY20, cat #69-151-1)

DND 39/IL-4 Cellular Assay for JAK3 kinase Inhibitors

The DND 39/IL-4 assay is designed to find inhibitors of JAK3 kinase activity which would be prime candidates for immunosupressive and/or allergy The assay uses a B-cell line called DND39 which has had the luciferase gene driven by the germ line IgE promoter stably integrated into one of the chromosomes When these cells are stimulated with IL-4, the kinase JAK3, which is associated with the IL-4 receptor, phosphorylates the signal transducer STAT6 STAT6 then blinds to the germline IgE promoter and starts transcription of the luciferase gene. Luciferase is measured in a lysate of these cells using the Promega luciferase assay reagent system

Note: DND39 cells are grown in RPMI 1640 supplemented with 10% heat inactivated FCS, 2 mM L-Glutamine, and 100 units/ml Pen /Strep The cells are maintained from $1x10^5$ to $1x10^6$ cells/ml. Split to $1x10^5$ on Friday, cells will be at about $1x10^6$ on Monday Then split 1:2 during the week keeping 200 ml in a flask as needed

$3x10^5$ DND39 cells are plated in 100 µl of RPMI 1640 supplemented with 1% heat inactivated FCS, 2 mM L-glutamine, and 100 units/ml Pen/Step in a 96 well Vee bottom plate (Nunc). Compounds are diluted serially 1:2 in DMSO starting at 4mM to 1.9µM In a 96 well polypropylene plate, changing tips after each dilution. Then 5µl of each dilution are added to 500µl of RPMI/1% serum in a 96 tube rack 125 µL of the compound dilutions are added to the cells and incubated at 37°C, 5% CO_2 for one hour After one hour, 25 µl of 25 ng/ml IL-4 is added to the cells and mixed Final concentration of IL-4 is 2 5 ng/ml and final concentration of compound is from 20 µM to 156 nM The cells are then in bated overnight 16-18 hours The plate is then centrifuged at 2500-3000 RPM in a table top centrifuge for 5 minutes. The culture supernatant is carefully removed by aspiration with an 8 well maifold 100 µl of PBS with calcium and magnesium is added to the pelletted cells The cells are

resuspended in the PBS and transferred to a Packard white OptiPlate 100 µl of Packard's LucLite reagent is added to the wells of the OptiPlate

The following Examples illustrate the preparation of the compounds of the present invention but it is not limited to the details thereof Melting points are uncorrected NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified) Commercial reagents were utilized without further purification THF refers to tetrahydrofuran DMF refers to N,N-dimethylformamide. Low Resolution Mass Spectra (LRMS) were recorded on either a Hewlett Packard 5989®, utilizing chemical ionization (ammonium), or a Fisons (or Micro Mass) Atmospheric Pressure Chemical Ionization (APCI) platform which uses a 50/50 mixture of acetonitrile/water with 0 1% formic acid as the ionizing agent. Room or ambient temperature refers to 20-25°C.

EXAMPLE 1

Cyclohexyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

METHOD A

Cyclohexyl-methyl-amine

To a solution of cyclohexanone (98 mg/1mmol) and acetic acid (120 mg/2 mmol) dissolved in 2 0 mL of 1,2-dichloroethane was added 2 0 mL of a 2 M solution of methylamine in methanol and the resulting mixture stirred at room temperature for 4 h Polymer supported borohydride (1 g/2 5 mmol) was added and the mixture stirred at room temperature for 1 h then filtered and concentrated to dryness in vacuo affording 66 mg (40%) of the title compound as the acetate salt. H NMR (400 MHz)(CD_3OD) δ· 1.17 - 1.37 (m, 5H), 1.67 (br d, 1H, J = 12.5 Hz), 1.83 (br d, 2H, J = 18 7 Hz), 1 86 (s, 3H), 2.04 (br d, 2H, J = 10.2 Hz), 2.60 (s, 3H), 2 86 - 2.92 (m, 1H)

METHOD B

Cyclohexyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

A mixture of 200 mg (1.30 mmol) of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (prepared by the method of Davoll, J. Am. Chem Soc., (1960), 82, 131), the product from Method A (589 mg/5.21 mmol) and 3 mL of tert-butanol was stirred in a sealed tube at 100 °C for 24 h The reaction mixture was added to water , acidified to pH 1 with 1 N HCl (aq), washed twice with diethylether (ether) and basified to pH 14 with 1 N sodium hydroxide (NaOH). The resulting precipitate was filtered and dried in vacuo to obtain 263 mg (88%) of the title compound, mp 177-180 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 1 11-1.22 (m, 1H), 1.43-1.63 (m, 4H), 1.73 (br d, 1H, J = 13 3 Hz), 1.83-1.90 (m, 4 H), 3 23 (s, 3H), 4 69 (br, 1H), 6 53 (d, 1H, J = 3 5 Hz), 7.03 (d, 1H, J = 3.5 Hz), 8.30 (s, 1H), 10.6 (br, 1H). LRMS. 231 (M+1)

The title compounds of Examples 2-84 were prepared by a method analogous to that described in Example 1

EXAMPLE 2

Benzyl-ethyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Benzylethylamine. Melting Point 170 - 172°C, LRMS. 252 3

EXAMPLE 3

Methyl-(S)-1-phenyl-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(S)-1-phenylethylamine Melting Point 131°C, LRMS: 253

EXAMPLE 4

Cyclopentyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclopentylmethylamine LRMS: 217 3

EXAMPLE 5

Allyl-cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Allylcyclohexylamine. LRMS. 257.

