PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF ABNORMAL CELL GROWTH

Background of the Invention

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

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

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

Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, erbstatin, a tyrosine kinase inhibitor, selectively attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma that expresses epidermal growth factor receptor tyrosine kinase (EGFR) but is without effect on the growth of another carcinoma that does not express the EGF receptor. Thus, selective inhibitors of certain receptor tyrosine kinases, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals. In addition to receptor tyrosine kinses, selective inhibitors of certain non-receptor tyrosine kinases, such as FAK (focal adhesion kinase), lck, src, abl or serine/threonine kinases (e.g.: cyclin dependent

kinases, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals. FAK is also known as the Protein-Tyrosine Kinase 2, PTK2.

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

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

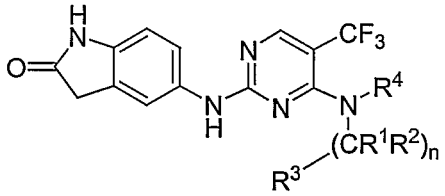
Also, World Patent Application WO 92/20642 (published November 26, 1992), refers to certain bis-mono and bicyclic aryl and heteroaryl compounds as tyrosine kinase inhibitors that are useful in inhibiting abnormal cell proliferation. World Patent Applications WO96/16960 (published June 6, 1996), WO 96/09294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

U.S. Patent Application Serial No. 60/435,670, filed December 20, 2002 (Attorney Docket No. PC25339) relates to a broad class of novel pyrimidine derivatives that are selective inhibitors of FAK. As such, these compounds are useful in the treatment of abnormal cell growth.

Accordingly, a need exists for additional selective inhibitors of certain receptor and non-receptor tyrosine kinases, useful in the treatment of abnormal cell growth, such as cancer, in mammals. The present invention provides for novel pyrimidine derivatives that are selective inhibitors of the non-receptor tyrosine kinase, FAK, and are useful in the treatment of abnormal cell growth.

Summary of the Invention

The present invention relates to a compound of the formula **1**



1

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof,

wherein n is an integer from 1 to 3;

each R^1 is a substituent independently selected from the group consisting of hydrogen, hydroxy, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -NR^5R^6, -SR^7, -SOR^7, -SO_2R^7, -CO_2R^5, -$CONR^5R^6$, --$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing R^1 substituents may not be bound to an sp^3 carbon atom bound to another heteroatom; and said R^1 substituents, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -NR^5R^6, -SR^7, -SOR^7, -SO_2R^7, -CO_2R^5, -$CONR^5R^6$, - $SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$ groups are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; with the proviso that a heteroatom of the foregoing optional R^1 moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

each R^2 is a substituent independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, and -$CONR^5R^6$; with the proviso that a heteroatom of any of the foregoing R^2 substituents may not be bound to an sp^3 carbon atom that is bound to another heteroatom; and said R^2 substituents, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, and -$CONR^5R^6$, are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-

O($(C_1$-$C_6)$alkyl), -NR^5R^6, -OR^5, -$(C_3$-$C_7)$cycloalkyl, -$(C_2$-$C_9)$heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -NHCOR^5, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –$(C_2$-$C_6)$alkenyl and –$(C_2$-$C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and with the proviso that a heteroatom of the foregoing optional R^2 moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

R^1 and R^2 may be taken together with the atom(s) to which they are attached to form a cyclic group, -$(C_3$-$C_{10})$cycloalkyl or -$(C_2$-$C_9)$heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C=N-OH, -C=N-O($(C_1$-$C_6)$alkyl), -NR^5R^6, -OR^5, -$(C_3$-$C_7)$cycloalkyl, -$(C_2$-$C_9)$heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -NHCOR^5, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –$(C_2$-$C_6)$alkenyl and –$(C_2$-$C_6)$alkynyl moieties of said cyclic group may be optionally substituted by one to three R^5 groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an sp^3 carbon atom that is bound to another heteroatom;

R^3 is a suitable substituent, including, but not limited to a substituent selected from the group consisting of:

