PYRROLOPYRAZINE KINASE INHIBITORS

The present invention relates to the use of novel pyrrolopyrazine derivatives which are JAK and SYK inhibitors and selectively inhibit JAK3 and are useful for the treatment of auto-immune and inflammatory diseases.

Protein kinases constitute one of the largest families of human enzymes and regulate many different signaling processes by adding phosphate groups to proteins; particularly tyrosine kinases phosphorylate proteins on the alcohol moiety of tyrosine residues. The tyrosine kinase family includes members that control cell growth, migration, and differentiation. Abnormal kinase activity has been implicated in a variety of human diseases including cancers, autoimmune and inflammatory diseases. Since protein kinases are among the key regulators of cell signaling they provide a means to modulate cellular function with small molecule inhibitors of kinase activity and thus make good drug design targets. In addition to treatment of kinase-mediated disease processes, selective and efficacious inhibitors of kinase activity are also useful for investigation of cell signaling processes and identification of other cellular targets of therapeutic interest.

The JAKs (JAnus Kinases) are a family of cytoplasmic protein tyrosine kinases including JAK1, JAK2, JAK3 and TYK2. Each of the JAKs is preferentially associated with the intracytoplasmic portion of discrete cytokine receptors (*Annu. Rev. Immunol.* **16** (1998), pp. 293–322). The JAKs are activated following ligand binding and initiate signaling by phosphorylating cytokine receptors that, *per se*, are devoid of intrinsic kinase activity. This phosphorylation creates docking sites on the receptors for other molecules known as STAT proteins (signal transducers and activators of transcription) and the phosphorylated JAKs bind various STAT proteins. STAT proteins, or STATs, are DNA binding proteins activated by phosphorylation of tyrosine residues, and function both as signaling molecules and transcription factors and ultimately bind to specific DNA sequences present in the promoters of cytokine-responsive genes (Leonard et al., (2000), J. Allergy Clin. Immunol. 105:877-888).

JAK/STAT signaling has been implicated in the mediation of many abnormal immune responses such as allergies, asthma, autoimmune diseases such as transplant (allograft) rejection,

rheumatoid arthritis, amyotrophic lateral sclerosis and multiple sclerosis, as well as in solid and hematologic malignancies such as leukemia and lymphomas.

Thus, the JAKs and STATs are components of multiple potentially intertwined signal-transduction pathways (*Oncogene* **19** (2000), pp. 5662–5679), which indicates the difficulty of specifically targeting one element of the JAK–STAT pathway without interfering with other signal transduction pathways.

The JAK kinases, including JAK3, are abundantly expressed in primary leukemic cells from children with acute lymphoblastic leukemia, the most common form of childhood cancer, and studies have correlated STAT activation in certain cells with signals regulating apoptosis (Demoulin et al., (1996), Mol. Cell. Biol. 16:4710-6; Jurlander et al., (1997), Blood. 89:4146-52; Kaneko et al., (1997), Clin. Exp. Immun. 109:185-193; andNakamura et al.,(1996), J. Biol. Chem. 271: 19483-8). They are also known to be important to lymphocyte differentiation, function and survival. JAK3 in particular plays an essential role in the function of lymphocytes, macrophages, and mast cells. Given the importance of this JAK kinase, compounds which modulate the JAK pathway, including those selective for JAK3, can be useful for treating diseases or conditions where the function of lymphocytes, macrophages, or mast cells is involved (Kudlacz et al., (2004) Am. J. Transplant 4:51-57; Changelian (2003) Science 302:875-878). Conditions in which targeting of the JAK pathway or modulation of the JAK kinases, particularly JAK3, are contemplated to be therapeutically useful include, leukemia, lymphoma, transplant rejection (e.g., pancreas islet transplant rejection, bone marrow transplant applications (e.g., graft-versus-host disease), autoimmune diseases (e.g., diabetes), and inflammation (e.g., asthma, allergic reactions). Conditions which can benefit for inhibition of JAK3 are discussed in greater detail below.

However, in contrast to the relatively ubiquitous expression of JAK1, JAK2 and Tyk2, JAK3 has a more restricted and regulated expression. Whereas some JAKs (JAK1, JAK2, Tyk2) are used by a variety of cytokine receptors, JAK3 is used only by cytokines that contain a γc in their receptor. JAK3, therefore, plays a role in cytokine signaling for cytokines which receptor was shown to date to use the common gamma chain; IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. JAK1 interacts with, among others, the receptors for cytokines IL-2, IL-4, IL-7, IL-9 and IL-21, while JAK2 interacts with, among others, the receptors for IL-9 and TNF-alpha. Upon the binding of certain cytokines to their receptors (e.g., IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21), receptor

oligomerization occurs, resulting in the cytoplasmic tails of associated JAK kinases being brought into proximity and facilitating the trans-phosphorylation of tyrosine residues on the JAK kinase. This trans-phosphorylation results in the activation of the JAK kinase.

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.

In particular, JAK3 has been implicated in a variety of biological processes. For example, the proliferation and survival of murine mast cells induced by IL-4 and IL-9 have been shown to be dependent on JAK3- and gamma chain-signaling (Suzuki et al., (2000), Blood 96:2172-2180). JAK3 also plays a crucial role in IgE receptor-mediated mast cell degranulation responses (Malaviya et al., (1999), Biochem. Biophys. Res. Commun. 257:807-813), and inhibition of JAK3 kinase has been shown to prevent type I hypersensitivity reactions, including anaphylaxis (Malaviya et al., (1999), J. Biol. Chem. 274:27028-27038). JAK3 inhibition has also been shown to result in immune suppression for allograft rejection (Kirken, (2001), Transpl. Proc. 33:3268-3270). JAK3 kinases have also been implicated in the mechanism involved in early and late stages of rheumatoid arthritis (Muller-Ladner et al., (2000), J. Immunal. 164:3894-3901); familial amyotrophic lateral sclerosis (Trieu et al., (2000), Biochem Biophys. Res. Commun. 267:22-25); leukemia (Sudbeck et al., (1999), Clin. Cancer Res. 5:1569-1582); mycosis fungoides, a form of T-cell lymphoma (Nielsen et al., (1997), Prac. Natl. Acad. Sci. USA 94:6764-6769); and abnormal cell growth (Yu et al., (1997), J. Immunol. 159:5206-5210; Catlett-Falcone et al., (1999), Immunity 10:105-115).

JAK3 inhibitors are useful therapy as immunosuppressive agents for organ transplants, xeno transplantation, 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.

Non-hematopoietic expression of JAK3 has also been reported, although the functional significance of this has yet to be clarified (*J. Immunol.* **168** (2002), pp. 2475–2482). Because bone marrow transplants for SCID are curative (*Blood* **103** (2004), pp. 2009–2018), it seems

unlikely that JAK3 has essential non-redundant functions in other tissues or organs. Hence, in contrast with other targets of immunosuppressive drugs, the restricted distribution of JAK3 is appealing. Agents that act on molecular targets with expression limited to the immune system might lead to an optimal efficacy:toxicity ratio. Targeting JAK3 would, therefore, theoretically offer immune suppression where it is needed (*i.e.* on cells actively participating in immune responses) without resulting in any effects outside of these cell populations. Although defective immune responses have been described in various $STAT^{-/-}$ strains (*J. Investig. Med.* **44** (1996), pp. 304–311; *Curr. Opin. Cell Biol.* **9** (1997), pp. 233–239), the ubiquitous distribution of STATs and the fact that those molecules lack enzymatic activity that could be targeted with small-molecule inhibitors has contributed to their non-selection as key targets for immunosuppression.

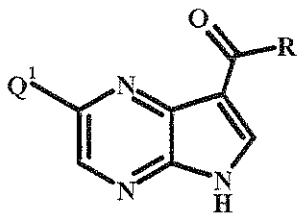
SYK (Spleen Tyrosine Kinase) is a non-receptor tyrosine kinase that is essential for B-cell activation through BCR signaling. SYK become activated upon binding to phosphoryated BCR and thus initiates the early signling events following BCR activation. Mice deficient in SYK exhibit an early block in B-cell development (Cheng et al. Nature 378:303, 1995; Turner et al. Nature 378:298, 1995). Therefore inhibition of SYK enzymatic activity in cells is proposed as a treatment for autoimmune disease through its effects on autoantibody production.

In addition to the role of SYK in BCR signaling and B-cell activation, it also plays a key role in FcεRI mediated mast cell degranulation and eosinophil activation. Thus, SYK is implicated in allergic disorders including asthma (reviewed in Wong et al. Expert Opin Investig Drugs 13:743, 2004). SYK binds to the phosphorylated gamma chain of FcεRI via its SH2 domains and is essential for downstream signaling (Taylor et al. Mol. Cell. Biol. 15:4149, 1995). SYK deficient mast cells demonstrate defective degranulation, arachidonic acid and cytokine secretion (Costello et al. Oncogene 13:2595, 1996). This also has been shown for pharmacologic agents that inhibit SYK activity in mast cells (Yamamoto et al. J Pharmacol Exp Ther 306:1174, 2003). Treatment with SYK antisense oligonucleotides inhibits antigen-induced infiltration of eosinophils and neutrophils in an animal model of asthma (Stenton et al. J Immunol 169:1028, 2002). SYK deficient eosinophils also show impaired activation in response to FcεR stimulation (Lach-Trifilieffe et al. Blood 96:2506, 2000). Therefore, small molecule inhibitors of SYK will be useful for treatment of allergy-induced inflammatory diseases including asthma.

In view of the numerous conditions that are contemplated to benefit by treatment involving modulation of the JAK and/or SYK pathways it is immediately apparent that new compounds that modulate JAK and/or SYK pathways and methods of using these compounds should provide substantial therapeutic benefits to a wide variety of patients. Provided herein are novel pyrrolopyrazine derivatives for use in the treatment of conditions in which targeting of the JAK and/or SYK pathways or inhibition of JAK or SYK kinases, particularly JAK3, and are therapeutically useful for the treatment of auto-immune and inflammatory diseases.

The novel pyrrolopyrazine derivatives provided herein selectively inhibit JAK3 and are useful for the treatment of auto-immune and inflammatory diseases. The compounds of the invention modulate the JAK and/or SYK pathways and are useful novel pyrrolopyrazine derivatives for the treatment of auto-immune and inflammatory diseases, wherein preferred compounds selectively inhibit JAK3. For example, the compounds of the invention may inhibit JAK3 and SYK, wherein preferred compounds are selective for JAK3 of the JAK kinases and are useful novel pyrrolopyrazine derivatives for the treatment of auto-immune and inflammatory diseases. Furthermore, the compounds of the invention may inhibit JAK3 and JAK2, wherein preferred compounds are selective for JAK3 of the JAK kinases, and are useful novel pyrrolopyrazine derivatives for the treatment of auto-immune and inflammatory diseases. Similarly, the compounds of the invention may inhibit JAK3 and JAK1, wherein preferred compounds are selective for JAK3 of the JAK kinases, and are useful novel pyrrolopyrazine derivatives for the treatment of auto-immune and inflammatory diseases.

The application provides a compound of Formula I



I wherein:

R is R^1, R^2, R^3, or R^4;

R^1 is lower alkyl, lower alkoxy, phenyl, benzyl, heteroaryl, cycloalkyl, heterocycloalkyl, or cycloalkylalkyl, optionally substituted with one or more R^{1a};

R^{1a} is R^{1b} or R^{1c};

R^{1b} is halogen, oxo, hydroxy, or –CN;

R^{1c} is $-C(=O)O(R^{1f})$, $-C(=O)CH_2(R^{1e})$, $-S(R^{1f})$, $-S(O)_2(R^{1f})$, or $-S(=O)(R^{1f})$, lower alkyl, lower alkoxy, amino, amido, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkyloxy, or heterocycloalkyloxy optionally substituted with one or more R^{1d};

R^{1d} is H, halogen, hydroxy, lower alkyl, lower alkoxy, or lower haloalkyl;

R^{1e} is H, lower alkyl, lower alkoxy, –CN, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^{1f} is H, lower alkyl, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^2 is $N(R^{2a})_2$;

each R^{2a} is independently H or R^{2b};

each R^{2b} is independently lower alkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, or heterocycloalkyl alkylene, optionally substituted with one or more R^{2c};

R^{2c} is R^{2d} or R^{2e};

R^{2d} is halogen, oxo, or hydroxy;

R^{2e} is $-N(R^{2g})_2$, $-C(=O)(R^{2g})$, $-C(=O)O(R^{2g})$, $-C(=O)N(R^{2g})_2$, $-N(R^{2g})C(=O)(R^{2g})$, $-S(=O)_2(R^{2g})$, $-S(O)_2N(R^{2g})_2$, lower alkyl, lower alkoxy, lower haloalkyl, phenyl, heteroaryl, heteroaryloxy, cycloalkyl, or heterocycloalkyl, optionally substituted with one or more R^{2f};

each R^{2f} is independently H, halogen, lower alkyl, lower alkoxy, lower haloalkyl;

each R^{2g} is independently H, lower alkyl, lower alkoxy, lower haloalkyl, or phenyl;

R^3 is $-C(=O)R^{3a}$;

R^{3a} is lower alkyl, lower alkoxy, phenyl, or $N(R^{3b})_2$;

each R^{3b} is independently H or lower alkyl;

R^4 is $-O(R^{4a})$;

R^{4a} is H or R^{4b};

R^{4b} is lower alkyl, phenyl, benzyl, lower haloalkyl, cycloalkyl, heterocycloalkyl, heteroaryl, optionally substituted with one or more R^{4c};

R^{4c} is halogen, hydroxy, lower alkyl, lower haloalkyl, or lower alkoxy;

Q^1 is phenyl, optionally substituted with two Q^{1a} which come together to form heterocyclic or heteroaryl ring system, optionally substituted with one or more Q^{1b} or Q^{1c};

Q^{1b} is halogen, hydroxy, oxo, or –CN;

Q^{1c} is Q^{1d} or Q^{1e};

Q^{1d} is $-O(Q^{1e})$, $-S(Q^{1e})$, $-S(=O)(Q^{1e})$, $-S(=O)_2(Q^{1e})$, $-C(=O)N(Q^{1e})_2$, $-N(Q^{1e})S(=O)_2(Q^{1e})$, $-C(=O)(Q^{1e})$, $-C(=O)O(Q^{1e})$, $-N(Q^{1e})_2$; $-N(Q^{1e})C(=O)(Q^{1e})$, $-N(Q^{1e})C(=O)O(Q^{1e})$, or $-N(Q^{1e})C(=O)N(Q^{1e})_2$;

each Q^{1e} is independently H or $Q^{1e'}$;

each $Q^{1e'}$ is independently lower alkyl, lower alkenyl, phenyl, benzyl, lower haloalkyl, lower hydroxyalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{1f};

Q^{1f} is Q^{1g} or Q^{1h};

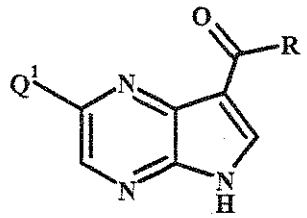
Q^{1g} is halogen, hydroxy, oxo, $-C(=O)(Q^{1h})$, or $-N(Q^{1h})C(=O)(Q^{1h})$;

each Q^{1h} is independently H, lower alkyl, lower haloalkyl, lower alkoxy, lower hydroxyalkyl, amino, phenyl, benzyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{1i};

each Q^{1i} is independently halogen, hydroxy, lower alkyl, lower haloalkyl, or lower alkoxy;

or a pharmaceutically acceptable salt thereof.