EXAMPLE 6

Allyl-cyclopentyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Allylcyclopentylamine Melting Point 173 - 175°C, LRMS· 243

EXAMPLE 7

Allyl-cyclopentyl 7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylethylamine. LRMS· 245.3

EXAMPLE 8

(1-Cyclohexyl-ethyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Cyclohexylethyl)methylamine. LRMS 259.4

EXAMPLE 9

Cycloheptyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cycloheptylmethylamine. Melting Point 177 - 178°C; LRMS· 245.3

EXAMPLE 10

Cyclooctyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclooctylmethylamine. Melting Point. 188 - 189°C; LRMS. 259 4

EXAMPLE 11

Methyl-(3-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(3-methylcyclohexyl)amine. LRMS 245.3

EXAMPLE 12

Methyl-(4-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(4-methylcyclohexyl)-amine LRMS: 245.3

EXAMPLE 13

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(3,3,5-trimethyl-cyclohexyl)-amine

Methyl-(3,3,5-trimethylcyclohexyl)-amine LRMS: 273 4

EXAMPLE 14

Cycloheptyl-ethyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cycloheptylethylamine Melting Point: 168 - 169°C; LRMS. 259.4

EXAMPLE 15

Cyclooctyl-ethyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclooctylethylamine Melting Point: 155 - 156°C, LRMS. 273.4

EXAMPLE 16

[1-(4-Chloro-phenyl)-propyl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[1-(4-Chlorophenyl)-propyl]methylamine. LRMS 301 7

EXAMPLE 17

[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-methylamine. LRMS: 297 4

EXAMPLE 18

(Decahydro-naphthalen-1-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Decahydronaphthalen-1-yl-methylamine LRMS 285.4.

EXAMPLE 19

Cyclodecyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclodecylmethylamine LRMS: 287 1.

EXAMPLE 20

Cyclononyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclononylmethyl. LRMS. 273.1.

EXAMPLE 21

2-[Cyclopentyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Cyclopentylaminoethanol Melting Point: 156 - 158°C; LRMS: 247.3.

EXAMPLE 22

Cycloheptyl-(2-methoxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cycloheptyl-(2-methoxy-ethyl)amine. LRMS: 289

EXAMPLE 23

Cycloheptyl-cyclopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cycloheptyl-cyclopropylamine. LRMS. 271 4

EXAMPLE 24

Cycloheptyl-cyclopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

Cyclohexylaminoethanol Melt Point 200 - 201°C; LRMS 261 3

EXAMPLE 25

Cyclooctyl-(2-methoxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclooctyl-(2-methoxy-ethyl)amine. LRMS 303

EXAMPLE 26

sec-Butyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

sec-Butyl-methylamine Melting Point. 146 - 148°C; LRMS. 205.

EXAMPLE 27

2-[Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-1-phenyl-propan-1-ol

2-Methyl-1- phenyl-propan-1-ol. LRMS 283, 265

EXAMPLE 28

[2-(4-Chloro-phenoxy)-1-methyl-ethyl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[2-(4-Chlorophenoxy)-1-methylethyl]-methylamine. Melting Point 139 - 141°C; LRMS. 319, 317, 189.

EXAMPLE 29

N-Cyclohexyl-N',N'-dimethyl-N-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-propane-1,3-diamine

N-Cyclohexyl-N',N'-dimethyl propane-1,3-diamine LRMS: 302 4

EXAMPLE 30

N-{2-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethyl}-acetamide

N-Cyclohexylaminoethyl acetamide LRMS: 302.4. N-

EXAMPLE 31

2-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Cyclohexylaminoethanol. Melting Point: 69 - 72°C, LRMS: 275.4

EXAMPLE 32

2-[Cyclooctyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Cyclooctylaminethanol Melting Point. 66 - 77°C, LRMS: 289.4

EXAMPLE 33

(3,5-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3,5-Dimethylcyclohexyl)methylamine. LRMS: 259.4.

EXAMPLE 34

2-[Benzyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Benzylaminoethanol. LRMS. 269, 251

EXAMPLE 35

3-[Cyclopentyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propan-1-ol

3-Cyclopentylamino-propan-1-ol Melting Point: 162 - 164°C, LRMS 261 3

EXAMPLE 36

3-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propan-1-ol

3-Cycloheptylaminopropan-1-ol Melting Point 62 - 66°C; LRMS: 289 4

EXAMPLE 37

2-[(Decahydro-naphthalen-2-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Decahydronaphthalen-2-yl-aminoethanol. Melting Point. 75°C; LRMS 315

EXAMPLE 38

2-[(1-Ethyl-propyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-(1-Ethylpropyl)amine ethanol Melting Point: 49 - 53°C; LRMS. 249.3.

EXAMPLE 39

1-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-butan-2-ol

Cyclohexylamino-butan-2-ol LRMS. 289.

EXAMPLE 40

Bicyclo[2.2.1]hept-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[2.2 1]hept-2-yl-methylamine. LRMS: 243

EXAMPLE 41

2(S)-{[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-methyl}-cyclohexanol

2-(Cyclohexylamine)methylcyclohexanol LRMS: 329.

EXAMPLE 42

2(R)-{[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-methyl}-cyclohexanol

2-(Cyclohexylamine)methylcyclohexanol. LRMS: 329.

EXAMPLE 43

(2-Ethyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2-Ethylcyclopentyl)methyl amine. LRMS: 287.

EXAMPLE 44

Cyclononyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclononylmethylamine. LRMS: 273

EXAMPLE 45

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,4,4-trimethyl-cyclopentyl)-amine

Methyl-2,4,4-trimethyl-cyclopentyl)-amine LRMS: 259.

EXAMPLE 46

(3-Ethyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3-Ethyl-cyclopentyl)methylamine LRMS 245

EXAMPLE 47

(2,5-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2,5-Dimethylcyclohexyl)methyl-amine LRMS 259

EXAMPLE 48

(3,4-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3,4-Dimethylcyclohexyl)methylamine LRMS: 259.

EXAMPLE 49

(4-Isopropyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(4-Isopropylcyclohexyl)methylamine. LRMS: 273

EXAMPLE 50

(Decahydro-naphthalen-1-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(Decahydronaphthalen-1-yl)methylamine LRMS 285.

EXAMPLE 51

(2,2-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2,2-Dimethylcyclohexyl)methylamine LRMS: 259

EXAMPLE 52

(2-Isopropyl-5-methyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2-Isopropyl-5-methylcyclohexyl)methylamine LRMS 287.

EXAMPLE 53

Methyl-(3-methyl-cyclopentyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(3-methyl-cyclopentyl)amine. LRMS. 231.

EXAMPLE 54

(1-Benzyl-piperidin-4-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Benzylpiperidin-4-yl)methylamine LRMS: 322.

EXAMPLE 55

(4-tert-Butyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(4-tert-Butylcyclohexyl)methylamine. LRMS: 287.