(a) hydrogen;

(b) -$(C_6$-$C_{10})$aryl or -$(C_1$-$C_9)$heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkyl-P(O)(O$(C_1$-$C_6)$alkyl)$_2$, -$(C_3$-$C_{10})$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_2$-$C_9)$heterocyclyl, -$(C_1$-$C_9)$heteroaryl, -NR^5R^6, -N<u>H</u>$SO_2(C_1$-$C_6)$alkyl, -$NHSO_2(C_3$-$C_6)$cycloalkyl, -N($(C_1$-$C_6)$alkyl)(SO_2-C_1-$C_6)$alkyl), -N($(C_1$-$C_6)$alkyl)($SO_2(C_3$-$C_6)$cycloalkyl), -O$(C_1$-$C_6)$alkyl, -O-$SO_2(C_1$-$C_6)$alkyl, -(CO)$(C_1$-$C_6)$alkyl, -(CO)CF_3, -(CO)$(C_3$-$C_{10})$cycloalkyl, -(CO)$(C_6$-$C_{10})$aryl, -(CO)$(C_2$-$C_9)$heterocyclyl, -(CO)$(C_1$-$C_9)$heteroaryl, -(CO)O$(C_1$-$C_6)$alkyl, -(CO)O$(C_3$-$C_{10})$cycloalkyl, -(CO)O$(C_6$-$C_{10})$aryl, -(CO)O$(C_2$-$C_9)$heterocyclyl, -(CO)O$(C_1$-$C_9)$heteroaryl, -(CO)$(C_1$-$C_6)$alkyl-O$(C_1$-$C_6)$alkyl, -$SO_2(C_1$-$C_6)$alkyl, -$SO_2(C_3$-$C_6)$cycloalkyl, SO_2CF_3, SO_2NH_2, $SO_2NH(C_1$-$C_6)$alkyl, -$SO_2NH(C_3$-$C_6)$cycloalkyl, -$SO_2N((C_1$-$C_6)$alkyl)$_2$, -$SO_2N((C_3$-$C_6)$cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N(C_1$-$C_6)$alkyl-$(C_6$-$C_{10})$aryl; wherein said -$(C_6$-$C_{10})$ aryl or -$(C_1$-$C_9)$ heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -$(C_2$-$C_9)$heterocyclyl;

(c) -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocyclyl, and -(C_1-C_6)alkyl-(C_2-C_9) heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocyclyl, and -(C_1-C_6)alkyl-(C_2-C_9) heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

(d) -(C_1-C_6)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_1-C_6)alkyl is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and -NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

and wherein each R^3 (b)-(d) substituent, moiety, or element is optionally substituted by one to three radicals independently selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, -(C_1-C_9)heteroaryl, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -C=N-OH, -C=N-O(C_1-C_6 alkyl), -NR^5R^6, -SR^7,

-SOR^7, -SO_2R^7, -CO_2R^5, -$CONR^5R^6$, - $SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing R^3 (b)-(d) substituents, moieties, elements or radicals may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^5 and R^6 of said -NR^5R^6, -$CONR^5R^6$, -$SO_2NR^5R^6$, and -$NR^5CONR^5R^6$ groups may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

R^4 is a substituent selected from the group consisting of hydrogen, (C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, and -(C_2-C_9)heterocyclyl; wherein said (C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, and -(C_2-C_9)heterocyclyl R^4 substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -(C_1-C_6)alkyl, -CN, -NR^5_2, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, and -$CONR^5R^8$; with the proviso that a heteroatom of the foregoing R^4 substituents may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^5 and R^8 of said -$CONR^5R^8$ group may be taken together with the atoms to which they are attached to form a -(C_3-C_{10})cycloalkyl or -(C_2-C_9)heterocyclyl;