In a first aspect, there is provided a compound of Formula **I**



I wherein:

R is R^1, R^2, R^3, or R^4;

R^1 is $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, phenyl, benzyl, heteroaryl, cycloalkyl, heterocycloalkyl, or cycloalkylalkyl, optionally substituted with one or more R^{1a};

R^{1a} is R^{1b} or R^{1c};

R^{1b} is halogen, oxo, hydroxy, or –CN;

R^{1c} is $-C(=O)O(R^{1f})$, $-C(=O)CH_2(R^{1e})$, $-S(R^{1f})$, $-S(O)_2(R^{1f})$, or $-S(=O)(R^{1f})$, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, amino, amido, $C_{1\text{-}6}$ haloalkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkyloxy, or heterocycloalkyloxy optionally substituted with one or more R^{1d};

R^{1d} is H, halogen, hydroxy, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, or $C_{1\text{-}6}$ haloalkyl;

R^{1e} is H, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, –CN, $C_{1\text{-}6}$ haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^{1f} is H, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^2 is $N(R^{2a})_2$;

each R^{2a} is independently H or R^{2b};

each R^{2b} is independently $C_{1\text{-}6}$ alkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, or heterocycloalkyl alkylene, optionally substituted with one or more R^{2c};

R^{2c} is R^{2d} or R^{2e};

R^{2d} is halogen, oxo, or hydroxy;

R^{2e} is $-N(R^{2g})_2$, $-C(=O)(R^{2g})$, $-C(=O)O(R^{2g})$, $-C(=O)N(R^{2g})_2$, $-N(R^{2g})C(=O)(R^{2g})$, $-S(=O)_2(R^{2g})$, $-S(O)_2N(R^{2g})_2$,

C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, phenyl, heteroaryl, heteroaryloxy, cycloalkyl, or heterocycloalkyl, optionally substituted with one or more R^{2f};

each R^{2f} is independently H, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl;

each R^{2g} is independently H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or phenyl;

R^3 is $-C(=O)R^{3a}$;

R^{3a} is C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, or $N(R^{3b})_2$;

each R^{3b} is independently H or C_{1-6} alkyl;

R^4 is $-O(R^{4a})$;

R^{4a} is H or R^{4b};

R^{4b} is C_{1-6} alkyl, phenyl, benzyl, C_{1-6} haloalkyl, cycloalkyl, heterocycloalkyl, heteroaryl, optionally substituted with one or more R^{4c};

R^{4c} is halogen, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

Q^1 is phenyl substituted with two Q^{1a} which come together to form a heterocyclic or heteroaryl ring system, optionally substituted with one or more Q^{1b} or Q^{1c};

Q^{1b} is halogen, hydroxy, oxo, or –CN;

Q^{1c} is Q^{1d} or Q^{1e};

Q^{1d} is $-O(Q^{1e})$, $-S(Q^{1e})$, $-S(=O)(Q^{1e})$, $-S(=O)_2(Q^{1e})$, $-C(=O)N(Q^{1e})_2$, $-N(Q^{1e})S(=O)_2(Q^{1e})$, $-C(=O)(Q^{1e})$, $-C(=O)O(Q^{1e})$, $-N(Q^{1e})_2$; $-N(Q^{1e})C(=O)(Q^{1e})$, $-N(Q^{1e})C(=O)O(Q^{1e})$, or $-N(Q^{1e})C(=O)N(Q^{1e})_2$;

each Q^{1e} is independently H or $Q^{1e'}$;

each $Q^{1e'}$ is independently C_{1-6} alkyl, C_{1-6} alkenyl, phenyl, benzyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{1f};

Q^{1f} is Q^{1g} or Q^{1h};

Q^{1g} is halogen, hydroxy, oxo, $-C(=O)(Q^{1h})$, or $-N(Q^{1h})C(=O)(Q^{1h})$;

each Q^{1h} is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, amino, phenyl, benzyl,

cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{1i};

each Q^{1i} is independently halogen, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

or a pharmaceutically acceptable salt thereof wherein "phenyl substituted with two Q^{1a} which come together to form a heterocyclic or heteroaryl ring system" as used herein means the two Q^{1a} radicals on the phenyl ring join to form a saturated, partially saturated, or unsaturated ring system, containing four to eight atoms, incorporating one or more N, O, or S heteroatoms, the remaining ring atoms being carbon resulting in a bicyclic ring system.

In one variation of the above embodiment, R is R^1.

In one variation of the above embodiment, R^1 is lower alkyl.

In one variation of the above embodiment, R^1 is *tert*-butyl.

In another variation of the above embodiment, R^1 is *tert*-butyl, Q^{1a} is Q^{1c}, Q^{1c} is Q^{1e}, Q^{1e} is $Q^{1e'}$, and $Q^{1e'}$ is pyrrolidine.

In another variation of the above embodiment, R^1 is $-CHC(CH_3)_3$.

In another variation of the above embodiment, R^1 is *iso*-butyl.

In another variation of the above embodiment, R^1 is *iso*-propyl.

In one embodiment of the compound of Formula **I**, R^1 is cycloalkyl.

In one embodiment of the compound of Formula **I**, R^1 is heterocycloalkyl.

In one embodiment of the compound of Formula **I**, R^1 is benzyl.

In one embodiment of the compound of Formula **I**, R^1 is phenyl.

In one embodiment of the compound of Formula **I**, R is R^2.

In one embodiment of the compound of Formula **I**, R is R^2 and R^2 is $NH(R^{2a})$.

In one variation of the above embodiment, R^{2a} is R^{2b}.

In one variation of the above embodiment, R^{2b} is lower alkyl.

In one variation of the above embodiment, R^{2b} is *iso*-propyl.

In one embodiment of the compound of Formula **I**, R^{2b} is heterocycloalkyl.

In one embodiment of the compound of Formula **I**, R^{2b} is cycloalkyl.

In one embodiment of the compound of Formula **I**, R^{2b} is heterocycloalkyl alkylene.

In one variation of the above embodiment, R^{2b} is pyrrolidine.

In one variation of the above embodiment, R^{2b} is pyrrolidinyl methylene.

In one variation of the above embodiment, Q^{1a} is Q^{1c}.

In another variation of the above embodiment, Q^{1a} is Q^{1c}, Q^{1c} is Q^{1e}, Q^{1e} is $Q^{1e'}$, and $Q^{1e'}$ is heterocycloalkyl.

In yet another variation of the above embodiment, Q is Q^1, Q^{1a} is Q^{1c}, Q^{1c} is Q^{1e}, Q^{1e} is $Q^{1e'}$, $Q^{1e'}$ is pyrrolidine.

In yet another variation of the above embodiment, Q is Q^1, Q^{1a} is Q^{1c}, Q^{1c} is Q^{1d}, Q^{1d} is $-O(Q^{1e})$, Q^{1e} is $Q^{1e'}$, and $Q^{1e'}$ is lower alkyl.

In yet another variation of the above embodiment, Q is Q^1, Q^{1a} is Q^{1c}, Q^{1c} is Q^{1d}, Q^{1d} is $-O(Q^{1e})$, Q^{1e} is $Q^{1e'}$, $Q^{1e'}$ is methyl.

In one embodiment of the compound of Formula **I**, Q^{1a} is Q^{1b}.

In one variation of the above embodiment, Q^{1b} is halogen.

In another variation of the above embodiment, Q^{1b} is hydroxy.

In one embodiment of the compound of Formula **I**, Q^{1a} is Q^{1c}.

In one variation of the above embodiment, Q^{1c} is Q^{1d}, Q^{1d} is $-O(Q^{1e})$, Q^{1e} is $Q^{1e'}$, and $Q^{1e'}$ is lower alkyl, optionally substituted with one or more Q^{1f}.

In one variation of the above embodiment, $Q^{1e'}$ is methyl optionally substituted with one or more Q^{1f}.

In another variation of the above embodiment, Q^{1f} is Q^{1h} and Q^{1h} is heterocycloalkyl.

In one variation of the above embodiment, Q^{1h} is morpholine.

In one embodiment of the compound of Formula **I**, Q^{1a} is Q^{1c}, Q^{1c} is Q^{1e}, Q^{1e} is $Q^{1e'}$, and $Q^{1e'}$ is heterocycloalkyl, optionally substituted with one or more Q^{1f}.

In one variation of the above embodiment, $Q^{1e'}$ is pyrrolidine, optionally substituted with one or more Q^{1f}.

In another variation of the above embodiment, $Q^{1e'}$ is piperazine, optionally substituted with one or more Q^{1f}.

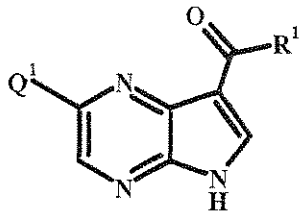
In yet another variation of the above embodiment, $Q^{1e'}$ is piperidine, optionally substituted with one or more Q^{1f}.

In yet another variation of the above embodiment, $Q^{1e'}$ is morpholine, optionally substituted with one or more Q^{1f}.

In yet another variation of the above embodiment, $Q^{1e'}$ is pyrrolidinone, optionally substituted with one or more Q^{1f}.

In one embodiment of the compound of Formula I, Q^{1a} is Q^{1c}, Q^{1c} is Q^{1d}, Q^{1d} is $-C(=O)(Q^{1e})$, Q^{1e} is $Q^{1e'}$, and $Q^{1e'}$ is heterocycloalkyl, optionally substituted with one or more Q^{1f}.

In certain embodiments of formula I, the subject compounds are more specifically of formula II:



II

wherein R^1 is lower alkyl, lower alkoxy, phenyl, benzyl, heteroaryl, cycloalkyl, heterocycloalkyl, or cycloalkylalkyl, optionally substituted with one or more R^{1a};

R^{1a} is R^{1b} or R^{1c};

R^{1b} is halogen, oxo, hydroxy, or –CN;

R^{1c} is $-C(=O)O(R^{1f})$, $-C(=O)CH_2(R^{1e})$, $-S(R^{1f})$, $-S(O)_2(R^{1f})$, or $-S(=O)(R^{1f})$, lower alkyl, lower alkoxy, amino, amido, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkyloxy, or heterocycloalkyloxy optionally substituted with one or more R^{1d};

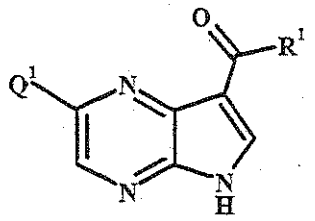
R^{1d} is H, halogen, hydroxy, lower alkyl, lower alkoxy, or lower haloalkyl;

R^{1e} is H, lower alkyl, lower alkoxy, –CN, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^{1f} is H, lower alkyl, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl; and

Q^1 is as defined herein.

In a second aspect, there is provided a compound of formula II as defined above:



II

wherein R^1 is C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, benzyl, heteroaryl, cycloalkyl, heterocycloalkyl, or cycloalkylalkyl, optionally substituted with one or more R^{1a};

R^{1a} is R^{1b} or R^{1c};

R^{1b} is halogen, oxo, hydroxy, or –CN;

R^{1c} is $-C(=O)O(R^{1f})$, $-C(=O)CH_2(R^{1e})$, $-S(R^{1f})$, $-S(O)_2(R^{1f})$, or $-S(=O)(R^{1f})$, C_{1-6} alkyl, C_{1-6} alkoxy, amino, amido, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkyloxy, or heterocycloalkyloxy optionally substituted with one or more R^{1d};

R^{1d} is H, halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl;

R^{1e} is H, C_{1-6} alkyl, C_{1-6} alkoxy, –CN, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^{1f} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl; and

Q^1 is defined above.

In certain embodiments of formula II, R^1 is lower alkyl, preferably tert-butyl.

In certain embodiments of either formula I or II, Q^1 is Dihydrobenzodioxinyl, benzodioxolyl, dihydrobenzoxazinyl, indolyl, dihydrobenzothiazinyl, quinolinyl or indazolyl optionally substituted with one or more Q^{1b} or Q^{1c} as defined herein. Preferably Q^1 is indolyl, dihydrobenzoxazinyl or benzoxazinone optionally substituted with one or more Q^{1b} or Q^{1c} as defined herein.

In one embodiment, the application provides a compound of Formula **I** selected from the group consisting of:

1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-3-methyl-butan-1-one;
1-(2-Benzo[1,3]dioxol-5-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-3-methyl-butan-1-one;
2,2-Dimethyl-1-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;
1-[2-(1H-Indol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;
1-[2-(1H-Indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;
1-[2-(1H-Indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;
6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one;
2,2-Dimethyl-1-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;
6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]oxazin-3-one;
6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-methyl-4H-benzo[1,4]oxazin-3-one;
2,2-Dimethyl-1-[2-(1-pyridin-3-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;
2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;
2,2-Dimethyl-1-[2-(1-pyridin-4-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;
6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2,4-trimethyl-4H-benzo[1,4]oxazin-3-one;
6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-ethyl-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one;
4-Benzyl-6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4H-

benzo[1,4]oxazin-3-one;

1-{2-[1-(1-Benzyl-pyrrolidin-3-yl)-1H-indol-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one;

2,2-Dimethyl-1-{2-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-propan-1-one;

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide;

2,2-Dimethyl-1-[2-(1-piperidin-4-yl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-6-[7-(1-methyl-cyclohexanecarbonyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]oxazin-3-one;

7-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]thiazin-3-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4-pyridin-2-ylmethyl-4H-benzo[1,4]oxazin-3-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4-(2-morpholin-4-yl-ethyl)-4H-benzo[1,4]oxazin-3-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-(3-hydroxy-2-hydroxymethyl-propyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one;

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-methanesulfonamide;

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide;

1-[2-(4-Benzenesulfonyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

N-(4-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-ylsulfamoyl}-phenyl)-acetamide;

N-(4-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,3-dihydro-benzo[1,4]oxazine-4-sulfonyl}-phenyl)-acetamide;

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-yl}-benzenesulfonamide;

1-{2-[4-(4-Amino-benzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one;

4-Chloro-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide;

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-4-fluoro-benzenesulfonamide;

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-4-methoxy-benzenesulfonamide;

6-Chloro-pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide;

Pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide;

6-Amino-pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide;

(1-Methyl-cyclohexyl)-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-methanone;

2,2-Dimethyl-1-(2-quinolin-5-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one;

1-[2-(1H-Indazol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

1-[2-(1H-Indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

2,2-Dimethyl-1-(2-quinolin-6-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one;

2,2-Dimethyl-1-[2-(1-methyl-1H-indazol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-[2-(3-methyl-1H-indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

1-{2-[1-(1-Benzyl-pyrrolidin-3-yl)-1H-indol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one;

2,2-Dimethyl-1-[2-(1-pyridin-3-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-[2-(1-pyridin-4-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-{2-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-propan-1-one;

2,2-Dimethyl-1-[2-(3-piperidin-4-yl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

[2-(1H-Indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-(1-methyl-cyclohexyl)-methanone;

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-yl}-N-methyl-benzenesulfonamide;

and

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-N-methyl-benzenesulfonamide.

In one embodiment, the application provides a method for treating an inflammatory and/or autoimmune condition comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I.

In one variation of the above method, the above method further comprises administering an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

In one embodiment, the application provides a method for treating an inflammatory condition comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I, wherein R is R^1.

In one embodiment, the application provides a method for inhibiting T-cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I.

In one embodiment, the application provides a method for inhibiting T-cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I, wherein R is R^2.

In one variation of the above method, the proliferative disorder is cancer.

In one embodiment, the application provides a method for treating a B-cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I.

In one embodiment, the application provides a method for treating an immune disorder including lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes, complications from organ transplants, xeno transplantation, diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, and Leukemia, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I.

In one embodiment, the application provides a method for preventing or treating all forms of organ rejection, including acute allograft or xenograft rejection and chronic allograft or xenograft rejection, of vascularized or non-vascularized transplants, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I.

In one embodiment, the application provides a method for preventing or treating all forms of organ rejection, including acute allograft or xenograft rejection and chronic allograft or xenograft rejection, of vascularized or non-vascularized transplants, comprising administering to a patient in need thereof the compound of Formula I.

In one embodiment, the application provides a method for inhibiting JAK3 activity comprising administering the compound of Formula I, wherein the compound exhibits an IC_{50} of 50 micromolar or less in an *in vitro* biochemical assay of JAK3 activity.