EXAMPLE 56

Indan-1-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Indan-1-yl-methylamine LRMS. 265

EXAMPLE 57

(4-Ethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(4-Ethylcyclohexyl)methylamine LRMS 259

EXAMPLE 58

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amine

Methyl-1,2,3,4-tetrahydro-naphthalen-2-yl)-amine LRMS 279

EXAMPLE 59

Bicyclo[3.2.1]oct-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[3.2.1]oct-2-yl-methylamine LRMS: 257.

EXAMPLE 60

Methyl-(octahydro-4,7-methano-inden-5-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(octahydro-4,7-methano-inden-5-yl)amine LRMS. 283.

EXAMPLE 61

Bicyclo[2.2.1]hept-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[2.2.1]hept-2-yl-methylamine. LRMS: 243

EXAMPLE 62

(5-Chloro-indan-1-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(5-Chloro-indan-1-yl)methylamine LRMS: 299

EXAMPLE 63

Adamantan-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Adamantan-2-yl-methylamine. LRMS. 283.

EXAMPLE 64

(Decahydro-naphthalen-2-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(Decahydro-naphthalen-2-yl)methylamine LRMS: 285.

EXAMPLE 65

(3,5-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3,5-Dimethylcyclohexyl)methylamine LRMS· 259.

EXAMPLE 66

Bicyclo[3.3.1]non-9-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[3 3 1]non-9-yl-methylamine. LRMS: 271

EXAMPLE 67

(1-Isopropyl-4-methyl-bicyclo[3.1.0]hex-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Isopropyl-4-methylbicyclo[3.1 0]hex-3-yl)-methylamine. LRMS· 285

EXAMPLE 68

Cyclobutyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclobutylmethylamine LRMS: 203

EXAMPLE 69

(2,2-Dimethyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2,2-Dimethyl-cyclopentyl)methylamine. LRMS 245

EXAMPLE 70

4-[Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohexanecarboxylic acid ethyl ester

4-[Methylamino]cyclohexanecarboxylic acid LRMS: 303

EXAMPLE 71

(2-Isopropyl-5-methyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2-Isopropyl-5-methyl-cyclohexyl)methylamine LRMS: 287.

EXAMPLE 72

(3,3-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3,3-Dimethyl-cyclohexyl)methylamine LRMS. 259.

EXAMPLE 73

1(S)-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propan-2-ol

1-[Cyclohexylamino]-propan-2-ol. LRMS: 275 4.

EXAMPLE 74

1(R)-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propan-2-ol

1-[Cyclohexylamino]-propan-2-ol. LRMS: 275 4.

EXAMPLE 75

3-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propane-1,2-diol

3-[Cyclohexylamino]-propane-1,2-diol. LRMS· 291.4

EXAMPLE 76

2-[(Decahydro-naphthalen-1-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-[(Decahydro-naphthalen-1-yl) -amino]-ethanol. LRMS. 315.4.

EXAMPLE 77

{2-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethyl}-carbamic acid tert-butyl ester

2-[(Cycloheptylamino)ethyl]carbamic acid LRMS 374 5

EXAMPLE 78

Methyl-(3-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(3-methylcyclohexyl)amine LRMS: 359 4.

EXAMPLE 79

Methyl-(2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(2-methylcyclohexyl)amine LRMS· 359 4

EXAMPLE 80

(2-Ethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2-Ethyl-cyclohexyl)methylamine. LRMS. 373.4.

EXAMPLE 81

Methyl-(2-propyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(2-propylcyclohexyl)amine LRMS. 387 4.

EXAMPLE 82

(2,4-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2,4-Dimethylcyclohexyl)methylamine. LRMS. 373 4.

EXAMPLE 83

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,5,5-trimethyl-cyclohexyl)-amine

Methyl- (2,5,5-trimethylcyclohexyl)-amine. LRMS: 387.4.

EXAMPLE 84

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,5,5-tetramethyl-cyclohexyl)-amine

Methyl-(2,2,5,5-tetramethylcyclohexyl)-amine. LRMS: 401.

EXAMPLE 85

Cyclohexyl-methyl-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylmethylamine.

METHOD C

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

In a flame-dried flask under nitrogen, 780 mg of 60 % sodium hydride (19 5 mmol) in mineral oil was added to 30 mL of dimethylformamide (DMF) and the resulting mixture cooled to 0 °C A solution of 2 0 g (13.0 mmol) of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine in 10 mL of DMF was added slowly over a 5 min period The reaction was stirred for 10 min at which time generation of hydrogen (H_2) ceased. Benzenesulfonylchloride (1 7 mL/13.0 mmol) was added, the reaction warmed to room temperature and stirred for 1 h Water was added, and the resulting precipitate was filtered and dried in vacuo to obtain 3 4 g (89%) of the title compound as a crystalline solid, mp 163-167 °C

METHOD D

7-Benzenesulfonyl-4-chloro-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine

In a flame-dried flask under nitrogen, 0 53 mL (3 79 mmol) of diisopropylamine were dissolved in 5 mL of tetrahydrofuran (THF) and the solution cooled to -78 °C. n-Butyllithium (3 75 mmol as a 2.5 M solution in hexanes) was added and the resulting mixture brought to 0 °C with continued stirring for 10 min. The reaction mixture was again cooled to -78 °C and to this mixture added a solution of 1.0 g (3 40 mmol) of the product from Method C in 10 mL of THF over a 10 min period The reaction mixture was stirred for 1 h at -78 °C, at which time, 8 2 mL (4.10 mmol) of a 0.5 M solution of zinc chloride in THF was added, the reaction mixture was brought to room temperature and stirred for 1 h. Iodobenzene (0 46 mL/4.11 mmol) and a suspension of 197 mg of tetrakis(triphenylphosphine) palladium in 2 mL of THF were added. The resulting mixture was stirred at reflux for 3 h., cooled to room temperature, and partitioned between dichloromethane and water The aqueous layer was acidified with 1 N HCl and extracted twice with dichloromethane The dichloromethane layers were combined, washed with 1 N HCl and brine, dried over magnesium sulfate ($MgSO_4$), filtered and concentrated in vacuo to obtain the title compound. LRMS. 370, 372 (M+2)

METHOD E

4-Chloro-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine

The product from Method D was dissolved in 10 mL of THF and to this solution was added 5.0 mL of methanol and 1.0 g of NaOH The reaction mixture was stirred for 15 min., concentrated in vacuo and partitioned between a saturated aqueous solution of ammonium chloride (NH_4Cl) and ethyl acetate The resulting aqueous layer was extracted twice with ethyl acetate. The ethylacetate layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica-gel chromatography (1·5 ethyl- acetate/hexane) to obtain 0 59 g (76 %) of the title compound as a pale yellow solid, mp 145 °C (dec). LRMS· 230, 232 (M+2).