R^5 and R^6 are each substituents independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein said -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl R^5 or R^6 substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -CF_3, -CN, -(C_1-C_6)alkyl, -NH(C_1-C_6)alkyl, -NH(C_3-C_7)cycloalkyl, -NH(C_2-C_9)heterocyclyl, -NH(C_6-C_{10})aryl, -NH(C_1-C_9)heteroaryl, -N((C_1-C_6)alkyl)$_2$, -N((C_3-C_7)cycloalkyl)$_2$, -N((C_2-C_9)heterocyclyl)$_2$, -N((C_6-C_{10})aryl)$_2$, -N((C_1-C_9)heteroaryl)$_2$, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -O(C_6-C_{10})aryl, -O(C_1-C_9)heteroaryl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^7, -$CONH_2$, -$CONHR^7$, and -$CONR^7R^8$; with the proviso that a heteroatom of the foregoing R^5 or R^6 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatoms; and wherein R^7 and R^8 of said -$CONR^7R^8$ group may be taken together with the atoms to which they are attached to form a –(C_1-C_9) heteroaryl;

R^5 and R^6 may be taken together with the atom(s) to which they are attached to form a cyclic group, -(C_3-C_{10})cycloalkyl or -(C_2-C_9)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R^7 groups, and said cyclic group is

optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $–NR^5$, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an sp^3 carbon atom that is bound to another heteroatom;

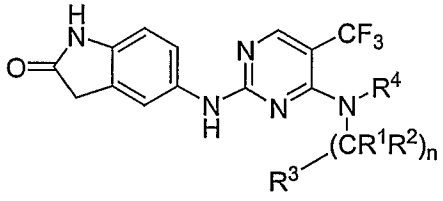
R^7 is a substituent selected from the group consisting of $–(C_1\text{-}C_6)$alkyl, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-(C_6\text{-}C_{10})$aryl, and $-(C_1\text{-}C_9)$ heteroaryl; wherein said $–(C_1\text{-}C_6)$alkyl, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-(C_6\text{-}C_{10})$aryl, and $-(C_1\text{-}C_9)$ heteroaryl R^7 substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1\text{-}C_6)$alkyl, $-NR^5{}_2$, and $–O(C_1\text{-}C_6)$alkyl, with the proviso that a heteroatom of the foregoing R^7 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

R^8 is a substituent selected from the group consisting of hydrogen, $-(C_1\text{-}C_6)$alkyl, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-(C_6\text{-}C_{10})$aryl, and $-(C_1\text{-}C_9)$ heteroaryl; wherein said $-(C_1\text{-}C_6)$alkyl, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-(C_6\text{-}C_{10})$aryl, and $-(C_1\text{-}C_9)$ heteroaryl R^8 radicals are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1\text{-}C_6)$alkyl, $-NH_2$, $-NHR^9$, $-NR^9{}_2$, OR^9, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-CO_2R^{10}$, $-CONH_2$, $-CONHR^{10}$, and $-CONR^{10}R^{11}$; with the proviso that a heteroatom of the foregoing R^8 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^{10} and R^{11} of $-CONR^{10}R^{11}$ may be taken together with the atoms to which they are attached to form a $-(C2\text{-}C_9)$heterocyclyl;

R^9 and R^{10} are each $-(C_1\text{-}C_6)$alkyl and may be taken together with the atoms to which they are attached to form a $-(C_2\text{-}C_9)$heterocyclyl; and

R^{11} is hydrogen or $-(C_1\text{-}C_6)$alkyl.

In a preferred embodiment, the present invention relates to a compound of the formula 1



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or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof,

wherein n is an integer from 1 to 3;

each R^1 is a substituent independently selected from the group consisting of hydrogen, hydroxy, $-(C_1\text{-}C_6)$alkyl, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-O(C_1\text{-}C_6)$alkyl, -