In one variation of the above method, the compound exhibits an IC_{50} of 100 nanomolar or less in an *in vitro* biochemical assay of JAK3 activity.

In one variation of the above method, the compound exhibits an IC_{50} of 10 nanomolar or less in an *in vitro* biochemical assay of JAK3 activity.

In one embodiment, the application provides a method for inhibiting SYK activity comprising administering the compound of Formula I, wherein the compound exhibits an IC_{50} of 50 micromolar or less in an *in vitro* biochemical assay of SYK activity.

In one variation of the above method, the compound exhibits an IC_{50} of 100 nanomolar or less in an *in vitro* biochemical assay of SYK activity.

In one variation of the above method, the compound exhibits an IC_{50} of 10 nanomolar or less in an *in vitro* biochemical assay of SYK activity.

In one embodiment, the application provides a method for treating an inflammatory condition comprising co-administering to a patient in need thereof an anti-inflammatory compound in combination with a therapeutically effective amount of the compound of Formula I.

In one embodiment, the application provides a method for treating an inflammatory condition comprising co-administering to a patient in need thereof a therapeutically effective amount of an anti-inflammatory compound in combination with the compound of Formula I.

In one embodiment, the application provides a method for treating an immune disorder comprising co-administering to a patient in need thereof an immunosuppressant compound in combination with a therapeutically effective amount of the compound of Formula I.

In one embodiment, the application provides a method for treating an immune disorder comprising co-administering to a patient in need thereof a therapeutically effective amount of an immunosuppressant compound in combination with the compound of Formula I.

The application provides a pharmaceutical composition comprising the compound of Formula I, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

In one variation, the above pharmaceutical composition further comprises an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

In one embodiment, the application provides a use of the compound of Formula **I or II** in the manufacture of a medicament for the treatment of an inflammatory disorder.

In one embodiment, the application provides a use of the compound of Formula I in the manufacture of a medicament for the treatment of an inflammatory disorder.

In one embodiment, the application provides a use of the compound of Formula I or II, in the manufacture of a medicament for the treatment of an autoimmune disorder.

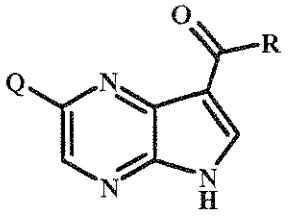
In one embodiment, the application provides a use of the compound of Formula I in the manufacture of a medicament for the treatment of an autoimmune disorder.

In a third aspect, there is provided the use of the compound as defined above in the manufacture of a medicament for the treatment of an inflammatory disorder or of an autoimmune disorder.

In one embodiment, the application provides a compound of Formula **I, II or III,** for use in the treatment of an inflammatory disorder or of an autoimmune disorder.

In a fourth aspect, there is provided a compound as defined above for use in the treatment of an inflammatory disorder or of an autoimmune disorder.

The application provides a compound of Formula **III**



III wherein:

R is R^1, R^2, R^3, or R^4;

R^1 is lower alkyl, lower alkoxy, phenyl, benzyl, heteroaryl, cycloalkyl, heterocycloalkyl, or cycloalkylalkyl, optionally substituted with one or more R^{1a};

R^{1a} is R^{1b} or R^{1c};

R^{1b} is halogen, oxo, hydroxy, or –CN;

R^{1c} is $-C(=O)O(R^{1f})$, $-C(=O)CH_2(R^{1e})$, $-S(R^{1f})$, $-S(O)_2(R^{1f})$, or $-S(=O)(R^{1f})$, lower alkyl, lower alkoxy, amino, amido, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkyloxy, or heterocycloalkyloxy optionally substituted with one or more R^{1d};

R^{1d} is H, halogen, hydroxy, lower alkyl, lower alkoxy, or lower haloalkyl;

R^{1e} is H, lower alkyl, lower alkoxy, –CN, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^{1f} is H, lower alkyl, lower haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^2 is $N(R^{2a})_2$;

each R^{2a} is independently H or R^{2b};

each R^{2b} is independently lower alkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, or heterocycloalkyl alkylene, optionally substituted with one or more R^{2c};

R^{2c} is R^{2d} or R^{2e};

R^{2d} is halogen, oxo, or hydroxy;

R^{2e} is $-N(R^{2g})_2$, $-C(=O)(R^{2g})$, $-C(=O)O(R^{2g})$, $-C(=O)N(R^{2g})_2$, $-N(R^{2g})C(=O)(R^{2g})$, $-S(=O)_2(R^{2g})$, $-S(O)_2N(R^{2g})_2$, lower alkyl, lower alkoxy, lower haloalkyl, phenyl,

heteroaryl, heteroaryloxy, cycloalkyl, or heterocycloalkyl, optionally substituted with one or more R^{2f};

each R^{2f} is independently H, halogen, lower alkyl, lower alkoxy, lower haloalkyl;

each R^{2g} is independently H, lower alkyl, lower alkoxy, lower haloalkyl, or phenyl;

R^3 is $-C(=O)R^{3a}$;

R^{3a} is lower alkyl, lower alkoxy, phenyl, or $N(R^{3b})_2$;

each R^{3b} is independently H or lower alkyl;

R^4 is $-O(R^{4a})$;

R^{4a} is H or R^{4b};

R^{4b} is lower alkyl, phenyl, benzyl, lower haloalkyl, cycloalkyl, heterocycloalkyl, heteroaryl, optionally substituted with one or more R^{4c};

R^{4c} is halogen, hydroxy, lower alkyl, lower haloalkyl, or lower alkoxy;

Q is Q^1, Q^2, Q^3, or Q^4;

Q^1 is phenyl, optionally substituted with one or more Q^{1a};

Q^{1a} is Q^{1b} or Q^{1c};

Q^{1b} is halogen, hydroxy, $-CN$, $-S(Q^{1e})$, $-S(O)_2(Q^{1e})$, or $-S(=O)(Q^{1e})$;

Q^{1c} is Q^{1d} or Q^{1e};

or two Q^{1a} come together to form a bicyclic ring system, optionally substituted with one or more Q^{1b} or Q^{1c};

Q^{1d} is $-O(Q^{1e})$, $-S(=O)_2(Q^{1e})$, $-C(=O)N(Q^{1e})_2$, $-S(=O)_2(Q^{1e})$, $-C(=O)(Q^{1e})$, $-C(=O)O(Q^{1e})$, $-N(Q^{1e})_2$; $-N(Q^{1e})C(=O)(Q^{1e})$, $-N(Q^{1e})C(=O)O(Q^{1e})$, or $-N(Q^{1e})C(=O)N(Q^{1e})_2$;

each Q^{1e} is independently H or $Q^{1e'}$;

each $Q^{1e'}$ is independently lower alkyl, phenyl, benzyl, lower haloalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{1f};

Q^{1f} is Q^{1g} or Q^{1h};

Q^{1g} is halogen, hydroxy, oxo, or $-C(=O)(Q^{1h})$;

Q^{1h} is lower alkyl, lower haloalkyl, lower alkoxy, phenyl, benzyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{1i};

Q^{1i} is halogen, hydroxy, lower alkyl, lower haloalkyl, or lower alkoxy;

Q^2 is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{2a};

Q^{2a} is Q^{2b} or Q^{2c};

Q^{2b} is halogen, oxo, hydroxy, –CN, $–SCH_3$, $–S(O)2CH_3$, or $–S(=O)CH_3$;

Q^{2c} is Q^{2d} or Q^{2e};

or two Q^{2a} come together to form a bicyclic ring system, optionally substituted with one or more Q^{2b} or Q^{2c};

Q^{2d} is $–O(Q^{2e})$, $–S(=O)_2(Q^{2e})$, $–C(=O)N(Q^{2e})_2$, $–S(O)_2(Q^{2e})$, $–C(=O)(Q^{2e})$, $–C(=O)O(Q^{2e})$, $–N(Q^{2e})_2$; $–N(Q^{2e})C(=O)(Q^{2e})$, $–N(Q^{2e})C(=O)O(Q^{2e})$, or $–N(Q^{2e})C(=O)N(Q^{2e})_2$;

each Q^{2e} is independently H or $Q^{2e'}$;

each $Q^{2e'}$ is independently lower alkyl, phenyl, benzyl, lower haloalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{2f};

Q^{2f} is Q^{2g} or Q^{2h};

Q^{2g} is halogen, hydroxy, oxo, or $–C(=O)(Q^{2h})$;

Q^{2h} is lower alkyl, lower haloalkyl, lower alkoxy, phenyl, benzyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{2i};

Q^{2i} is halogen, hydroxy, lower alkyl, lower haloalkyl, or lower alkoxy;

Q^3 is $–O-Q^{3a}$, $–S-Q^{3a}$, $–C(=O)(Q^{3a})$, $–S(=O)(Q^{3a})$, $–S(=O)_2(Q^{3a})$, $–N(Q^{3a})_2$, $–NHC(=O)(Q^{3a})$, $–C(=O)N(Q^{3a})_2$, or $–NHC(=O)N(Q^{3a})_2$;

each Q^{3a} is independently Q^{3b} or Q^{3c};

Q^{3b} is H;

Q^{3c} is lower alkyl, lower haloalkyl, phenyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{3d};

Q^{3d} is halogen, hydroxyl, lower alkyl, lower alkoxy, or lower haloalkyl;

Q^4 is Q^{4a} or Q^{4b};

Q^{4a} is H or halogen; and

Q^{4b} is lower alkyl, lower alkenyl, lower alkynyl, or lower haloalkyl;

with the proviso that when R is R^4, R^4 is $-O(R^{4a})$, R^{4a} is H, and Q^4 is Q^{4a}, then Q^{4a} is not H; or a pharmaceutically acceptable salt thereof.

The phrase "a" or "an" entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

The phrase "as defined herein above" refers to the broadest definition for each group as provided in the Summary of the Invention or the broadest claim. In all other embodiments provided below, substituents which can be present in each embodiment and which are not explicitly defined retain the broadest definition provided in the Summary of the Invention.

As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

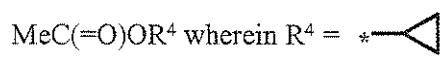
As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or".

The term "independently" is used herein to indicate that a variable is applied in any one instance without regard to the presence or absence of a variable having that same or a different definition within the same compound. Thus, in a compound in which R" appears twice and is defined as

"independently carbon or nitrogen", both R"s can be carbon, both R"s can be nitrogen, or one R" can be carbon and the other nitrogen.

When any variable (e.g., R, R', or Q) occurs more than one time in any moiety or formula depicting and describing compounds employed or claimed in the present invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such compounds result in stable compounds.

The symbols "*" at the end of a bond or " ------ " drawn through a bond each refer to the point of attachment of a functional group or other chemical moiety to the rest of the molecule of which it is a part. Thus, for example:

$MeC(=O)OR^4$ wherein R^4 =  or  .

A bond drawn into ring system (as opposed to connected at a distinct vertex) indicates that the bond may be attached to any of the suitable ring atoms.

The term "optional" or "optionally" as used herein means that a subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted" means that the optionally substituted moiety may incorporate a hydrogen or a substituent.

The phrase "phenyl substituted with two Q^{1a} which come together to form a heterocyclic or heteroaryl ring system" as used herein means the two Q^{1a} radicals on the phenyl ring join to form a saturated, partially saturated, or unsaturated ring system, containing four to eight atoms, incorporating one or more N, O, or S heteroatoms, the remaining ring atoms being carbon, resulting in a bicyclic ring system.

The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

The definitions described herein may be appended to form chemically-relevant combinations, such as "heteroalkylaryl," "haloalkylheteroaryl," "arylalkylheterocyclyl," "alkylcarbonyl," "alkoxyalkyl," "cycloalkylalkyl" and the like. When the term "alkyl" is used as a suffix following another term, as in "phenylalkyl," or "hydroxyalkyl," this is intended to refer to an alkyl group, as defined above, being substituted with one to two substituents selected from the other specifically-named group. Thus, for example, "phenylalkyl" refers to an alkyl group having one to two phenyl substituents, and thus includes benzyl, phenylethyl, and biphenyl. An "alkylaminoalkyl" is an alkyl group having one to two alkylamino substituents. "Hydroxyalkyl" includes 2-hydroxyethyl, 2-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 2,3-dihydroxybutyl, 2-(hydroxymethyl), 3-hydroxypropyl, and so forth. Accordingly, as used herein, the term "hydroxyalkyl" is used to define a subset of heteroalkyl groups defined below. The term -(ar)alkyl refers to either an unsubstituted alkyl or an aralkyl group. The term (hetero)aryl or (het)aryl refers to either an aryl or a heteroaryl group.

Compounds of formula **I** may exhibit tautomerism. Tautomeric compounds can exist as two or more interconvertable species. Prototropic tautomers result from the migration of a covalently bonded hydrogen atom between two atoms. Tautomers generally exist in equilibrium and attempts to isolate an individual tautomers usually produce a mixture whose chemical and physical properties are consistent with a mixture of compounds. The position of the equilibrium is dependent on chemical features within the molecule. For example, in many aliphatic aldehydes and ketones, such as acetaldehyde, the keto form predominates while; in phenols, the enol form predominates. Common prototropic tautomers include keto/enol (-C(=O)-CH- ⇆ -C(-OH)=CH-), amide/imidic acid (-C(=O)-NH- ⇆ -C(-OH)=N-) and amidine (-C(=NR)-NH- ⇆ -C(-NHR)=N-) tautomers. The latter two are particularly common in heteroaryl and heterocyclic rings and the present invention encompasses all tautomeric forms of the compounds.

Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th Ed., McGraw Hill Companies Inc., New York (**2001**). Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described.

Materials, reagents and the like to which reference are made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

The term "acyl" as used herein denotes a group of formula -C(=O)R wherein R is hydrogen or lower alkyl as defined herein. The term or "alkylcarbonyl" as used herein denotes a group of formula C(=O)R wherein R is alkyl as defined herein. The term C_{1-6} acyl refers to a group -C(=O)R contain 6 carbon atoms. The term "arylcarbonyl" as used herein means a group of formula C(=O)R wherein R is an aryl group; the term "benzoyl" as used herein an "arylcarbonyl" group wherein R is phenyl.

The term "alkyl" as used herein denotes an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 to 10 carbon atoms. The term "lower alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 6 carbon atoms. "C_{1-10} alkyl" as used herein refers to an alkyl composed of 1 to 10 carbons. Examples of alkyl groups include, but are not limited to, lower alkyl groups include methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl or pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl.

When the term "alkyl" is used as a suffix following another term, as in "phenylalkyl," or "hydroxyalkyl," this is intended to refer to an alkyl group, as defined above, being substituted with one to two substituents selected from the other specifically-named group. Thus, for example, "phenylalkyl" denotes the radical R'R"-, wherein R' is a phenyl radical, and R" is an alkylene radical as defined herein with the understanding that the attachment point of the phenylalkyl moiety will be on the alkylene radical. Examples of arylalkyl radicals include, but are not limited to, benzyl, phenylethyl, 3-phenylpropyl. The terms "arylalkyl", "aryl alkyl", or "aralkyl" are interpreted similarly except R' is an aryl radical. The terms "heteroaryl alkyl" or "heteroarylalkyl" are interpreted similarly except R' is optionally an aryl or a heteroaryl radical.

The term "haloalkyl" as used herein denotes a unbranched or branched chain alkyl group as defined above wherein 1, 2, 3 or more hydrogen atoms are substituted by a halogen. The term "lower haloalkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 6 carbon atoms, wherein 1, 2, 3 or more hydrogen atoms are substituted by a halogen. Examples are 1-fluoromethyl, 1-chloromethyl, 1-bromomethyl, 1-iodomethyl, difluoromethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, 1-fluoroethyl, 1-chloroethyl, 1-

bromoethyl, 1-iodoethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-dichloroethyl, 3-bromopropyl or 2,2,2-trifluoroethyl.