METHOD F

Cyclohexyl-methyl-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

The product from Method E (50 mg/0 218 mmol) was reacted with 0.12 mL of N-methylcyclohexylamine (0.920 mmol) as described in Method B The reaction mixture was concentrate in vacuo, methanol was added, and the resulting precipitate filtered to provide 7 mg (10%) of the title compound as a yellow solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.25 (m, 1H), 1 47-1.66 (m, 4H), 1 75-1.90 (m, 5H), 3 30 (s, 3H), 4 74 (br, 1H), 6.79 (s, 1H), 7 32-7 36 (m, 1H), 7 47-7 51 (m, 2H), 7 77 (d, 2H, J = 7.9 Hz), 8.33 (s, 1H) LRMS: 307 (M+1)

The title compound of Example 86 was prepared by a method analogous to that described in Example 85

EXAMPLE 86

(1H-Indol-5-yl)-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

IH-Indolamine LRMS. 326.4.

EXAMPLE 87

Cyclohexyl-methyl-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylmethylamine.

METHOD G

7-Benzenesulfonyl-4-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine

To flame-dried flask under N_2 was charged 0 57 ml (4 07 mmol) of diisopropylamine and 5 0 mL of dry THF The solution was cooled to -78 °C and 1.63 mL (4 08 mmol) of a 2.5 M solution of n-butyllithium in hexanes added The resulting mixture was brought to 0 °C and stirred for 10 min After cooling the mixture again to -78 °C, a solution of 1.0 g (3.40 mmol) of crude product from Method C in 10 mL of dry THF was added over a 10 min period. The resulting mixture was stirred for 1 h, at which time, 0.28 mL (4.50 mmol) of iodomethane were added The reaction mixture was stirred for 2 h, quenched with a saturated solution of NH_4Cl and warmed to room temperature. The mixture was stirred for 5 min., diluted with water and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo to obtain the title compound LRMS: 308, 310 (M+2).

METHOD H

4-Chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine

The product from Method G was deprotected as described in Method E The crude product was purified by trituration with hexanes and dichloromethane to obtain 250 mg (44%) of the title compound as a yellow solid. Mp 205 °C dec. LRMS 168, 170 (M+2)

METHOD I

Cyclohexyl-methyl-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

The product from Method H (50 mg/0.298 mmol) was reacted with 100 mg (0.883 mmol) of N-methylcyclohexylamine as described in Method B The reaction mixture was worked up as in Method B with the exception that ethyl acetate was used in place of ether. The title compound (42 mg, 58 % yield) was obtained as a white solid Mp 221 °C dec ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15-1.25 (m, 1H), 1.43-1.62 (m, 4H), 1.73 (br s, 1H, J = 13.7 Hz), 1 82-1.90 (m, 4H), 2 41 (d, 3H, J = 0.8 Hz), 3.21 (s, 3H) 4 63 (br s, 1H), 6.20 (s, 1H), 8 22 (s, 1H), 10 1 (br s, 1H) LRMS 245 (M+1)

The title compound of Example 88 were prepared by a method analogous to that described in Example 87.

EXAMPLE 88

Cyclohexyl-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylamine. LRMS. 231.3

EXAMPLE 89

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

METHOD L

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

To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (250 mg/1 63 mmol) in 12 mL of DMF was added 676 mg (4.89 mmol) of potassium carbonate and the resulting mixture stirred at room temperature for 20 min Benzylchloride (310 mg/2.45 mmol) was added and the new mixture stirred at room temperature for 24 h then filtered, concentrated and the residue purified by silica gel chromatography (3·1 hexanes/ethyl acetate) affording 318 mg (80%) of the title compound. LRMS: 244 1 (M+1).

METHOD M

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

To a flame dried flask under nitrogen was charged 84 mg (2 10 mmol) of 60 % sodium hydride in mineral oil and 3.0 mL of THF and the mixture cooled to 0 °C C, ,ohexanol (0.18 mL/1.70 mmol) was added and the reaction mixture stirred for 5 min. A solution of 102 mg (0.419 mmol) of the product from Method L in 1 0 mL of THF was added and the mixture heated to reflux for 3 h After cooling to room temperature, the reaction mixture was acidified

to pH 1 with 2 N HCl and concentrated in vacuo The resulting residue was then slurried in ethyl acetate, filtered and the filtrate concentrated in vacuo to provide 76 mg (59%) of the title compound as an oil LRMS 308 (M+1)

METHOD N

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

To liquid ammonia (6 0 mL) at -78 °C was added 33 mg (1.43 mmol) sodium metal and the resulting dark blue solution stirred at -78 °C 10 min. A solution of 75 mg (0.244 mmol) of the product from Method M in 3.0 mL of ether was added dropwise over a 5 min period. The resulting solution stirred at -78 °C for 1 h followed by quenching upon addition of 500 mg of solid ammonium chloride After evaporation at room temperature, the residual solid was triturated with 25 mL of ethylacetate containing 1 mL of acetic acid for 1 h. Filtration and concetration in vacuo afforded crude material which was purified by preparative thin layer chromatography (silica-gel; 2:1 ethyl acetate/hexanes) to produce 5 mg of the title compound ^{1}H NMR (400 MHz) ($CDCl_3$) δ. 1.27 - 1 35 (m, 6H), 1.62 - 1 67 (m, 4H), 5 30 - 5.36 (m, 1H), 6.55 (d, 1H, J = 3.2 Hz), 7 11 (d, 1H, J = 3.2 Hz), 8.37 (br s 1H) LRMS 218.2 (M+1)

EXAMPLE 90

METHOD O

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

To a solution of 100 mg (0.651mmol) of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine dissolved in 3.0 mL of THF was added 0.10 mL (0.818 mmol) of cyclohexylmercaptan and 100 mg (0.847 mmol) of 95 % potassium tert-butoxide and the resulting mixture heated at reflux for 3 5 hr. After cooling to room temperature, the reaction mixture was acidified to pH 1 with 2 N HCl and concentrated in vacuo The residue was then partitioned between ethylacetate and 1 N HCl The aqueous layer was extracted with ethyl acetate, the ethyl acetate layers were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The cude product was purified by silica-gel chromatography (1.3 ethylacetate/hexanes) providing 34 mg (22%) of the title compound as a white solid. Mp 162-163 °C. ^{1}H NMR (400 MHz) **d**: 1.22-1.36 (m, 1H), 1.45-1.64 (m, 5H), 1.75-1.79 (m, 2H), 2.12-2.14 (m, 2H), 4.18-4.20 (m, 1H), 6.50 (d, 1H, J = 3.7 Hz), 7.19 (d, 1H, J = 3.5 Hz), 8.61 (s, 1H), 10 0 (br s, 1H) LRMS: 234 (M+1).