$O(C_3\text{-}C_7)$cycloalkyl, $-O(C_2\text{-}C_9)$heterocyclyl, $-NR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-CO_2R^5$, $-CONR^5R^6$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing R^1 substituents may not be bound to an sp^3 carbon atom bound to another heteroatom; and said R^1 substituents, $-(C_1\text{-}C_6)$alkyl, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-O(C_1\text{-}C_6)$alkyl, $-O(C_3\text{-}C_7)$cycloalkyl, $-O(C_2\text{-}C_9)$heterocyclyl, $-NR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-CO_2R^5$, $-CONR^5R^6$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$ groups are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-CF_3$, $-CN$, $-(C_1\text{-}C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^8$; with the proviso that a heteroatom of the foregoing optional R^1 moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

each R^2 is a substituent independently selected from the group consisting of hydrogen, $-(C_1\text{-}C_6)$alkyl, $-(C_2\text{-}C_6)$alkenyl, $-(C_2\text{-}C_6)$alkynyl, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-CO_2R^5$, and $-CONR^5R^6$; with the proviso that a heteroatom of any of the foregoing R^2 substituents may not be bound to an sp^3 carbon atom that is bound to another heteroatom; and said R^2 substituents, $-(C_1\text{-}C_6)$alkyl, $-(C_2\text{-}C_6)$alkenyl, $-(C_2\text{-}C_6)$alkynyl, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-CO_2R^5$, and $-CONR^5R^6$, are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-CF_3$, $-NO_2$, $-CN$, $-(C_1\text{-}C_6)$alkyl, $-(C_2\text{-}C_6)$alkenyl, $-(C_2\text{-}C_6)$alkynyl, $-C{=}N\text{-}OH$, $-C{=}N\text{-}O((C_1\text{-}C_6)\text{alkyl})$, $-NR^5R^6$, $-OR^5$, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2\text{-}C_6)$alkenyl and $-(C_2\text{-}C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and with the proviso that a heteroatom of the foregoing optional R^2 moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

R^1 and R^2 may be taken together with the atom(s) to which they are attached to form a cyclic group, $-(C_3\text{-}C_{10})$cycloalkyl or $-(C_2\text{-}C_9)$heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, $-CF_3$, $-NO_2$, $-CN$, $-(C_1\text{-}C_6)$alkyl, $-(C_2\text{-}C_6)$alkenyl, $-(C_2\text{-}C_6)$alkynyl, $-C{=}N\text{-}OH$, $-C{=}N\text{-}O((C_1\text{-}C_6)\text{alkyl})$, $-NR^5R^6$, $-OR^5$, $-(C_3\text{-}C_7)$cycloalkyl, $-(C_2\text{-}C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2\text{-}C_6)$alkenyl and $-(C_2\text{-}C_6)$alkynyl moieties of said cyclic group may be optionally substituted by one to three R^5 groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of $-(C{=}O)$, $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an sp^3 carbon atom that is bound to another heteroatom;

R^3 is a substituent selected from the group consisting of:

(a) hydrogen;

(b) -(C_6-C_{10})aryl or -(C_1-C_9)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -$NHSO_2$(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_6-C_{10}) aryl or -(C_1-C_9) heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-,--O-, -N-, -NH- and –NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

(c) -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocyclyl, and -(C_1-C_6)alkyl-(C_2-C_9) heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocyclyl, and -(C_1-C_6)alkyl-(C_2-C_9) heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

(d) -(C_1-C_6)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$,

-(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_1-C_6)alkyl is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and -NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

and wherein each R^3 (b)-(d) substituent, moiety, or element is optionally substituted by one to three radicals independently selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, -(C_1-C_9)heteroaryl, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -C=N-OH, -C=N-O(C_1-C_6 alkyl), -NR^5R^6, -SR^7, -SOR^7, -SO_2R^7, -CO_2R^5, -$CONR^5R^6$, - $SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing R^3 (b)-(d) substituents, moieties, elements or radicals may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^5 and R^6 of said -NR^5R^6, -$CONR^5R^6$, -$SO_2NR^5R^6$, and -$NR^5CONR^5R^6$ groups may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