The term "alkylene" as used herein denotes a divalent saturated linear hydrocarbon radical of 1 to 10 carbon atoms (*e.g.*, $(CH_2)_n$)or a branched saturated divalent hydrocarbon radical of 2 to 10 carbon atoms (*e.g.*, -CHMe- or -$CH_2CH(i\text{-}Pr)CH_2$-), unless otherwise indicated. Except in the case of methylene, the open valences of an alkylene group are not attached to the same atom. Examples of alkylene radicals include, but are not limited to, methylene, ethylene, propylene, 2-methyl-propylene, 1,1-dimethyl-ethylene, butylene, 2-ethylbutylene.

The term "alkoxy" as used herein means an -O-alkyl group, wherein alkyl is as defined above such as methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy, pentyloxy, hexyloxy, including their isomers. "Lower alkoxy" as used herein denotes an alkoxy group with a "lower alkyl" group as previously defined. "C_{1-10} alkoxy" as used herein refers to an-O-alkyl wherein alkyl is C_{1-10}.

The term "hydroxyalkyl" as used herein denotes an alkyl radical as herein defined wherein one to three hydrogen atoms on different carbon atoms is/are replaced by hydroxyl groups.

The term "cycloalkyl" as used herein refers to a saturated carbocyclic ring containing 3 to 8 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. "C_{3-7} cycloalkyl" as used herein refers to an cycloalkyl composed of 3 to 7 carbons in the carbocyclic ring.

The term "halogen" or "halo" as used herein means fluorine, chlorine, bromine, or iodine.

The term "heteroaryl" or "heteroaromatic" as used herein means a monocyclic, bicyclic, or tricyclic radical of 5 to 18 ring atoms having at least one aromatic ring containing four to eight atoms per ring, incorporating one or more N, O, or S heteroatoms, the remaining ring atoms being carbon, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. As well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counter parts. Thus, for the purposes of the invention, a heteroaryl group need only have some degree of aromatic character. Examples of heteroaryl moieties include monocyclic aromatic heterocycles having 5 to 6 ring atoms and 1 to 3 heteroatoms include, but is not limited to, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl,

imidazolyl, oxazol, isoxazole, thiazole, isothiazole, triazoline, thiadiazole and oxadiaxoline which can optionally be substituted with one or more, preferably one or two substituents selected from hydroxy, cyano, alkyl, alkoxy, thio, lower haloalkoxy, alkylthio, halo, haloalkyl, alkylsulfinyl, alkylsulfonyl, halogen, amino, alkylamino,dialkylamino, aminoalkyl, alkylaminoalkyl, and dialkylaminoalkyl, nitro, alkoxycarbonyl and carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, arylcarbamoyl, alkylcarbonylamino and arylcarbonylamino. Examples of bicyclic moieties include, but are not limited to, quinolinyl, isoquinolinyl, benzofuryl, benzothiophenyl, benzoxazole, benzisoxazole, benzothiazole and benzisothiazole. Bicyclic moieties can be optionally substituted on either ring; however the point of attachment is on a ring containing a heteroatom.

The term "heterocycloalkyl", "heterocyclyl" or "heterocycle" as used herein denotes a monovalent saturated cyclic radical, consisting of one or more rings, preferably one to two rings, or three rings, of three to eight atoms per ring, incorporating one or more ring carbon atoms and one or more ring heteroatoms (chosen from N,O or $S(=O)_{0-2}$), wherein the point of attachment can be through either a carbon atom or a heteroatom, and which can optionally be independently substituted with one or more, preferably one or two or three substituents selected from hydroxy, oxo, cyano, lower alkyl, lower alkoxy, lower haloalkoxy, alkylthio, halo, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, unless otherwise indicated. Examples of heterocyclic radicals include, but are not limited to, azetidinyl, pyrrolidinyl, hexahydroazepinyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, thiazolidinyl, isoxazolidinyl, morpholinyl, piperazinyl, piperidinyl, tetrahydropyranyl, thiomorpholinyl, quinuclidinyl and imidazolinyl.

The phrase "organ rejection" includes acute allograft or xenograft rejection and chronic allograft or xenograft rejection in the setting of vascularized and/or non-vascularized (e.g. bone marrow, pancreatic islet cells) transplants.

Commonly used abbreviations include: acetyl (Ac), azo-*bis*-isobutyrylnitrile (AIBN), atmospheres (Atm), 9-borabicyclo[3.3.1]nonane (9-BBN or BBN), *tert*-butoxycarbonyl (Boc), di-*tert*-butyl pyrocarbonate or boc anhydride (BOC_2O), benzyl (Bn), butyl (Bu), Chemical Abstracts Registration Number (CASRN), benzyloxycarbonyl (CBZ or Z), carbonyl diimidazole

(CDI), 1,4-diazabicyclo[2.2.2]octane (DABCO), diethylaminosulfur trifluoride (DAST), dibenzylideneacetone (dba), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), N,N'-dicyclohexylcarbodiimide (DCC), 1,2-dichloroethane (DCE), dichloromethane (DCM), diethyl azodicarboxylate (DEAD), di-*iso*-propylazodicarboxylate (DIAD), di-*iso*-butylaluminumhydride (DIBAL or DIBAL-H), di-iso-propylethylamine (DIPEA), N,N-dimethyl acetamide (DMA), 4-N,N-dimethylaminopyridine (DMAP), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,1'-*bis*-(diphenylphosphino)ethane (dppe), 1,1'-*bis*-(diphenylphosphino)ferrocene (dppf), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), ethyl (Et), ethyl acetate (EtOAc), ethanol (EtOH), 2-ethoxy-2*H*-quinoline-1-carboxylic acid ethyl ester (EEDQ), diethyl ether (Et_2O), O-(7-azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate acetic acid (HATU), acetic acid (HOAc), 1-N-hydroxybenzotriazole (HOBt), high pressure liquid chromatography (HPLC), *iso*-propanol (IPA), lithium hexamethyl disilazane (LiHMDS), methanol (MeOH), melting point (mp), $MeSO_2$- (mesyl or Ms), , methyl (Me), acetonitrile (MeCN), *m*-chloroperbenzoic acid (MCPBA), mass spectrum (ms), methyl *t*-butyl ether (MTBE), N-bromosuccinimide (NBS), N-carboxyanhydride (NCA), N-chlorosuccinimide (NCS), N-methylmorpholine (NMM), N-methylpyrrolidone (NMP), pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), phenyl (Ph), propyl (Pr), *iso*-propyl (*i*-Pr), pounds per square inch (psi), pyridine (pyr), room temperature (rt or RT), *tert*-butyldimethylsilyl or *t*-$BuMe_2Si$ (TBDMS), triethylamine (TEA or Et_3N), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), triflate or CF_3SO_2- (Tf), trifluoroacetic acid (TFA), 1,1'-*bis*-2,2,6,6-tetramethylheptane-2,6-dione (TMHD), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), thin layer chromatography (TLC), tetrahydrofuran (THF), trimethylsilyl or Me_3Si (TMS), *p*-toluenesulfonic acid monohydrate (TsOH or pTsOH), 4-$Me-C_6H_4SO_2$- or tosyl (Ts), N-urethane-N-carboxyanhydride (UNCA),. Conventional nomenclature including the prefixes *normal* (*n*), *iso* (*i*-), *secondary* (*sec*-), *tertiary* (*tert*-) and *neo* have their customary meaning when used with an alkyl moiety. (J. Rigaudy and D. P. Klesney, *Nomenclature in Organic Chemistry,* IUPAC **1979** Pergamon Press, Oxford.).

COMPOUNDS AND PREPARATION

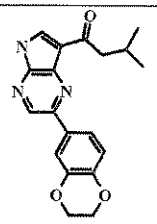
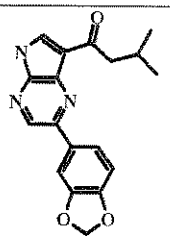
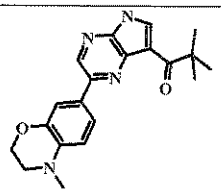
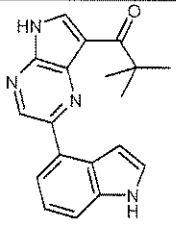
Examples of representative compounds encompassed by the present invention and within the scope of the invention are provided in the following Table. These examples and preparations which follow are provided to enable those skilled in the art to more clearly understand and to

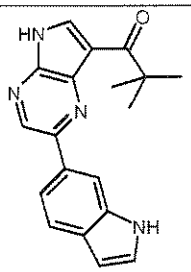
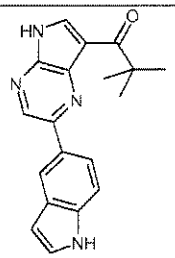
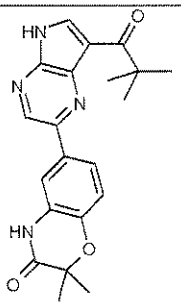
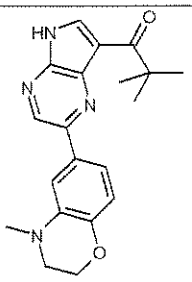
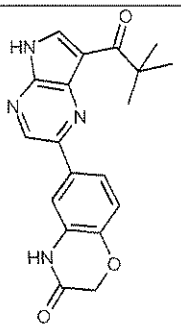
practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

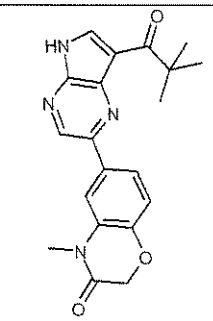
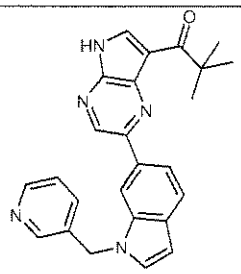
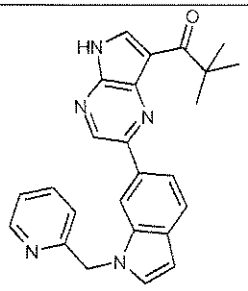
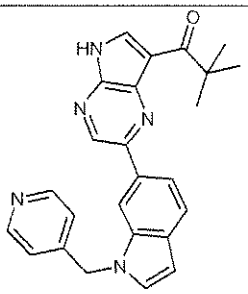
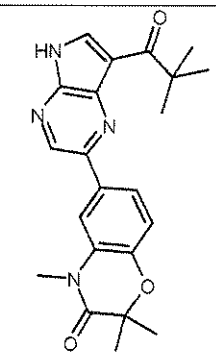
In general, the nomenclature used in this Application is based on AUTONOMTM v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. If there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

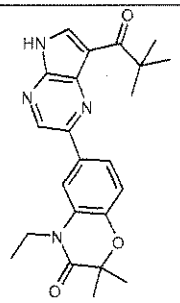
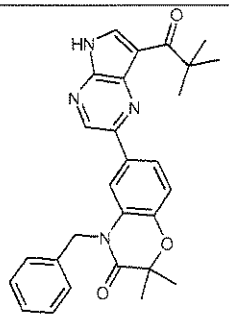
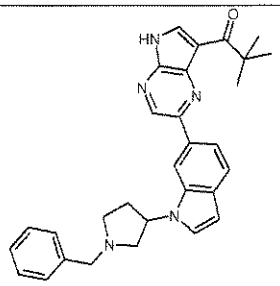
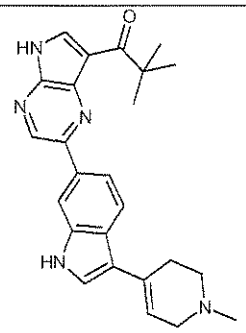
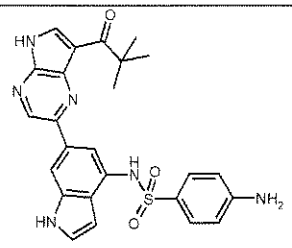
TABLE I depicts exemplified compounds according to Formula I.

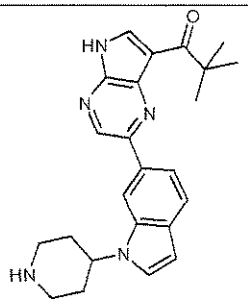
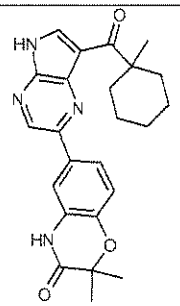
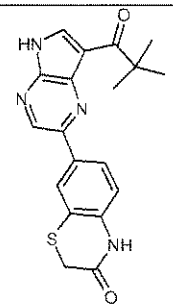
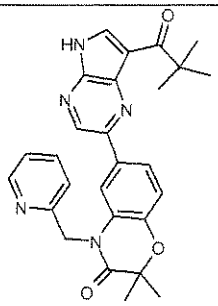
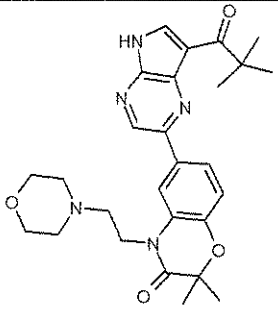
TABLE I.

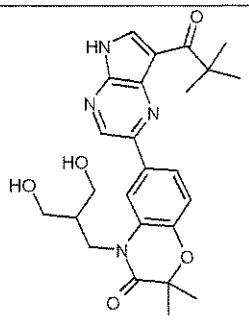
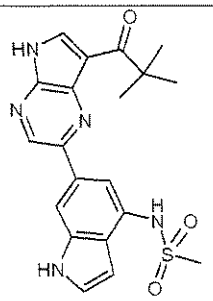
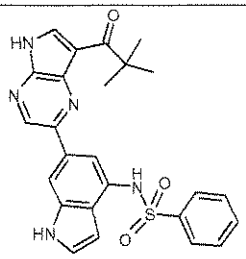
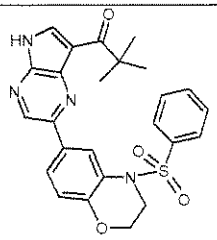
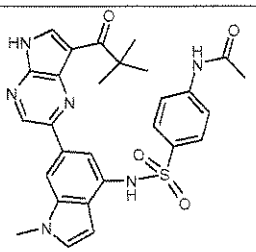
COMPOUND	SYSTEMATIC NAME	STRUCTURE	MP
I-1	1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-3-methyl-butan-1-one		
I-2	1-(2-Benzo[1,3]dioxol-5-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-3-methyl-butan-1-one		
I-3	2,2-Dimethyl-1-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		233.0-234.0
I-4	1-[2-(1H-Indol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one		

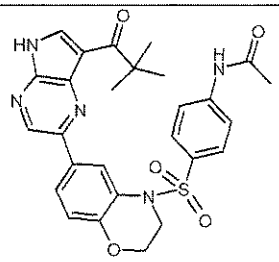
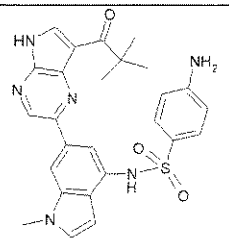
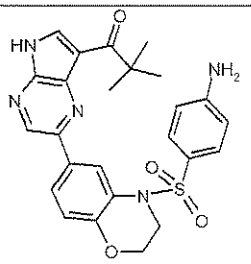
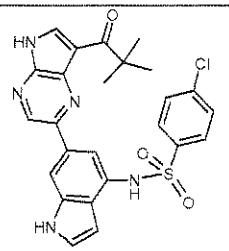
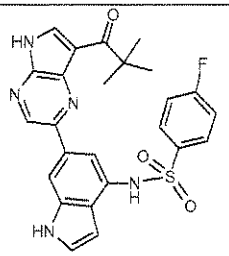
I-5	1-[2-(1H-Indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one		
I-6	1-[2-(1H-Indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one		
I-7	6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one		
I-8	2,2-Dimethyl-1-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-9	6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]oxazin-3-one		