EXAMPLE 91

5-Chloro-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

METHOD R

4,5-Dichloro-7H-pyrrolo[2,3-d]pyrimidine

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (154 mg, 1 0 mmol) was suspended in 6 0 mL of dry dichloromethane in a flame-dried flask and to this mixture was added N-chlorosuccinimide (147 mg, 1 1 mmol) in one portion. The resulting mixture stirred at room temperature for 18 h, at which time the solvent was removed under reduced pressure. The residue was triturated with water and isolated by filtration to afford 137 mg (72%) of the title compound as a gray solid, mp 224-227 °C(dec) LRMS: 188 (M+1)

METHOD S

5-Chloro-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

The product from Method R (57 mg, 0.3 mmol) was suspended in 3.0 mL of tert-butanol and to this solution was added piperidine (90μL, 0.9 mmol) and the resulting system heated at reflux for 1 h The reaction mixture was cooled to room temperature and water was added (4.0 mL). The solution was adjusted to pH 1 with 1 N HCl and then washed with ether The aqueous layer was removed and adjusted to pH 12 with 2 N NaOH. The solution was then extracted 2 x 15 mL with dichloromethane and the combined organics washed with water then brine and dried over $MgSO_4$ Evaporation of solvent afforded 45 mg of a yellow solid that was purified by silica-gel chromatography (3 1 ethyl acetate/hexanes) to yield 23 mg (32%) of the title compound as a light yellow solid. Mp 170 - 172 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ. 1.67 - 1.74 (m, 6H), 3 65 - 3 67 (m, 4H), 7 10 (s, 1H), 8.31 (s, 1H). LRMS. 237 (M + 1).

The title compounds of Examples 92-94 were prepared by a method analogous to that described in Example 91

EXAMPLE 92

(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(3-ethynyl-phenyl)-amine

3-Ethynylphenyl)amine. Melting Point. 250°C.

EXAMPLE 93

(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-cycloheptyl-methyl-amine

Cycloheptylmethylamine. Melting Point: 152 - 153°C; LRMS: 279.8.

EXAMPLE 94

(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-cyclooctyl-methyl-amine

Cyclooooctylmethylamine. Melting Point: 151 - 153°C; LRMS: 293.8.

EXAMPLE 95

5-Phenyl-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

METHOD T

5-Bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (30 g/0.02 mol) dissolved in 75 mL of chloroform was added 3 5 g (0 02 mol) of N-bromosuccinamide and the resulting mixture refluxed for 1 h After cooling to room temperature, the precipitate was removed by filtration and dried under reduced pressure affording 4 1 g (89%) of the title compound. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7 93 (d, 1H, J = 2 8 Hz), 8 60 (s, 1H)

METHOD U

7-Benzenesulfonyl-5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine

To a slurry of the product from Method T (4 1 g/0.018 mol) in DMF (15 mL) and cooled to 0 °C was added 1.0 g (0.025 mol) of 60% sodium hydride in mineral oil and the resulting mixture stirred at 0 °C for 15 min Benzenesulfonyl chloride (3.2 g/0 018 mol) was added, the reaction mixture warmed to room temperature and stirred for 2 h Water was then added (15 mL) and the resulting solid removed by filtration and dried in vacuo affording 5.9 g (89%) of the title compound.

METHOD V

7-Benzenesulfonyl-5-bromo-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

A mixture of 2.0 g (5 37 mmol) of the product from Method U and 1 1 g (13 4 mmol) of piperidine in 10 mL of *tert*-butanol was heated with stirring at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was partitioned between dichloromethane (25 mL) and water (25 mL) The dichloromethane layer was dried over sodium sulfate (Na_2SO_4) and concentrated to dryness in vacuo affording 2.2 g (97%) of the title compound. ^{1}H NMR (400 MHz) ($CDCl_3$) δ· 1.63 - 1.72 (m, 6H), 3.54 - 3.57 (m, 4H), 7 53 (t, 2H, J = 2.0 Hz), 7.60 (s, 1H), 7 61 (t, 1H, J = 2.0 Hz), 8.17 - 8 20 (m, 2H), 8.43 (s, 1H) LRMS· 422.7, 420.7 (M+1).

METHOD W

5-Phenyl-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of the product from Method V (100 mg/0.237 mmol) in 1 0 mL of dioxane was added 32 mg (0.261 mmol) of phenylboronic acid and 75 mg (0.356 mmol) of tribasic potassium phosphate followed by 7 mg (0 006 mmol) of tetrakis(triphenylphosphine) palladium. The resulting mixture was degassed with nitrogen and stirred at 100 °C for 48 h. After cooling to room temperature, 1.0 mL of methanol was added followed by 50 mg of NaOH and the new mixture stirred at room temperature for 1 h The resulting mixture was then partitioned between dichloromethane and water, the dichloromethane layer dried over $MgSO_4$ and concentrated to dryness in vacuo The crude product was purified by silica-gel chromatography (2 1 ethyl acetate/hexanes) affording 13 mg (20%) of the title compound. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.33 - 1 34 (m, 4H), 1 43 - 1 44 (m, 2H), 3.26 - 3 28 (m, 4H),

7 12 (s, 1H), 7 27 (t, 1H, J = 7.2 Hz), 7 38 (t, 2H, J = 8 0 Hz), 7.45 (d, 2H, J = 0 8 Hz), 8.42 (s, 1H) LRMS 279.2 (M+1)

The title compounds of Examples 96-99 were prepared by a method analogous to that described in Example 95

EXAMPLE 96

Cyclohexyl-methyl-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylmethylamine. Melting Point: 200°C; LRMS. 307.4

EXAMPLE 97

Cyclohexyl-[5-(4-fluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-methyl-amine

Cyclohexylmethylamine Melting Point 220°C, LRMS: 325.4.