R^4 is a substituent selected from the group consisting of hydrogen, (C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, and -(C_2-C_9)heterocyclyl; wherein said (C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, and (C_2-C_9)heterocyclyl R^4 substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -(C_1-C_6)alkyl, -CN, -NR^5_2, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, and -$CONR^5R^8$; with the proviso that a heteroatom of the foregoing R^4 substituents may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^5 and R^8 of said -$CONR^5R^8$ group may be taken together with the atoms to which they are attached to form a -(C_3-C_{10})cycloalkyl or -(C_2-C_9)heterocyclyl;

R^5 and R^6 are each substituents independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein said -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl R^5 or R^6 substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -CF_3,

-CN, -(C_1-C_6)alkyl, -NH(C_1-C_6)alkyl, -NH(C_3-C_7)cycloalkyl, -NH(C_2-C_9)heterocyclyl, -NH(C_6-C_{10})aryl, -NH(C_1-C_9)heteroaryl, -N((C_1-C_6)alkyl)$_2$, -N((C_3-C_7)cycloalkyl)$_2$, -N((C_2-C_9)heterocyclyl)$_2$, -N((C_6-C_{10})aryl)$_2$, -N((C_1-C_9)heteroaryl)$_2$, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -O(C_6-C_{10})aryl, -O(C_1-C_9)heteroaryl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^7, -$CONH_2$, -$CONHR^7$, and -$CONR^7R^8$; with the proviso that a heteroatom of the foregoing R^5 or R^6 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatoms; and wherein R^7 and R^8 of said -$CONR^7R^8$ group may be taken together with the atoms to which they are attached to form a -(C_1-C_9) heteroaryl;

R^5 and R^6 may be taken together with the atom(s) to which they are attached to form a cyclic group, -(C_3-C_{10})cycloalkyl or -(C_2-C_9)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -O_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R^7 groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an sp^3 carbon atom that is bound to another heteroatom;

R^7 is a substituent selected from the group consisting of –(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9) heteroaryl; wherein said -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9) heteroaryl R^7 substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5_2, and -O(C_1-C_6)alkyl, with the proviso that a heteroatom of the foregoing R^7 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

R^8 is a substituent selected from the group consisting of hydrogen, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9) heteroaryl; wherein said -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9) heteroaryl R^8 radicals are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NH_2, -NHR^9, -NR^9_2, OR^9, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^{10}, -$CONH_2$, -$CONHR^{10}$, and -$CONR^{10}R^{11}$; with the proviso that a heteroatom of the foregoing R^8 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^{10} and R^{11} of -$CONR^{10}R^{11}$

may be taken together with the atoms to which they are attached to form a -(C2-C_9)heterocyclyl;

R^9 and R^{10} are each -(C_1-C_6)alkyl and may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl; and

R^{11} is hydrogen or -(C_1-C_6)alkyl.

The present invention also includes isotopically-labeled compounds, which are identical to those recited in Formula 1, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H, ^3H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labelled compounds of Formula 1 of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labelled reagent for a non-isotopically-labelled reagent.

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

The invention also relates to base addition salts of formula 1. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those

compounds of formula 1 that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

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

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula 1. Compounds of formula 1 having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula 1. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters that are covalently bonded to the above substituents of formula 1 through the carbonyl carbon prodrug sidechain.

This invention also encompasses compounds of formula 1 containing protective groups. One skilled in the art will also appreciate that compounds of the invention can also be prepared with certain protecting groups that are useful for purification or storage and can be removed before administration to a patient. The protection and deprotection of functional

groups is described in "Protective Groups in Organic Chemistry", edited by J.W.F. McOmie, Plenum Press (1973) and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of this invention include all stereoisomers (e.g., cis and trans isomers) and all optical isomers of compounds of the formula 1 (e.g., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

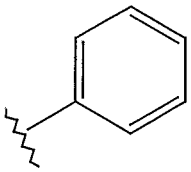
The compounds, salts and prodrugs of the present invention can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist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

The present invention also includes atropisomers of the present invention. Atropisomers refer to compounds of formula 1 that can be separated into rotationally restricted isomers.