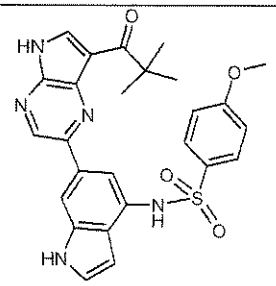
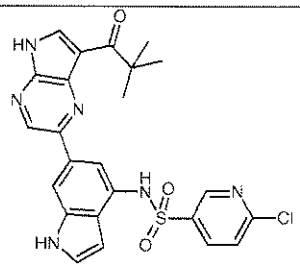
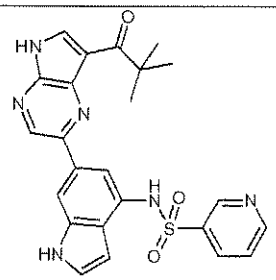
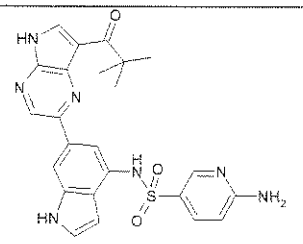
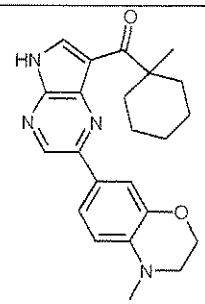
I-10	6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-methyl-4H-benzo[1,4]oxazin-3-one		
I-11	2,2-Dimethyl-1-[2-(1-pyridin-3-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-12	2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-13	2,2-Dimethyl-1-[2-(1-pyridin-4-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-14	6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2,4-trimethyl-4H-benzo[1,4]oxazin-3-one		

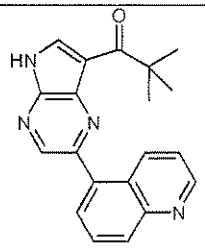
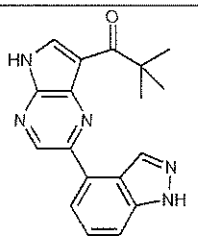
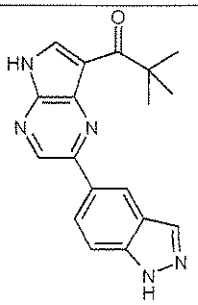
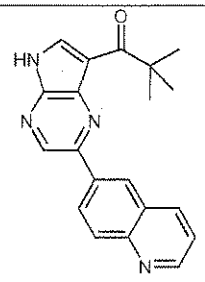
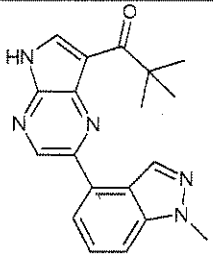
I-15	6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-ethyl-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one		
I-16	4-Benzyl-6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one		
I-17	1-{2-[1-(1-Benzyl-pyrrolidin-3-yl)-1H-indol-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one		
I-18	2,2-Dimethyl-1-{2-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-propan-1-one		
I-19	4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide		

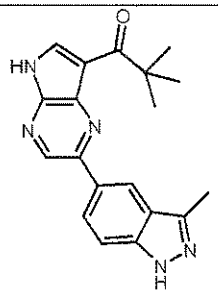
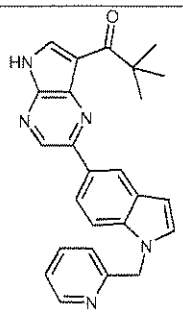
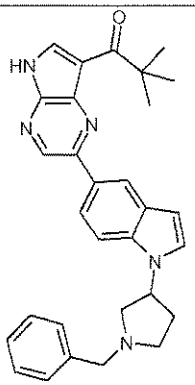
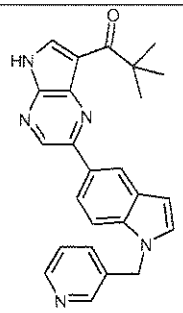
I-20	2,2-Dimethyl-1-[2-(1-piperidin-4-yl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-21	2,2-Dimethyl-6-[7-(1-methyl-cyclohexanecarbonyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]oxazin-3-one		
I-22	7-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]thiazin-3-one		
I-23	6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4-pyridin-2-ylmethyl-4H-benzo[1,4]oxazin-3-one		
I-24	6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4-(2-morpholin-4-yl-ethyl)-4H-benzo[1,4]oxazin-3-one		

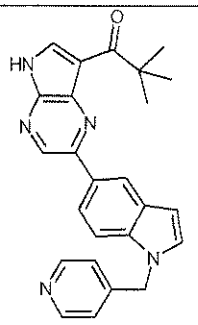
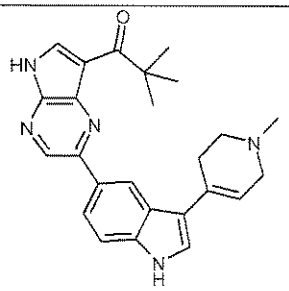
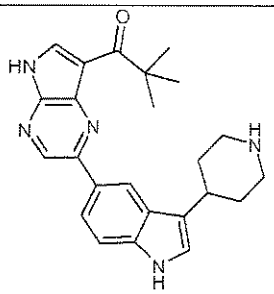
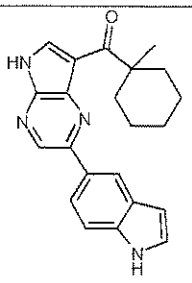
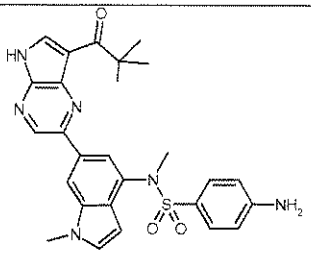
I-25	6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-(3-hydroxy-2-hydroxymethyl-propyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one		
I-26	N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-methanesulfonamide		
I-27	N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide		
I-28	1-[2-(4-Benzenesulfonyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one		
I-29	N-(4-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-ylsulfamoyl}-phenyl)-acetamide		

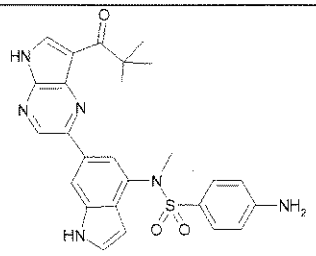
I-30	N-(4-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,3-dihydro-benzo[1,4]oxazine-4-sulfonyl}-phenyl)-acetamide		
I-31	4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-yl}-benzenesulfonamide		
I-32	1-{2-[4-(4-Amino-benzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one		
I-33	4-Chloro-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide		
I-34	N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-4-fluoro-benzenesulfonamide		

I-35	N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-4-methoxy-benzenesulfonamide		
I-36	6-Chloro-pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide		
I-37	Pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide		
I-38	6-Amino-pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide		
I-39	(1-Methyl-cyclohexyl)-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-methanone		

I-40	2,2-Dimethyl-1-(2-quinolin-5-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one		
I-41	1-[2-(1H-Indazol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one		
I-42	1-[2-(1H-Indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one		
I-43	2,2-Dimethyl-1-(2-quinolin-6-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one		
I-44	2,2-Dimethyl-1-[2-(1-methyl-1H-indazol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		

I-45	2,2-Dimethyl-1-[2-(3-methyl-1H-indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-46	2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-47	1-{2-[1-(1-Benzyl-pyrrolidin-3-yl)-1H-indol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one		
I-48	2,2-Dimethyl-1-[2-(1-pyridin-3-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		

I-49	2,2-Dimethyl-1-[2-(1-pyridin-4-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-50	2,2-Dimethyl-1-{2-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-propan-1-one		
I-51	2,2-Dimethyl-1-[2-(3-piperidin-4-yl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one		
I-52	[2-(1H-Indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-(1-methyl-cyclohexyl)-methanone		
I-53	4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-yl}-N-methyl-benzenesulfonamide		

I-54	4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-N-methyl-benzenesulfonamide		

DOSAGE AND ADMINISTRATION

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions, syrups, or suspensions. Compounds of the present invention are efficacious when administered by other routes of administration including continuous (intravenous drip) topical parenteral, intramuscular, intravenous, subcutaneous, transdermal (which may include a penetration enhancement agent), buccal, nasal, inhalation and suppository administration, among other routes of administration. The preferred manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the degree of affliction and the patient's response to the active ingredient.

A compound or compounds of the present invention, as well as their pharmaceutically useable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled

in the art will appreciate that an active ingredient can exist in different preparations depending on the target organ or tissue and on the desired dose and pharmacokinetic parameters.

The term "excipient" as used herein refers to a compound that is useful in preparing a pharmaceutical composition, generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. The compounds of this invention can be administered alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

A "pharmaceutically acceptable salt" form of an active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which were absent in the non-salt form, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body. The phrase "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or

coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

The compounds of the present invention may be formulated for parenteral administration (*e.g.*, by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion 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, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (*e.g.*, olive oil), and injectable organic esters (*e.g.*, ethyl

oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, *e.g.*, sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will

generally have a small particle size for example of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of *e.g.*, gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylaza-cycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into to the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polyactic acid.

Suitable formulations along with pharmaceutical carriers, diluents and expcipients are described in *Remington: The Science and Practice of Pharmacy* **1995,** edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity.

The modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (salt formulation, esterification, etc.), which are well within the ordinary skill in the art. It is also well within the

ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.01 and about 1000 mg/kg body weight per day should be appropriate in monotherapy and/or in combination therapy. A preferred daily dosage is between about 0.1 and about 500 mg/kg body weight, more preferred 0.1 and about 100 mg/kg body weight and most preferred 1.0 and about 10 mg/kg body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 7 mg to 0.7 g per day. The daily dosage can be administered as a single dosage or in divided dosages, typically between 1 and 5 dosages per day. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect for the individual patient is reached. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and the disclosures of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease and patient.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

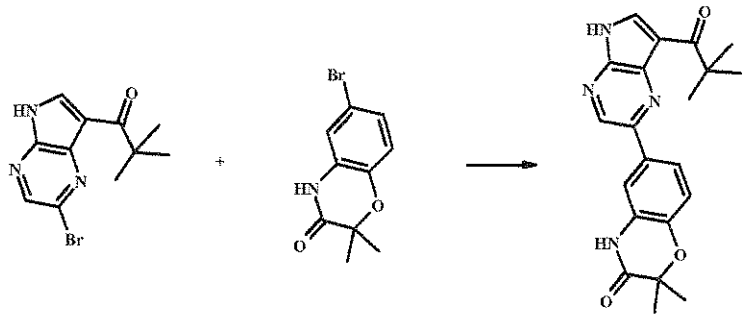
The following examples illustrate the preparation and biological evaluation of compounds within the scope of the invention. These examples and preparations which follow are provided to enable those skilled in the art to more clearly understand and to practice the present invention.

They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLES

Example 1.

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one



6-Bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one (61mg, 0.24mmol, *Bioorg. Med. Chem.*, 15 (2007), 5912) and bispinacolato diboron (73mg, 0.29mmol) were dissolved in 2.5ml 1,4-dioxane. The solution and flask were purged with argon. Potassium acetate (59mg, 0.6mmol) and palladium bis(diphenylphosphino)ferrocene dichloride (10mg, 0.012mmol) were added and the sealed reaction was stirred at 100C for 3hr. The reaction was cooled to room temperature and 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one (0.1g, 0.35mmol) was added. The reaction was diluted with 1ml 1,4-dioxane and 0.6ml water. Palladium bis(diphenylphosphino)ferrocene dichloride (15mg, 0.019mmol) and potassium carbonate (98mg, 0.71mmol) were added. The sealed vial was placed in a microwave reactor and run at 150C for 30min. More palladium catalyst (7mg, 0.0095mmol) was added and the reaction repeated at 140C for 30min. The reaction mixture was poured into ethyl acetate and sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted once more with ethyl acetate. The combined ethyl acetate layers were washed with saturated sodium chloride solution and dried over sodium sulfate. After filtration and evaporation, the residue was purified by silica gel chromatography (methanol/dichloromethane) to give 31mg (35%) of the product. MP = >300C, $(M+H)^+$ = 379.

Prepared as above:

2,2-Dimethyl-1-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one. Substituting 6-bromo-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 255-265C, $(M+H)^+ = 351$.

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]oxazin-3-one. Substituting 6-bromo-4H-benzo[1,4]oxazin-3-one for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = >350C, $(M+H)^+ = 351$.

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-methyl-4H-benzo[1,4]oxazin-3-one. Substituting 6-bromo-4-methyl-4H-benzo[1,4]oxazin-3-one for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 277-278C, $(M+H)^+ = 365$.

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2,4-trimethyl-4H-benzo[1,4]oxazin-3-one. Substituting 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one, and alkylating the final product with sodium hydride and iodomethane in N,N-dimethylformamide, following general procedures for deprotection as described in these Examples. MP = 265-266C, $(M+H)^+ = 393$.

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-ethyl-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. Substituting 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one, and alkylating the final product with sodium hydride and bromoethane in N,N-dimethylformamide, following general procedures for deprotection as described in these Examples. MP = 224-226C, $(M+H)^+ = 407$.

4-Benzyl-6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. Substituting 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one, and alkylating the final product with sodium hydride and benzyl bromide in N,N-dimethylformamide, following general procedures for deprotection as described in these Examples. MP = 248-249C, $(M+H)^+ = 469$.

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide. Substituting 4-amino-N-(6-bromo-1H-indol-4-yl)-benzenesulfonamide for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 285-292C, $(M+H)^+$ = 489.

2,2-Dimethyl-6-[7-(1-methyl-cyclohexanecarbonyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]oxazin-3-one. Substituting (2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-(1-methyl-cyclohexyl)-methanone for 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one. MP = >300C, $(M+H)^+$ = 419. 7-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]thiazin-3-one. Substituting 7-bromo-4H-benzo[1,4]thiazin-3-one for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = >300C, $(M+H)^+$ = 367.

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4-pyridin-2-ylmethyl-4H-benzo[1,4]oxazin-3-one. Substituting 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one, and alkylating the final product with sodium hydride and 2-picolyl chloride, HCl salt in N,N-dimethylformamide, following general procedures for deprotection as described in these Examples. MP = 245-247C, $(M+H)^+$ = 470.

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4-(2-morpholin-4-yl-ethyl)-4H-benzo[1,4]oxazin-3-one. Substituting 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one, and alkylating the final product with sodium hydride and 2-(4-morpholino)-ethyl bromide in N,N-dimethylformamide, following general procedures for deprotection as described in these Examples. MP = 271-273C, $(M+H)^+$ = 492.

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-(3-hydroxy-2-hydroxymethyl-propyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one.

Substituting 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one, and alkylating the final product with sodium hydride and methanesulfonic acid 2-phenyl-[1,3]dioxan-5-ylmethyl ester in N,N-dimethylformamide, followed by deprotection with aqueous HCl in addition to the methods of deprotection as generally described in these Examples. MP = 271-273C, $(M+H)^+$ = 492.

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-methanesulfonamide. Substituting N-(6-bromo-1H-indol-4-yl)-methanesulfonamide (prepared by treatment of 6-bromo-1H-indol-4-ylamine with methane sulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = >300C, $(M+H)^+$ = 412.

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide. Substituting N-(6-bromo-1H-indol-4-yl)-benzenesulfonamide (prepared by treatment of 6-bromo-1H-indol-4-ylamine with benzene sulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 275-285C, $(M+H)^+$ = 474.

2-{2-Benzenesulfonylamino-4-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-phenoxy}-2-methyl-propionic acid ethyl ester. Substituting 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one, and alkylating the final product with potassium *tert*-butoxide and benzene sulfonyl chloride in N,N-dimethylformamide, following general procedures for deprotection as described in these Examples. MP = 93-95C, $(M+H)^+$ = 565.

1-[2-(4-Benzenesulfonyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one. Substituting 4-benzenesulfonyl-6-bromo-3,4-dihydro-2H-benzo[1,4]oxazine (prepared by treatment of 6-bromo-3,4-dihydro-2H-benzo[1,4]oxazine(*Bioorg. Med. Chem.*, 15 (2007), 5912) with benzene sulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 217-219C, $(M+H)^+$ = 477.