EXAMPLE 98

Bicyclo[2.2.1]hept-2-yl-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[2.2.1]hept-2-yl-amine. LRMS· 305 4.

EXAMPLE 99

[5-(3-Chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-cyclohexyl-methyl-amine

Cyclohexyl-methylamine. LRMS: 455 9

EXAMPLE 100

METHOD X

4-Piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (54 mg/0.3 mmol) (prepared by the method of Townsend, et al., J Am. Chem. Soc., 1969, 91, 2102) suspended in 3.0 mL tert-Butanol was added piperidine (59 µL/0.60 mmol). The resulting mixture was then heated at reflux for 2 5 h and after cooling to room temperature, was transferred to a separatory funnel and diluted with ether (20 mL) The solution was extracted 2 x 10 mL with 1N HCl, the combined aqueous layers were adjusted to pH 7 with 2 N potassium hydroxide (KOH) solution forming a precipitate which was collected by filtration, washed with water and dried under reduced pressure to give 29 mg (42%) of the title compound as a colorless solid. Mp 209 - 211 °C; ^{1}H NMR (400 MHz) (acetone-d6) δ: 1.72 - 1.74 (m, 6H), 3.72 - 3.79 (m, 4H), 8.12 (s, 1H), 8.29 (s, 1H). LRMS. 228 (M + 1).

EXAMPLE 101

5-Ethynyl-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

METHOD Y

4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (30 g/0 02 mol) dissolved in 80 mL of chloroform was added 4.5 g (0 02 mol) of N-iodosuccinimide and the resulting mixture heated at reflux for 1 h After cooling to room temperature, the percipitate was removed by filtration and dried under reduced pressure affording 4 6 g (82%) of the title compound

METHOD Z

7-Benzenesulfonyl-4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine

The title compound was prepared as previously described in Method U using the product from Method X affording 5 4 g (80%) of material LRMS: 419.6 (M+1), 279.7.

METHOD AA

7-Benzenesulfonyl-5-iodo-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

The title compound was prepared by the procedure described in Method V using the product from Method Z to produce the title compound LRMS: 469 (M+1), 329.1

METHOD BB

7-Benzenesulfonyl-4-piperidin-1-yl-5-triethylsilanylethynyl-7H-pyrrolo[2,3-d]pyrimidine

To a flamed-dried flask under nitrogen was charged 211 mg (0 5 mmol) of the product from Method AA, 19 mg (0.1 mmol) of copper (I) iodide and 58 mg (0 05 mmol) of tetrakis(triphenylphosphine)palladium To this mixture was then added 0 14 mL (1 0 mmol) of triethylamine and 0 27 mL (1.5 mmol) of triethylsilylacetylene as a solution in 1.5 mL of dry DMF. The resulting mixture stirred at room temperature for 3 h, at which time, 5 0 mL of water were added and the mixture extracted with ethylacetate The ethyl acetate extract was dried over $MgSO_4$ and concentrated in vacuo. The resulting crude product was then purified by silica-gel chromatography (7:1 hexanes/ethyl acetate) affording 194 mg (89%) of the title compound LRMS: 481 (M+1), 341

METHOD CC

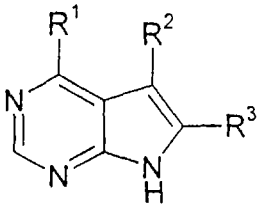
5-Ethynyl-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of the product from Method BB (194 mg/0 40 mmol) dissolved in 2.0 mL of dry THF was added dropwise 0 4 mL (0 4 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. The resulting mixture stirred at room temperature for 10 min, then was transferred to a methanol solution (3 0 mL) containing 1 g of KOH, the new mixture stirred at room temperature for 15 min and concentrated in vacuo The residue was partitioned between water and ethyl acetate, the ethyl acetate layer washed with water and brine, dried over $MgSO_4$ and concentrated to dryness in vacuo. The crude product was

purified by silica-gel chromatography (2 1 ethyl acetate/hexanes) affording 72 mg (64%) of the title compound as a white crystalline solid Mp 179 - 181 °C ^{1}H NMR (400 MHz) ($CDCl_3$) d 1 72 (br s, 6H), 3 20 (s, 1H), 3 82 - 3 83 (m, 4H), 7 47 (s, 1H), 8 35 (s, 1H) LRMS 227 (M+1)

CLAIMS

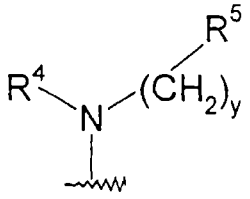
1 A compound of the formula



I

or the pharmaceutically acceptable salt thereof, wherein

R^1 is a group of the formula



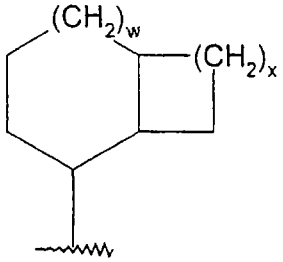
wherein y is 0, 1 or 2,

R^4 is selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_6)$acyloxy, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, cyano, nitro, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl or $(C_1$-$C_6)$acylamino; or R^4 is $(C_3$-$C_{10})$cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1$-$C_6)$acyloxy, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, cyano, cyano$(C_1$-$C_6)$alkyl, trifluoromethyl$(C_1$-$C_6)$alkyl, nitro, nitro$(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$acylamino;