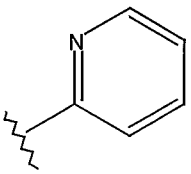
The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

A "suitable substituent" is intended to mean a chemically and pharmaceutically acceptable functional group i.e., a moiety that does not negate the biological activity of the inventive compounds. Such suitable substituents may be routinely selected by those skilled in the art. Illustrative examples of suitable substituents include, but are not limited to halo groups, perfluoroalkyl groups, perfluoroalkoxy groups, alkyl groups, alkenyl groups, alkynyl groups, hydroxy groups, oxo groups, mercapto groups, alkylthio groups, alkoxy groups, aryl or heteroaryl groups, aryloxy or heteroaryloxy groups, aralkyl or heteroaralkyl groups, aralkoxy or heteroaralkoxy groups, HO-(C=O)- groups, amino groups, alkyl- and dialkylamino groups, carbamoyl groups, alkylcarbonyl groups, alkoxycarbonyl groups, alkylaminocarbonyl groups dialkylamino carbonyl groups, arylcarbonyl groups, aryloxycarbonyl groups, alkylsulfonyl groups, arylsulfonyl groups and the like. Those skilled in the art will appreciate that many substituents can be substituted by additional substituents. Further examples of suitable substituents include those recited in the definition of compounds of Formula 1, including R^1 through R^{11}, as defined hereinabove.

The term "interrupted by" refers to compounds in which a ring carbon atom is replaced by an element selected from the group consisting of –(C=O), -SO^2, -S-, -O-, -N-, -NH-, and –NR^5. For example, if R^7 is –(C_6-C_{10})aryl, such as



the ring may be interrupted or replaced by a nitrogen heteroatom to form the following ring:



such that a ring carbon is replaced by the heteroatom nitrogen. Compounds of the invention can accommodate up to three such replacements or interruptions.

As used herein, the term "alkyl," as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched (such as methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl); optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl. The phrase "each of said alkyl" as used herein refers to any of the preceding alkyl moieties within a group such alkoxy, alkenyl or alkylamino. Preferred alkyls include (C_1-C_6)alkyl, more preferred are (C_1-C_4)alkyl, and most preferred are methyl and ethyl.

As used herein, the term "cycloalkyl" refers to a mono, bicyclic or tricyclic carbocyclic ring (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1 or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl.

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

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

As used herein, the term "alkynyl" is used herein to mean straight or branched hydrocarbon chain radicals having one triple bond including, but not limited to, ethynyl, propynyl, butynyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined

above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl.

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

As used herein, the term "aryl" means aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like; optionally substituted by 1 to 3 suitable substituents as defined above.

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

The term "heterocyclic" as used herein refers to a cyclic group containing 1-9 carbon atoms and 1 to 4 hetero atoms selected from N, O, $S(O)_n$ or NR. Examples of such rings include azetidinyl, tetrahydrofuranyl, imidazolidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, thiomorpholinyl, tetrahydrothiazinyl, tetrahydrothiadiazinyl, morpholinyl, oxetanyl, tetrahydrodiazinyl, oxazinyl, oxathiazinyl, indolinyl, isoindolinyl, quinuclidinyl, chromanyl, isochromanyl, benzoxazinyl, and the like. Examples of said monocyclic saturated or partially saturated ring systems are tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 1,3-oxazolidin-3-yl, isothiazolidine, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, thiomorpholin-yl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazin-yl, morpholin-yl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-oxazin-2-yl, 1,2,5-oxathiazin-4-yl and the like; optionally containing 1 or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as

defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl.

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

"Embodiment" as used herein refers to specific groupings of compounds or uses into discrete subgenera. Such subgenera may be cognizable according to one particular substituent such as a specific R^1 or R^3 group. Other subgenera are cognizable according to combinations of various substituents, such as all compounds wherein R^2 is hydrogen and R^1 is (C_1-C_6)alkyl.

Thus, the present invention provides a compound of formula 1, wherein R^1 is selected from hydrogen, hydroxy, and -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$.