N-(4-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-ylsulfamoyl}-phenyl)-acetamide. Substituting N-[4-(6-bromo-1-methyl-1H-indol-4-ylsulfamoyl)-phenyl]-acetamide (prepared by treatment of 6-bromo-1H-indol-4-ylamine first with sodium hexamethyldisilazide and iodomethane in N,N-dimethylformamide, then with 4-acetylamino-benzenesulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 275-276C, $(M+H)^+$ = 545.

N-(4-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,3-dihydrobenzo[1,4]oxazine-4-sulfonyl}-phenyl)-acetamide. Substituting N-[4-(6-bromo-2,3-dihydro-benzo[1,4]oxazine-4-sulfonyl)-phenyl]-acetamide (prepared by treatment of 6-bromo-

3,4-dihydro-2H-benzo[1,4]oxazine(*Bioorg. Med. Chem.*, 15 (2007), 5912) with 4-acetylamino-benzenesulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 273-274C, $(M+H)^+$ = 534.

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-yl}-benzenesulfonamide. Substituting N-[4-(6-bromo-1-methyl-1H-indol-4-ylsulfamoyl)-phenyl]-acetamide (prepared by treatment of 6-bromo-1H-indol-4-ylamine first with sodium hexamethyldisilazide and iodomethane in N,N-dimethylformamide, then with 4-acetylamino-benzenesulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. Followed by treatment with aqueous sodium hydroxide. MP = 243-245C, $(M+H)^+$ = 503.

1-{2-[4-(4-Amino-benzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one. Substituting N-[4-(6-bromo-2,3-dihydro-benzo[1,4]oxazine-4-sulfonyl)-phenyl]-acetamide (prepared by treatment of 6-bromo-3,4-dihydro-2H-benzo[1,4]oxazine(*Bioorg. Med. Chem.*, 15 (2007), 5912) with 4-acetylamino-benzenesulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. Followed by treatment with aqueous sodium hydroxide. MP = 174-176C, $(M+H)^+$ = 492.

4-Chloro-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide. Substituting N-(6-bromo-1H-indol-4-yl)-4-chloro-benzenesulfonamide (prepared by treatment of 6-bromo-1H-indol-4-ylamine with 4-chloro-benzenesulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 264-266C, $(M+H)^+$ = 508.

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-4-fluoro-benzenesulfonamide. Substituting N-(6-bromo-1H-indol-4-yl)-4-fluoro-benzenesulfonamide (prepared by treatment of 6-bromo-1H-indol-4-ylamine with 4-fluoro-benzenesulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 295-297C, $(M+H)^+$ = 492.

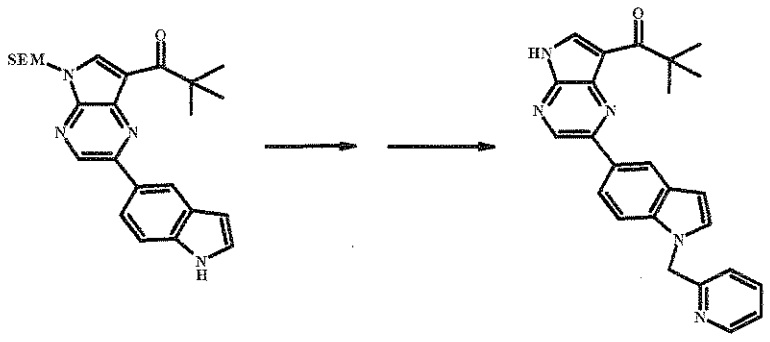
N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-4-methoxy-benzenesulfonamide. Substituting N-(6-bromo-1H-indol-4-yl)-4-methoxy-benzenesulfonamide (prepared by treatment of 6-bromo-1H-indol-4-ylamine with 4-methoxy-benzenesulfonyl chloride in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 231-233C, $(M+H)^+$ = 504.

6-Chloro-pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide. Substituting (6-bromo-1H-indol-4-yl)-carbamic acid tert-butyl ester for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one, followed by deprotection with trifluoroacetic acid in dichloromethane, and then treatment with 6-chloro-pyridine-3-sulfonyl chloride in pyridine. MP = 267-269C, $(M+H)^+ = 509$.

Pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide. Substituting pyridine-3-sulfonic acid (6-bromo-1H-indol-4-yl)-amide (prepared by treatment of 6-bromo-1H-indol-4-ylamine with 3-pyridinesulfonyl chloride, HCl salt in pyridine) for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. MP = 305-307C, $(M+H)^+ = 475$.

6-Amino-pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide. Substituting (6-bromo-1H-indol-4-yl)-carbamic acid tert-butyl ester for 6-bromo-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one, followed by deprotection with trifluoroacetic acid in dichloromethane, and then treatment with 6-chloro-pyridine-3-sulfonyl chloride in pyridine. Then using the methods found in *J.Org.Chem.*, 2007, (72), 6797 to introduce the amine. MP = 213-217C, $(M+H)^+ = 490$.

Example 2.



2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5Hpyrrolo[2,3-b]pyrazin-7-yl]propan-1-one.

To a DMF (1 mL) solution of 1-[2-(1H-Indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one (50 mg, 0.11 mmol; prepared as described in Ex. 45, only using the Sem-protected starting material) was added NaHMDS (0.25 mL, 1M in THF) and stirred for 20 min at RT. 2-Chloromethylpyridine hydrochloride (21.6 mg, 0.13 mmol) was added in a single portion. After stirring for 1 hr at RT TLC analysis (25%

EtOAc/hexanes) shows a new more-polar product. The reaction mixture was poured into 25 mL of saturated sodium bicarbonate solution and extracted with EtOAc (2 x 15 mL). The organic layers were combined, washed with brine, dried over MgSO4, and concentrated to give a yellow oil. Chromatography (SiO_2; 0%-13%-25% EtOAc in hexanes) gives 2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one as a clear oil. Following general deprotection procedures as described in these Examples, the SEM group was removed to give 2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5Hpyrrolo[2,3-b]pyrazin-7-yl]propan-1-one (47%; MS = 410 [M+H]; MP: 194-196 °C).

Prepared as above:

2,2-Dimethyl-1-[2-(1-pyridin-3-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one. Substituting 1-[2-(1H-indol-6-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-[2-(1H-indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one and 3-picolyl chloride, HCl salt for 2-chloromethylpyridine hydrochloride. MP = 225-227C, $(M+H)^+$ = 410.

2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one. Substituting 1-[2-(1H-indol-6-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-[2-(1H-indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one and 2-picolyl chloride, HCl salt for 2-chloromethylpyridine hydrochloride. MP = 256-260C, $(M+H)^+$ = 410.

2,2-Dimethyl-1-[2-(1-pyridin-4-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one. Substituting 1-[2-(1H-indol-6-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-[2-(1H-indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one and 4-bromomethylpyridine, HCl salt for 2-chloromethylpyridine hydrochloride. MP = 267-272C, $(M+H)^+$ = 410.

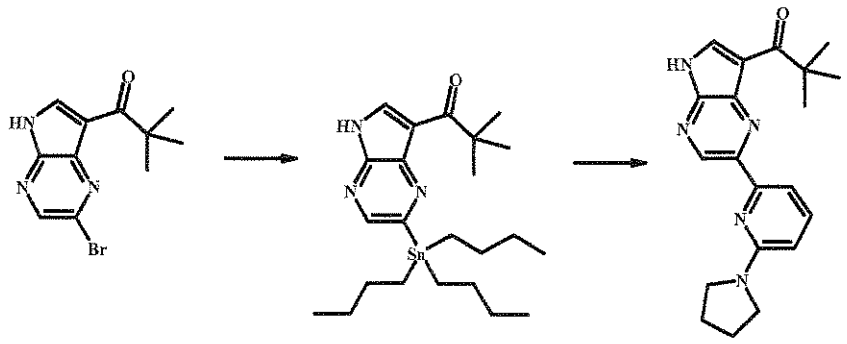
1-{2-[1-(1-Benzyl-pyrrolidin-3-yl)-1H-indol-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one. Substituting 1-[2-(1H-indol-6-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-

pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-[2-(1H-indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one and methanesulfonic acid 1-benzyl-pyrrolidin-3-yl ester for 2-chloromethylpyridine hydrochloride. MP = 126-133C, $(M+H)^+ = 478$.

2,2-Dimethyl-1-{2-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-propan-1-one. Substituting 1-[2-(1H-indol-6-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-[2-(1H-indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one, and 1-methyl-4-piperidone for 2-chloromethylpyridine hydrochloride, and sodium methoxide for sodium hexamethyldisilazide. MP = 247-254C, $(M+H)^+ = 414$.

2,2-Dimethyl-1-[2-(1-piperidin-4-yl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one. Substituting 1-[2-(1H-indol-6-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one for 1-[2-(1H-indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one and 4-methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester for 2-chloromethylpyridine hydrochloride. MP = 201-207C, $(M+H)^+ = 402$.

Example 3.



2,2-Dimethyl-1-(2-tributylstannanyl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one

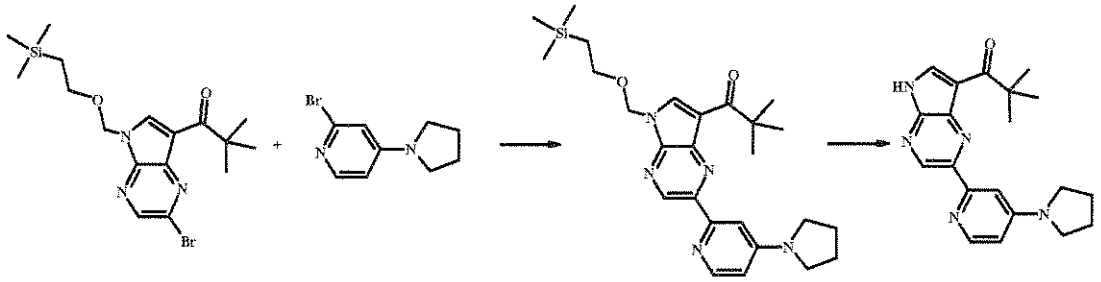
A mixture of 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one (1 g, 3.5 mmol), hexabutyldistannane (2 mL, 4.1 mmol), and $Pd(PPh_3)_4$ (200 mg, 0.17 mmol) in dioxane (16 mL) was stirred at 140 °C in a microwave for 30 min. The resulting mixture was treated with additional $Pd(PPh_3)_4$ (135 mg, 0.12 mmol), stirred at 150 °C in a microwave for 30 min, and concentrated. The crude product was purified by flash chromatography using 90 g of silica gel and EtOAc in hexanes as eluant to afford 425 mg (25%) of 2,2-dimethyl-1-(2-tributylstannanyl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one as a tan oil. M+H 494.

Example 4.

2,2-Dimethyl-1-[2-(6-pyrrolidin-1-yl-pyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one

A mixture of 2,2-dimethyl-1-(2-tributylstannanyl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one (115 mg, 0.23 mmol), 2-bromo-6-pyrrolidin-1-yl-pyridine (53 mg, 0.23 mmol), and $Pd(PPh_3)_4$ (27 mg, 0.023 mmol) in dioxane (1 mL) was stirred at 140 °C in a microwave for 1 h. The resulting mixture was treated with additional $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), stirred at 150 °C in a microwave for 30 min, and concentrated. The crude product was purified by flash chromatography using 4 g of silica gel and EtOAc in hexanes as eluant, 3 consecutive purifications by preparative thin layer chromatography using 2:1 hexanes:EtOAc as eluant, and a recrystallization from CH_2Cl_2 and ethyl ether to provide 1.5 mg of 2,2-dimethyl-1-[2-(6-pyrrolidin-1-yl-pyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one as a yellow powder. M+H 350.

Example 5.



2,2-Dimethyl-1-[2-(4-pyrrolidin-1-yl-pyridin-2-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one

To THF (1 mL) at -78 °C was added dropwise a solution of *t*-BuLi (0.78 mL, 1.3 M solution in pentane, 1 mmol). To the resultant yellow solution was added dropwise a brown solution of 2-bromo-4-pyrrolidin-1-yl-pyridine (110 mg, 0.5 mmol) in THF (2.5 mL). The resultant brown solution was stirred for 1 h, treated dropwise with a solution of $ZnCl_2$ (163 mg, 1.2 mmol) in THF (2.4 mL), stirred at room temperature for 2.5 h, treated with a solution of 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one (164 mg, 0.4 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) in THF (2 mL), and stirred overnight. The brown solution was quenched with saturated aqueous ethylenediaminetetraacetic acid (2.4 mL), stirred for 15 min, slowly treated with saturated Na_2CO_3, and extracted with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and concentrated to give 300 mg of a residue. The crude product was purified by flash chromatography using 12 g of silica gel and 0-50% EtOAc in hexanes as eluant to afford 100 mg (61%) of starting 1-[2-bromo-5-(2-

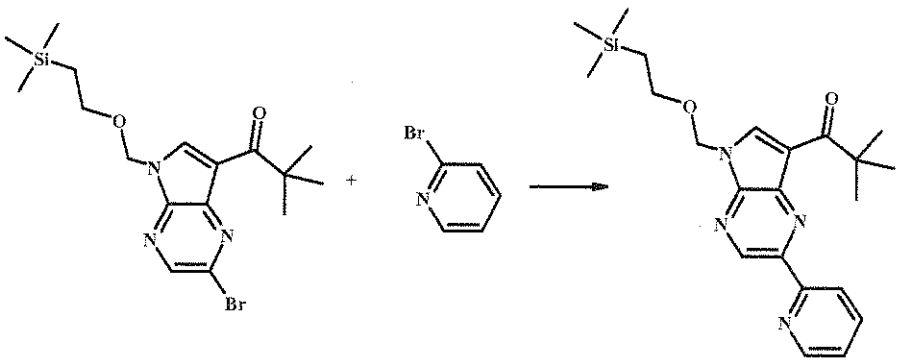
trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one as a yellow oil and 50 mg (26%) of 2,2-dimethyl-1-[2-(4-pyrrolidin-1-yl-pyridin-2-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one. M+H 480.

Example 6.

2,2-Dimethyl-1-[2-(4-pyrrolidin-1-yl-pyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one

A yellow solution of 2,2-dimethyl-1-[2-(4-pyrrolidin-1-yl-pyridin-2-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one (25 mg, 0.05 mmol) in CH_2Cl_2 (1 mL)and trifluoroacetic acid (0.5 mL) was stirred at room temperature for 3 h, concentrated, and azeotroped with toluene twice. A suspension of the residue and $NaOAc·3H_2O$ (70 mg, 0.5 mmol) in EtOH (0.5 mL) was stirred at room temperature overnight, diluted with EtOAc, and concentrated. The resultant residue was partitioned between H_2O and CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and concentrated to give 40 mg of a yellow foam. The crude product was purified by preparative thin layer chromatography using 90:9.5:0.5 CH_2Cl_2:MeOH:conc NH_4OH as eluant to afford 16 mg (88%) of 2,2-dimethyl-1-[2-(4-pyrrolidin-1-yl-pyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one as a yellow solid. MP 260-263 °C, M+H 350.

Example 7.