R^5 is selected from the group consisting of trifluoromethyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkyl(difluoromethylene)$(C_1$-$C_3)$alkyl, $(C_3$-$C_{10})$cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo, $(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkylamino, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-CO-NH, $(C_1$-$C_6)$alkylamino-CO-, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_1$-$C_6)$alkylamino, amino$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_1$-$C_6)$alkyl, nitro, cyano$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, nitro$(C_1$-$C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$acylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$acylamino, amino$(C_1$-$C_6)$acyl, amino$(C_1$-$C_6)$acyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$acyl, $((C_1$-$C_6)$alkyl$)_2$amino$(C_1$-$C_6)$acyl, $R^{15}R^{16}$N-CO-O-, $R^{15}R^{16}$N-CO-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-S$(O)_m$, $R^{15}R^{16}$NS$(O)_m$, $R^{15}R^{16}$NS$(O)_m$ $(C_1$-$C_6)$alkyl, R^{15}S$(O)_m$ R^{16}N, R^{15}S$(O)_m R^{16}$N$(C_1$-$C_6)$alkyl wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1$-$C_6)$alkyl, or R^5 is $(C_3$-$C_{10})$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl,

piperazinyl(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by one to five cyano, nitro, halo, deuterium, hydroxy, carboxy, (C_1-C_6)acylamino, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl or ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl; or R^5 is $R^{13}CO(C_1$-$C_6)$alkyl or $R^{13}CO(C_3$-$C_{10})$cycloalkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, deuterium, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl(C_1-C_6)alkyl; or R^5 is R^{14}, $R^{14}(C_1$-$C_6)$alkyl or $R^{14}(C_3$-$C_{10})$cycloalkyl wherein R^{14} is (C_2-C_9)heterocycloalkyl, (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidinyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6)acylpiperidyl,

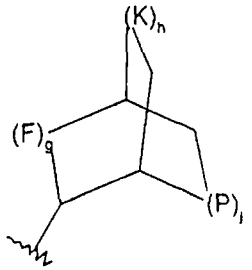
or R^5 is a group of the formula



wherein w is 0, 1 or 2,

x is 0, 1, 2 or 3;

or R^5 is a group of the formula



II

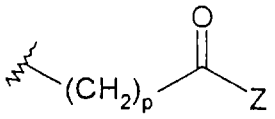
wherein g, h and j are each independently 0 to 3,

F, K and P are each independently oxygen, $S(O)_d$ wherein d is 0, 1 or 2, NR^6 or CR^7R^8,

R^6 is selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl (difluoromethylene), $(C_1$-$C_3)$alkyl(difluoromethylene)$(C_1$-$C_3)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$acyl, $((C_1$-$C_6)$alkyl$)_2$amino$(C_1$-$C_6)$acyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl, hydroxy$(C_2$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_2$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_2$-$C_6)$alkyl, piperazinyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acylamino$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylthio$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylthio$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfinyl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfinyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfonyl$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, $((C_1$-$C_6)$alkyl$)_2$amino$(C_1$-$C_6)$alkyl, $R^{13}CO(C_1$-$C_6)$alkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl or $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl; or $R^{14}(C_2$-$C_6)$alkyl wherein R^{14} is $(C_1$-$C_6)$acylpiperazino, $(C_6$-$C_{10})$arylpiperazino, $(C_5$-$C_9)$heteroarylpiperazino, $(C_1$-$C_6)$alkylpiperazino, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkylpiperazino, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, $(C_1$-$C_6)$alkylpiperidyl, $(C_6$-$C_{10})$arylpiperidyl, $(C_5$-$C_9)$heteroarylpiperidyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkylpiperidyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkylpiperidyl, $(C_1$-$C_6)$alkoxyacyl, $(C_1$-$C_6)$alkylaminoaryl, $((C_1$-$C_6)$alkyl$_2$aminoacyl or $(C_1$-$C_6)$acylpiperidyl,

R^7 and R^8 are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, amino, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl)amino, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$acyl$(C_1$-$C_6)$alkylamino, carboxy, $(C_1$-$C_6)$alkoxyacyl, $(C_1$-$C_6)$alkylaminoacyl, $((C_1$-$C_6)$alkyl$)_2$aminoacyl, aminoacyl, trifluoromethyl, trifluoromethyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl (difluoromethylene), $(C_1$-$C_3)$alkyl(difluoromethylene)$(C_1$-$C_3)$alkyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, piperazinyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acylamino$(C_1$-$C_6)$alkyl, piperidyl, $(C_1$-$C_6)$alkylpiperidyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylthio$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylthio$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfinyl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfinyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfonyl$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, $((C_1$-$C_6)$alkyl$)_2$amino$(C_1$-$C_6)$alkyl, $R^{13}CO(C_1$-$C_6)$alkyl or $R^{13}CO(C_3$-$C_{10})$cycloalkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl or $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl; R^{14}, $R^{14}(C_1$-

C_6)alkyl or $R^{14}(C_3-C_{10})$cycloalkyl wherein R^{14} is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6)acylpiperidyl, or a group of the formula



III

wherein p is 0, 1, 2 or 3, and

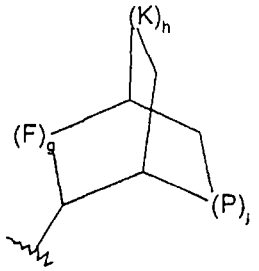
Z is hydroxy, (C_1-C_6)alkoxy or NR^1R^2 wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)acylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, $R^5(C_1-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^5)(C_1-C_6)$alkyl wherein R^5 is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, $((C_1-C_6)alkyl)_2$ amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino, $R^6(C_1-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^6)(C_1-C_6)$alkyl wherein R^6 is piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroarylpiperidyl or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl,

or R^1 is defined as OR^9 or $S(O)_qR^9$ wherein q is 0, 1 or 2, and

R^9 is selected from the group consisting of trifluoromethyl(C_1-C_6)alkyl, (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five carboxy, cyano, amino, hydroxy, (C_1-C_6) alkoxy, halo, (C_1-C_6)alkyl $S(O)_m$ wherein m is 0, 1 or 2; $R^{15}R^{16}NS(O)_m$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl, (C_1-C_6)acyl, (C_1-C_6)alkylamino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, $R^{15}R^{16}$N-CO-O-, $R^{15}R^{16}$N-CO-(C_1-C_6)alkyl wherein R^{15} and R^{16} are as defined above, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, (C_1-C_6)alkylamino, amino(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, nitro, cyano(C_1-C_6)alkyl, nitro(C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)acylamino, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino$(C_1-$