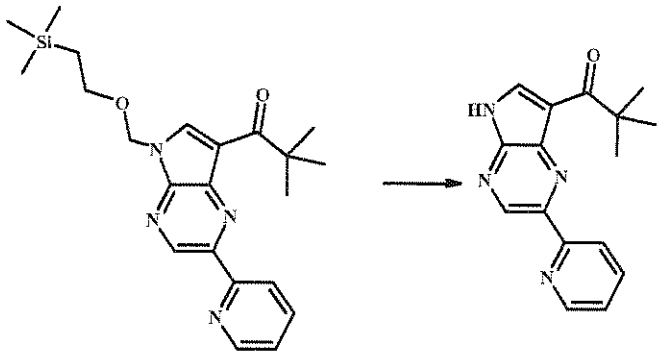


2,2-Dimethyl-1-[2-pyridin-2-yl-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one

To THF (1 mL) at -78 °C was added dropwise a solution of *t*-BuLi (1.1 mL, 1.3 M solution in pentane, 1.2 mmol). To the resultant yellow solution was added dropwise a solution of 2-bromo-pyridine (60 uL, 0.6 mmol) in THF (2.5 mL). The reaction was stirred for 1 h, treated dropwise with a solution of $ZnCl_2$ (204 mg, 1.5 mmol) in THF (2.8 mL), stirred at room temperature for 2.5 h, treated with a solution of 1-[2-bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one (206 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.026

mmol) in THF (2 mL), and stirred overnight. The reaction was quenched with saturated aqueous ethylenediaminetetraacetic acid (2.5 mL), stirred for 15 min, slowly treated with saturated Na_2CO_3, (~4 mL) until pH~9, and partitioned between H_2O and EtOAc. The combined organic phases were dried with Na_2SO_4 and concentrated to give 300 mg of a brown oil. The crude product was purified by flash chromatography using 12 g of silica gel and 5-40% EtOAc in hexanes as eluant to afford 87 mg (42%) of 2,2-dimethyl-1-[2-pyridin-2-yl-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one as a tan oil. M+H 411.

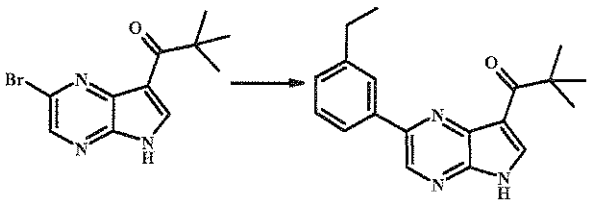
Example 8.



2,2-Dimethyl-1-(2-pyridin-2-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one

A yellow solution of 2,2-dimethyl-1-[2-pyridin-2-yl-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one (87 mg, 0.2 mmol) in CH_2Cl_2 (1 mL)and trifluoroacetic acid (0.5 mL) was stirred at room temperature for 4 h, concentrated, and azeotroped with toluene twice. A suspension of the residue and $NaOAc{\cdot}3H_2O$ (290 mg, 2 mmol) in EtOH (1.5 mL) was stirred at room temperature overnight, diluted with EtOAc, and concentrated. The resultant residue was partitioned between H_2O and CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and concentrated to give 85 mg of a yellow solid. The crude product was purified by preparative thin layer chromatography using 90:9.5:0.5 CH_2Cl_2:MeOH:conc NH_4OH as eluant to provide 55 mg of a yellow solid. The yellow solid was washed with MeOH, CH_2Cl_2 and Et_2O to afford 28 mg (47%) of 2,2-dimethyl-1-(2-pyridin-2-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one as a tan solid. MP 276-278 °C, M+H 281.

Example 9.



1-[2-(3-Ethyl-phenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one

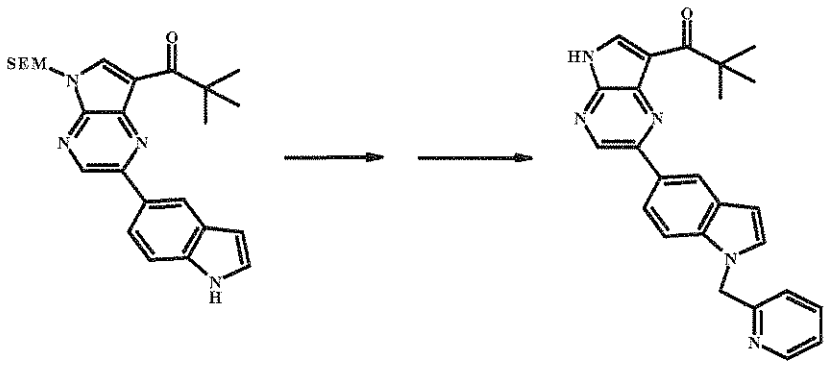
A microwave tube was charged with 1-(2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one (152 mg, 0.54 mmol), 3-ethylphenylboronic acid (89 mg, 0.59 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) (35 mg, 0.042 mmol), and K_2CO_3 (186 mg, 1.34 mmol). Dioxane (4 ml) and water (1 ml) were added, and the tube was microwaved at 150 °C for 45 min. The reaction mixture was filtered through a plug of celite. The filtrate was collected and partitioned between EtOAc/ water. The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated giving a dark brown solid. The crude product was purified by silica gel chromatography using 20-50% EtOAc in hexanes as eluant provided 82 mg (50%) of 1-[2-(3-ethyl-phenyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one as a yellow solid. MP 199-200.1 °C, M+H = 308.

Example 10.

(1-Methyl-cyclohexyl)-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-methanone.

(1-Methyl-cyclohexyl)-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-methanone was prepared starting from (2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-(1-methyl-cyclohexyl)-methanone and 4-methyl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[1,4]oxazine following general procedures as described in these Examples. MP 243-244 °C, M+H = 391.

Example 11.



2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5Hpyrrolo[2,3-b]pyrazin-7-yl]propan-1-one.

To a DMF (1 mL) solution of 1-[2-(1H-Indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one (50 mg, 0.11 mmol; prepared as described in Ex. 45, only using the Sem-protected starting material) was added NaHMDS (0.25 mL, 1M in THF) and stirred for 20 min at RT. 2-Chloromethylpyridine hydrochloride (21.6 mg, 0.13 mmol) was added in a single portion. After stirring for 1 hr at RT TLC analysis (25% EtOAc/hexanes) shows a new more-polar product. The reaction mixture was poured into 25 mL of saturated sodium bicarbonate solution and extracted with EtOAc (2 x 15 mL). The organic layers were combined, washed with brine, dried over MgSO4, and concentrated to give a yellow oil. Chromatography (SiO_2; 0%-13%-25% EtOAc in hexanes) gives 2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one as a clear oil. Following general procedures as described in these Examples, the SEM group was removed to give 2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5Hpyrrolo[2,3-b]pyrazin-7-yl]propan-1-one (47%; MS = 410 [M+H]; MP: 194-196 °C).

Compounds prepared using the alkylation and SEM removal route described herein:

1-{2-[1-(1-Benzyl-pyrrolidin-3-yl)-1H-indol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one: $(M+H)^+ = 478$; ^1H NMR (DMSO): δ 8.97 (s), 8.48 (s), 3.73 (d), 3.65 (d) ppm;

2,2-Dimethyl-1-[2-(1-pyridin-3-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one: $(M+H)^+ = 410$; MP = 170-171 °C;

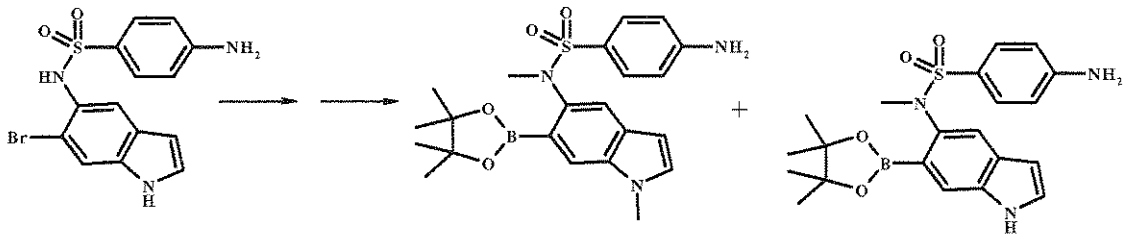
2,2-Dimethyl-1-[2-(1-pyridin-4-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one: $(M+H)^+ = 410$; MP = 241-243 °C;

2,2-Dimethyl-1-{2-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-propan-1-one: $(M+H)^+ = 414$; MP = 263-265 °C; only using N-methylpiperidine-4-one and sodium methoxide in methanol at reflux in the first step;

2,2-Dimethyl-1-[2-(3-piperidin-4-yl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one: $(M+H)^+ = 402$; ^1H NMR (DMSO): δ 8.98 (s), 8.47 (s), 3.1 (d, br), 2.95 (m), 2.73 (t, br), 1.54 (s) ppm; only using N-Boc-piperdine-4-one and sodium methoxide in methanol at reflux in the first step, followed by transfer hydrogenation using ammonium formate and Pd/C in

methanol at reflux prior to removal of protecting groups; sodium methoxide in methanol was used in place of sodium acetate in ethanol in the deprotection step.

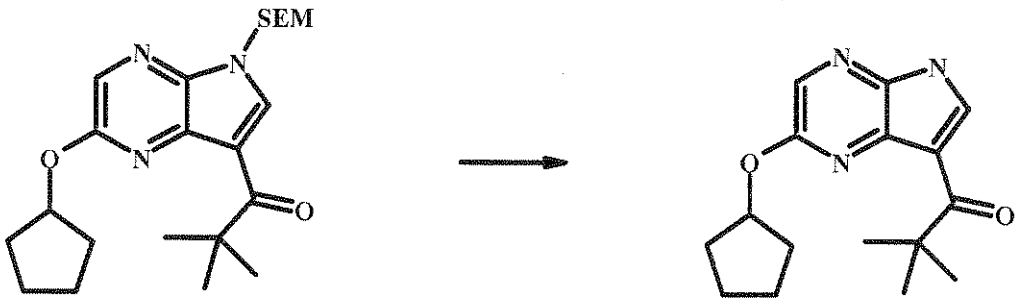
Example 12.



4-Amino-N-methyl-N-[1-methyl-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indol-5-yl]-benzenesulfonamide and 4-Amino-N-methyl-N-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indol-5-yl]-benzenesulfonamide.

To a DMF (6mL) solution of 4-Amino-N-(6-bromo-1H-indol-5-yl)-benzenesulfonamide (750 mg, 2.05 mmol) was added NaHMDS (2.77 mL, 1M in THF) and stirred for 20 min at RT. Methyl iodide (0.153 mL, 2.46 mmol) was added in a single portion. After stirring for 2.5 hr at RT TLC analysis (10% MeOH/dichloromethane) shows two new less-polar products. The reaction mixture was poured into 75 mL of saturated sodium bicarbonate solution and extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine, dried over MgSO4, and concentrated to give a yellow oil. Chromatography (SiO_2; 0%-5% MeOH/dichloromethane) gives 4-amino-N-(6-bromo-1-methyl-1H-indol-5-yl)-N-methyl-benzenesulfonamide as the less-polar product (MS = 394, 396 [M+H]) and 4-amino-N-(6-bromo-1H-indol-5-yl)-N-methyl-benzenesulfonamide (only 85% pure) as the more-polar product (MS = 380, 382 [M+H]). The corresponding boronates were separately prepared following general procedures as described in these Examples: 4-Amino-N-methyl-N-[1-methyl-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indol-5-yl]-benzenesulfonamide: (MS = 442 [M+H]); 4-Amino-N-methyl-N-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indol-5-yl]-benzenesulfonamide, following chromatography (SiO_2; 1%-5% MeOH/dichloromethane): (MS = 428 [M+H]).

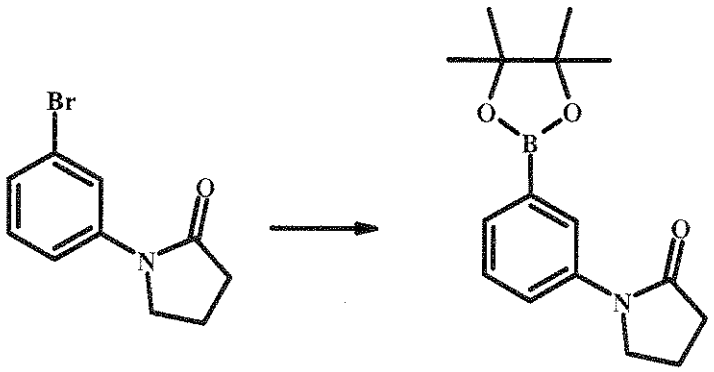
Example 13.



1-(2-cyclopentyloxy-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one

A solution of 1-[2-cyclopentyloxy-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one (0.017 g, 0.041 mmol) in 1 mL of dichloromethane and 1 mL of trifluoroacetic acid was stirred for 5 h then concentrated to a yellow oil. Silica gel chromatography (0->40% EtOAc/hexanes) afforded 0.012 g of a white solid. ^{1}H NMR spectroscopy indicated that this intermediate was the formaldehyde adduct of the desired product. The solid was dissolved in 1 mL of ethanol and the solution was treated with sodium acetate trihydrate (0.064 g, 0.47 mmol). The colorless mixture was stirred for 5 h then concentrated. The residue was partitioned between 5 mL of ethyl acetate and 5 mL of water. The organic layer was sequentially washed with 5 mL of water and 5 mL of a sat. aq. NaCl solution, dried over $MgSO_4$, filtered and concentrated to 0.007 g (57%) of 1-(2-cyclopentyloxy-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2,2-dimethyl-propan-1-one as a slightly impure white solid.

Example 14.



1-[3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrrolidin-2-one

To a flask charged with 1-(3-Bromo-phenyl)-pyrrolidin-2-one (713 mg), bis(pinacolato)diboron (1.51 g), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex (121 mg) and potassium acetate (874 mg) was added 10 mL of DMSO and the resulting mixture stirred at 90

°C for 16 h. The reaction mixture was cooled and filtered over celite. The mixture was then partitioned between water and dichloromethane and the organic phase was dried over Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (0-100% ethyl acetate in hexanes) afforded a 286 mg of 1-[3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrrolidin-2-one. Subsequent steps involved the standard Suzuki coupling, iodination, and aminocarbonylation.

JAK Assay Information

Determination of IC_{50} of Janus Kinase (JAK) inhibition:

Enzymes and peptide substrate used are described below:

JAK1: Recombinant human kinase domain from Invitrogen (Cat # PV4774)

JAK3: Recombinant human kinase domain from Millipore (Cat # 14-629) or prepared.

JAK2: Recombinant human kinase domain from Millipore (Cat # 14-640)

Substrate: N-terminally biotinylated 14-mer peptide derived from activation loop of JAK1 with sequence of the peptide substrate: Biotin-KAIETDKEYYTVKD

Assay conditions used are described below:

Assay Buffer: JAK Kinase Buffer: 50mM Hepes [pH 7.2], 10mM $MgCl_2$, 1mM DTT, 1mg/ml BSA. The assay is carried out in this buffer.

Assay Format: The kinase activity of all three JAK kinases is measured using a radioactive, end-point assay and with trace amounts of ^{33}P-ATP. The assays are carried out in 96-well polypropylene plates.

Experimental Method:

All concentrations are final in the reaction mixture and all incubations are carried at room temperature. Assay steps are described below:

Compounds are serially diluted in 100% DMSO typically at a 10x starting concentration of 1mM. Final concentration of DMSO in the reaction is 10%.

Compounds are preincubated with enzyme (0.5nM JAK3 (commercially available), 0.2nM JAK3 (prepared), 1nM JAK2, 5nM JAK1) for 10 minutes.

Reactions are initiated by the addition of a cocktail of the two substrates (ATP and peptide premixed in the JAK Kinase Buffer). In the JAK2/JAK3 assays, ATP and the peptide are used at concentrations of 1.5uM and 50uM, respectively. JAK1 assay is carried out at an ATP concentration of 10uM and a peptide concentration of 50uM. The duration of the assay for JAK2 and JAK3 is 20 minutes. JAK1 assay is carried out for 40 minutes. With all three enzymes, reactions are terminated by the addition of 0.5M EDTA to a final concentration of 100mM.

25 ul of terminated reactions are transferred to 150 ul of a 7.5% (v/v) slurry of streptavidin-coated sepharose beads in $MgCl_2$- and $CaCl_2$-free 1x Phosphate Buffered Saline containing 50mM of EDTA in 96-well, 1.2um MultiScreen-BV filter plates. After a 30-minute incubation, the beads are washed under vacuum with the following buffers:

3 to 4 washes with 200 ul of 2M NaCl.

3 to 4 washes with 200 ul of 2M NaCl plus 1% (v/v) phosphoric acid.

1 wash with water.

Washed plates are dried in a 60°C oven for between 1 to 2 hours.

70 ul of Microscint 20 scintillation fluid is added to each well of filter plates and after at least 30 minutes of incubation, radioactive counts are measured in a Perkinelmer microplate scintillation counter.

Representative IC_{50} results are in Table II below:

TABLE II.

Compound	IC_{50} h-jak3-sf21-c
I-49	0.1522
I-50	0.1548
I-52	0.03242
I-54	0.1579

SYK Assay Information

Determination of IC_{50} of Spleen Tyrosine Kinase (SYK) inhibition:

SYK kinase assay is a standard kinase assay adapted to a 96 well plate format. This assay is performed in 96-well format for IC_{50} determination with 8 samples which represented 10 half log dilutions and a 40 µL reaction volume. The assay measures the incorporation of radiolabeled ^{33}P ATP into an N-terminally biotinylated peptide substrate, derived from naturally occurring phosphoacceptor consensus sequence (Biotin-11aa DY*E). Phosphorylated products were detected upon termination of reactions with EDTA and the addition of Streptavidin coated beads. Representative results are in Table II above.

Assay plates: 96-well MultiScreen 0.65um filter plates (Millipore Cat. No.: MADVNOB10)

Streptavidin coated beads: Streptavidin Sepharose TM, suspension 5.0mL, in 50mM EDTA/PBS diluted (1:100), (Amersham, Cat. No.: 17-5113-01)

Compounds: 10 mM in 100% dimethylsulfoxide (DMSO), final conc.: compound 0.003-100uM in 10% DMSO

Enzyme: SYK RPA purified, truncated construct of Spleen Tyrosine Kinase aa 360-635, stock solution 1 mg/mL, MW: 31.2 KDa, final conc.:0.0005 µM.

Peptide 1: biotinylated peptide is derived from a naturally occurring phosphor-acceptor consensus sequence (Biotin-EPEGDYEEVLE), special order from QCB, stock solution 20mM, final conc.: 5.0 µM.

ATP: Adenosine-5'-triphosphate 20 mM, (ROCHE Cat. No.: 93202720), final concentration: 20µM

Buffer: HEPES: 2-Hydroxyethyl piperazine-2-ethanesulfonic acid (Sigma , Cat. No.: H-3375) final concentration: 50mM HEPES pH7.5

BSA: Bovine Serum Albumin Fraction V, fatty acid free (Roche Diagnostics GmbH, Cat. No. 9100221) diluted to a final concentration of 0.1%

EDTA: EDTA stock solution 500 mM, (GIBCO, Cat. No.: 15575-038) final concentration: 0.1mM

DTT: 1,4-Dithiothreitol (Roche Diagnostics GmbH, Cat. No.: 197777), final conc.: 1mM

$MgCl_2$ x $6H_2O$: MERCK, Cat. No.: 105833.1000, final concentration: 10mM

Assay Dilution Buffer (ADB): 50 mM HEPES, 0.1mM EGTA, 0.1mM Na Vanadate, 0.1mM β-glycerophosphate, 10 mM $MgCl_2$, 1 mM DTT, 0,1% BSA, pH 7.5

Bead wash buffer: 10 g/L PBS (Phosphate buffered saline) with 2M NaCl+ 1% phosphoric acid.

Experimental Method:

In 40μL volume, 26μL of ADB diluted, purified recombinant human SYK360-635 [0.5 nM] was mixed with 4 μL of 10X concentrations of the test compounds, [usually 100μM- 0.003μM] in [10%] DMSO and the mixture was incubated for 10 min at RT.

The kinase reaction was initiated by the addition of 10μL 4x substrate cocktail containing the DYE peptide substrate [0 or 5 μM], ATP [20 μM] and ^{33} PγATP [2μCi/rxn]. After incubation at 30° C for 15 min, the reaction was terminated by the transfer of 25μL pf the reaction sample to a 96 well 0.65μm Millipore MADVNOB membrane/plate containing 200μL 5mM EDTA and 20% Streptavidine coated beads in PBS.

The unbound radionucleotides were washed under vacuum with 3 x 250μL 2M NaCl; 2 x 250 μL 2M NaCl+1% phosphoric acid; 1 x 250μL H_2O. After the last wash membrane/ plates were transferred to an adaptor plate, heat dried for 15 min at 60° C, and 50 μL scintillation cocktail was added to each well and 4 h later the amount of radioactivity was counted in a top counter.

The percent inhibition was calculated based on the uninhibited enzyme rate:

$$\% \text{ Inhibition} = 100 / (1 + (IC_{50}/\text{Inhibitor conc})^n)$$

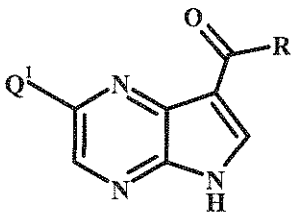
The IC_{50} was calculated using a non-linear curve fit with XLfit software (ID Business Solution Ltd., Guilford, Surrey, UK).

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

Claims

1. A compound of Formula **I**



I wherein:

R is R^1, R^2, R^3, or R^4;

R^1 is C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, benzyl, heteroaryl, cycloalkyl, heterocycloalkyl, or cycloalkylalkyl, optionally substituted with one or more R^{1a};

R^{1a} is R^{1b} or R^{1c};

R^{1b} is halogen, oxo, hydroxy, or –CN;

R^{1c} is $–C(=O)O(R^{1f})$, $–C(=O)CH_2(R^{1e})$, $–S(R^{1f})$, $–S(O)_2(R^{1f})$, or $–S(=O)(R^{1f})$, C_{1-6} alkyl, C_{1-6} alkoxy, amino, amido, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkyloxy, or heterocycloalkyloxy optionally substituted with one or more R^{1d};

R^{1d} is H, halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl;

R^{1e} is H, C_{1-6} alkyl, C_{1-6} alkoxy, –CN, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^{1f} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^2 is $N(R^{2a})_2$;

each R^{2a} is independently H or R^{2b};

each R^{2b} is independently C_{1-6} alkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, or heterocycloalkyl alkylene, optionally substituted with one or more R^{2c};

R^{2c} is R^{2d} or R^{2e};

R^{2d} is halogen, oxo, or hydroxy;

R^{2e} is $–N(R^{2g})_2$, $–C(=O)(R^{2g})$, $–C(=O)O(R^{2g})$, $–C(=O)N(R^{2g})_2$, $–N(R^{2g})C(=O)(R^{2g})$, $–S(=O)_2(R^{2g})$, $–S(O)_2N(R^{2g})_2$,

C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, phenyl, heteroaryl, heteroaryloxy, cycloalkyl, or heterocycloalkyl, optionally substituted with one or more R^{2f};

each R^{2f} is independently H, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl;

each R^{2g} is independently H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or phenyl;

R^3 is $-C(=O)R^{3a}$;

R^{3a} is C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, or $N(R^{3b})_2$;

each R^{3b} is independently H or C_{1-6} alkyl;

R^4 is $-O(R^{4a})$;

R^{4a} is H or R^{4b};

R^{4b} is C_{1-6} alkyl, phenyl, benzyl, C_{1-6} haloalkyl, cycloalkyl, heterocycloalkyl, heteroaryl, optionally substituted with one or more R^{4c};

R^{4c} is halogen, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

Q^1 is phenyl substituted with two Q^{1a} which come together to form a heterocyclic or heteroaryl ring system, optionally substituted with one or more Q^{1b} or Q^{1c};

Q^{1b} is halogen, hydroxy, oxo, or –CN;

Q^{1c} is Q^{1d} or Q^{1e};

Q^{1d} is $-O(Q^{1e})$, $-S(Q^{1e})$, $-S(=O)(Q^{1e})$, $-S(=O)_2(Q^{1e})$, $-C(=O)N(Q^{1e})_2$, $-N(Q^{1e})S(=O)_2(Q^{1e})$, $-C(=O)(Q^{1e})$, $-C(=O)O(Q^{1e})$, $-N(Q^{1e})_2$; $-N(Q^{1e})C(=O)(Q^{1e})$, $-N(Q^{1e})C(=O)O(Q^{1e})$, or $-N(Q^{1e})C(=O)N(Q^{1e})_2$;

each Q^{1e} is independently H or $Q^{1e'}$;

each $Q^{1e'}$ is independently C_{1-6} alkyl, C_{1-6} alkenyl, phenyl, benzyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{1f};

Q^{1f} is Q^{1g} or Q^{1h};

Q^{1g} is halogen, hydroxy, oxo, $-C(=O)(Q^{1h})$, or $-N(Q^{1h})C(=O)(Q^{1h})$;

each Q^{1h} is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, amino, phenyl, benzyl,

cycloalkyl, heterocycloalkyl, or heteroaryl, optionally substituted with one or more Q^{1i};

each Q^{1i} is independently halogen, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

or a pharmaceutically acceptable salt thereof wherein "phenyl substituted with two Q^{1a} which come together to form a heterocyclic or heteroaryl ring system" as used herein means the two Q^{1a} radicals on the phenyl ring join to form a saturated, partially saturated, or unsaturated ring system, containing four to eight atoms, incorporating one or more N, O, or S heteroatoms, the remaining ring atoms being carbon resulting in a bicyclic ring system.

2. The compound of claim 1, wherein R is R^1.

3. The compound of claim 2, wherein R^1 is C_{1-6} alkyl, preferably *tert*-butyl.

4. The compound of claim 1, wherein R is R^2 and R^2 is $NH(R^{2a})$, preferably wherein R^{2a} is R^{2b} as defined in claim 1.

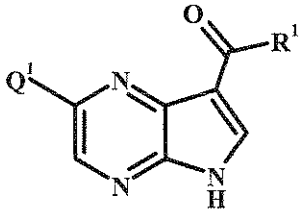
5. The compound of claim 1, wherein Q^{1a} is Q^{1b}, preferably wherein Q^{1b} is halogen or hydroxy.

6. The compound of any one of claims 1-4, wherein Q^{1a} is Q^{1c}.

7. The compound of claim 6, wherein Q^{1c} is Q^{1d}, Q^{1d} is $-O(Q^{1e})$, Q^{1e} is $Q^{1e'}$, and $Q^{1e'}$ is C_{1-6} alkyl, optionally substituted with one or more Q^{1f}.

8. The compound of claim 6, wherein Q^{1c} is Q^{1e}, Q^{1e} is $Q^{1e'}$, and $Q^{1e'}$ is heterocycloalkyl, optionally substituted with one or more Q^{1f}.

9. A compound of formula II according to claim 1:



II

wherein R^1 is C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, benzyl, heteroaryl, cycloalkyl, heterocycloalkyl, or cycloalkylalkyl, optionally substituted with one or more R^{1a};

R^{1a} is R^{1b} or R^{1c};

R^{1b} is halogen, oxo, hydroxy, or –CN;

R^{1c} is $-C(=O)O(R^{1f})$, $-C(=O)CH_2(R^{1e})$, $-S(R^{1f})$, $-S(O)_2(R^{1f})$, or $-S(=O)(R^{1f})$, C_{1-6} alkyl, C_{1-6} alkoxy, amino, amido, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkyloxy, or heterocycloalkyloxy optionally substituted with one or more R^{1d};

R^{1d} is H, halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl;

R^{1e} is H, C_{1-6} alkyl, C_{1-6} alkoxy, –CN, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^{1f} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, heteroaryl, cycloalkyl, or heterocycloalkyl; and

Q^1 is defined according to any of the claims 1 to 8.

10. A compound of Formula **I** according to claim 1 selected from the group consisting of:

1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-3-methyl-butan-1-one;

1-(2-Benzo[1,3]dioxol-5-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-3-methyl-butan-1-one;

2,2-Dimethyl-1-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

1-[2-(1H-Indol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

1-[2-(1H-Indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

1-[2-(1H-Indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one;

2,2-Dimethyl-1-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]oxazin-3-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-methyl-4H-benzo[1,4]oxazin-3-one;

2,2-Dimethyl-1-[2-(1-pyridin-3-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-[2-(1-pyridin-4-ylmethyl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2,4-trimethyl-4H-benzo[1,4]oxazin-3-

one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-ethyl-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one;

4-Benzyl-6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one;

1-{2-[1-(1-Benzyl-pyrrolidin-3-yl)-1H-indol-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one;

2,2-Dimethyl-1-{2-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-propan-1-one;

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide;

2,2-Dimethyl-1-[2-(1-piperidin-4-yl-1H-indol-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-6-[7-(1-methyl-cyclohexanecarbonyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]oxazin-3-one;

7-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4H-benzo[1,4]thiazin-3-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4-pyridin-2-ylmethyl-4H-benzo[1,4]oxazin-3-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,2-dimethyl-4-(2-morpholin-4-yl-ethyl)-4H-benzo[1,4]oxazin-3-one;

6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-4-(3-hydroxy-2-hydroxymethyl-propyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one;

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-methanesulfonamide;

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide;

1-[2-(4-Benzenesulfonyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

N-(4-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-ylsulfamoyl}-phenyl)-acetamide;

N-(4-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-2,3-dihydro-benzo[1,4]oxazine-4-sulfonyl}-phenyl)-acetamide;

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-yl}-benzenesulfonamide;

1-{2-[4-(4-Amino-benzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one;

4-Chloro-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-benzenesulfonamide;

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-4-fluoro-benzenesulfonamide;

N-{6-[7-(2,2-Dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-4-methoxy-benzenesulfonamide;

6-Chloro-pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide;

Pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide;

6-Amino-pyridine-3-sulfonic acid {6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-amide;

(1-Methyl-cyclohexyl)-[2-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-methanone;

2,2-Dimethyl-1-(2-quinolin-5-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one;

1-[2-(1H-Indazol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

1-[2-(1H-Indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-2,2-dimethyl-propan-1-one;

2,2-Dimethyl-1-(2-quinolin-6-yl-5H-pyrrolo[2,3-b]pyrazin-7-yl)-propan-1-one;

2,2-Dimethyl-1-[2-(1-methyl-1H-indazol-4-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-[2-(3-methyl-1H-indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-[2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

1-{2-[1-(1-Benzyl-pyrrolidin-3-yl)-1H-indol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-2,2-dimethyl-propan-1-one;

2,2-Dimethyl-1-[2-(1-pyridin-3-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-[2-(1-pyridin-4-ylmethyl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

2,2-Dimethyl-1-{2-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-7-yl}-propan-1-one;

2,2-Dimethyl-1-[2-(3-piperidin-4-yl-1H-indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-propan-1-one;

[2-(1H-Indol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]-(1-methyl-cyclohexyl)-methanone;

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1-methyl-1H-indol-4-yl}-N-methyl-benzenesulfonamide; and

4-Amino-N-{6-[7-(2,2-dimethyl-propionyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-1H-indol-4-yl}-N-methyl-benzenesulfonamide.

11. A compound according to claim 1 or 9 wherein Q^1 is dihydrobenzodioxinyl, benzodioxolyl, dihydrobenzoxazinyl, indolyl, dihydrobenzothiazinyl, quinolinyl or indazolyl optionally substituted with one or more Q^{1b} or Q^{1c} as defined in any one of claims 1 to 9.

12. A compound according to claim 1 or 9 wherein Q^1 is indolyl, dihydrobenzoxazinyl or benzoxazinone optionally substituted with one or more Q^{1b} or Q^{1c} as defined in any one of claims 1 to 9.

13. Use of the compound according to any one of the claims 1 to 10 in the manufacture of a medicament for the treatment of an inflammatory disorder or of an autoimmune disorder.

14. Compound according to any one of the claims 1 to 10 for use in the treatment of an inflammatory disorder or of an autoimmune disorder.