C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl or ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_{10})cycloalkyl(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, (C_2-C_6)alkoxy(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino, (C_1-C_6)alkyl wherein the alkyl group is optionally substituted by one to five cyano, nitro, hydroxy, carboxy, (C_1-C_6)acylamino, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl or ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl; $R^{13}CO$(C_1-C_6)alkyl or $R^{13}CO$(C_3-C_{10})cycloalkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl(C_1-C_6)alkyl; R^{14}, R^{14}(C_1-C_6)alkyl or R^{14}(C_3-C_{10})cycloalkyl wherein R^{14} is (C_2-C_9)heterocycloalkyl, (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidinyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6)acylpiperidyl,

or R^9 is a group of the formula



II

wherein g, h and j are each independently 0 to 6,

F, K and P are each independently oxygen, $S(O)_d$ wherein d is 0, 1 or 2, NR^6 or CR^7R^8 wherein R^6, R^7 and R^8 are as defined above;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydoxy, nitro, carboxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, trifluoromethyl, trifluoromethoxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy wherein the alkyl or alkoxy groups are optionally substittued by one to three groups selected from halo, hydroxy, carboxy, amino (C_1-C_6)alkylthio, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_5-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl, (C_3-C_9)cycloalkyl or (C_6-C_{10})aryl, or R^2 and R^3 are each independently (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkoxy, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_6-

C_{10})arylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)acyl, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyamino-CO-, (C_5-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl or (C_6-C_{10})aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, (C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-NH-, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyl-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkoxy, carboxy, carboxy(C_1-C_6)alkyl, carboxy(C_1-C_6)alkoxy, benzyloxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_6-C_{10})aryl, amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonylamino, (C_6-C_{10})aryl(C_1-C_6)alkoxycarbonylamino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyl-CO-NH-, cyano, (C_5-C_9)heterocycloalkyl, amino-CO-NH-, (C_1-C_6)alkylamino-CO-NH-, ((C_1-C_6)alkyl)$_2$amino-CO-NH-, (C_6-C_{10})arylamino-CO-NH-, (C_5-C_9)heteroarylamino-CO-NH-, (C_1-C_6)alkylamino-CO-NH-(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino-CO-NH-(C_1-C_6)alkyl, (C_6-C_{10})arylamino-CO-NH-(C_1-C_6)alkyl, (C_5-C_9)heteroarylamino-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonylamino, (C_6-C_{10})arylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_5-C_9)heteroaryl or (C_2-C_9)heterocycloalkyl;

with the proviso that when either R^4 and R^5 is hydrogen, the other of R^4 or R^5 cannot be (C_6-C_{10})aryl or (C_6-C_{10})aryl(C_1-C_6)alkyl;

with the proviso that when R^4 is hydrogen, unsubstituted (C_1-C_6)alkyl or unsubstituted (C_3-C_{10})cycloalkyl, R^5 cannot be (C_6-C_{10})aryl(C_1-C_6)alkyl; R^{20} and R^{21} cannot be (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^{14} cannot be (C_2-C_9)heterocycloalkyl, morpholino, thiomorphlino, piperidino, pyrrolidino, piperidinyl or (C_1-C_6)alkylpiperidinyl;

with the proviso that the sp^2 and sp carbons of alkenyl or alkynyl cannot be substituted by hydroxy or amino,

with the proviso that when R^4 is hydrogen, R^5 cannot be amino (C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)alkyl, furanyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl or carboxy(C_1-C_6)alkyl,

with the proviso that both R^4 and R^5 cannot both be hydroxy (C_1-C_6)alkyl,

with the proviso that when R^4 is (C_1-C_6)alkyl, R^5 cannot be (C_1-C_6)alkoxy(C_1-C_6)alkyl or carboxy(C_1-C_6)alkyl; and

with the proviso that R^1 cannot be carboxy(C_1-C_6)alkylthio or (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkylthio

2 A compound according to claim 1, wherein R^1 is NR^4R^5

3 A compound according to claim 1, wherein R^4 is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by hydroxy, amino, trifluoromethyl, (C_1-C_6)acyloxy, (C_1-C_6)alkylamino, $((C_1-C_6)alkyl)_2$amino or (C_1-C_6)acylamino, or R^4 is (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by hydroxy, trifluoromethyl or (C_1-C_6)acyloxy

4 A compound according to claim 1, wherein R^5 is (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five deuterium, hydroxy, trifluoromethyl, halo, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, $((C_1-C_6)alkyl)_2$amino(C_1-C_6)acyl, (C_1-C_6)acylamino, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, halo(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, $R^{15}S(O)_m$ $R^{16}N$, $R^{15}S(O)_mR^{16}N(C_1-C_6)$alkyl wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl.

5 A compound according to claim 1, wherein R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkoxy, (C_2-C_9)heterocycloalkyl, (C_5-C_9)heteroaryl or (C_6-C_{10})aryl

6 A compound according to claim 1, wherein said compound is selected from the group consisting of:

2-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohexyl}-propan-2-ol,

2-{3-[(2-Hydroxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-4-methyl-cyclohexyl}-propan-2-ol;

2-[(5-Isopropenyl-2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol,

(5-Isopropenyl-2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,2-trifluoro-ethyl)-amine;

2-{4-Methyl-3-[(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,2-trifluoro-ethyl)-amino]-cyclohexyl}-propan-2-ol;

2-{4-Methyl-5-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohex-3-enyl}-propan-2-ol;

2-[1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-azetidin-3-yl]-propan-2-ol,

2-[1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-azetidin-2-yl]-propan-2-ol;

(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(5-isopropenyl-2-methyl-cyclohexyl)-methyl-amine;

2-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-cyclohexyl}-propan-2-ol,

(2-Ethyl-4-isopropenyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine,

2-{3-Ethyl-4-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclopentyl}-propan-2-ol,

2-{3-Ethyl-4-[(2-hydroxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclopentyl}-propan-2-ol,

2-[(2-Ethyl-4-isopropenyl-cyclopentyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;

(5-(S)-Isopropenyl-2-methyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

3-Methyl-8-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-8-aza-bicyclo[3.2.1]octan-3-ol,

2-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;

2-[Cyclooctyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol,

Bicyclo[2.2.1]hept-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine; and

4-Piperidin-1-yl-5-m-tolyl-7H-pyrrolo[2,3-d]pyrimidine.

7. A pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

9. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof, alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human.

10. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof , alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, for the treatment or prevention of a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases in a mammal, including a human.

11. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof , alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, for the preparation of a medicament for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human.

12. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof , alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, for the preparation of a medicament for the treatment or prevention of a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases in a mammal, including a human.