The present invention further provides a compound of formula 1, wherein R^1 is -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of -(C_3-C_7)cycloalkyl and -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, and -O(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$. In a preferred embodiment, R^1 is -O(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$.

One embodiment of the invention is a compound of formula 1 wherein R^1 is -NR^5R^6, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from $-SR^7$, $-SOR^7$, $-SO_2R^7$, and $-SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and$-CONR^5R^8$. In a preferred embodiment, R^1 is $-SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and$-CONR^5R^8$.

The present invention also provides compounds of formula 1 wherein R^1 is $-CO_2R^5$, $-CONR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, or $-NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and$-CONR^5R^8$. In a preferred embodiment, R^1 is $-NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and$-CONR^5R^8$.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups.

Further provided is a compound of formula 1 wherein R^2 is $-(C_3-C_7)$cycloalkyl, or $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is $-CO_2R^5$ and $-CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$,

$-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups.

Also provided is a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; and R^2 is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups.

The invention further provides a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^8$; and R^2 is hydrogen.

The present invention further provides a compound of formula 1, wherein R^1 is $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; and R^2 is hydrogen.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of $-(C_3-C_7)$cycloalkyl and $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; and R^2 is hydrogen.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$cycloalkyl, and $-O(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; and R^2 is hydrogen.

One embodiment of the invention is a compound of formula 1 wherein R^1 is $-NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$,

-(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is hydrogen.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from -SR^7, -SOR^7, -SO_2R^7, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is hydrogen.

The present invention also provides compounds of formula 1 wherein R^1 is -CO_2R^5, -$CONR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is hydrogen.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and R^1 is hydrogen.

Further provided is a compound of formula 1 wherein R^2 is -(C_3-C_7)cycloalkyl, or -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and R^1 is hydrogen.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is -CO_2R^5 and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and R^1 is hydrogen.

The invention further provides a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and -$CONR^5R^8$; and R^2 is -(C_1-C_6)alkyl.

The present invention further provides a compound of formula 1, wherein R^1 is -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is -(C_1-C_6)alkyl.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of -(C_3-C_7)cycloalkyl and -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is -(C_1-C_6)alkyl.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, and -O(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is -(C_1-C_6)alkyl.

One embodiment of the invention is a compound of formula 1 wherein R^1 is -NR^5R^6, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is -(C_1-C_6)alkyl.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from -SR^7, -SOR^7, -SO_2R^7, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is -(C_1-C_6)alkyl.

The present invention also provides compounds of formula 1 wherein R^1 is -CO_2R^5, -$CONR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; and R^2 is -(C_1-C_6)alkyl.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and R^1 is -(C_1-C_6)alkyl.

Further provided is a compound of formula 1 wherein R^2 is -(C_3-C_7)cycloalkyl, or -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and R^1 is -(C_1-C_6)alkyl.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is -CO_2R^5 and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and R^1 is -(C_1-C_6)alkyl.

Also provided is a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and n is 1.

The invention further provides a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and -(C_1-C_6)alkyl, optionally substituted by one to three moieties

independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and -$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

The present invention further provides a compound of formula 1, wherein R^1 is -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of -(C_3-C_7)cycloalkyl and -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, and -O(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

One embodiment of the invention is a compound of formula 1 wherein R^1 is -NR^5R^6, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from -SR^7, -SOR^7, -SO_2R^7, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

The present invention also provides compounds of formula 1 wherein R^1 is -CO_2R^5, -$CONR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl,

-(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is -(C_1-C_6)alkyl; and n is 1.

Further provided is a compound of formula 1 wherein R^2 is -(C_3-C_7)cycloalkyl, or -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is -(C_1-C_6)alkyl; and n is 1.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is -CO_2R^5 and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is -(C_1-C_6)alkyl; and n is 1.

The invention further provides a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and -$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

The present invention further provides a compound of formula 1, wherein R^1 is -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of -(C_3-C_7)cycloalkyl and -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, and -O(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

One embodiment of the invention is a compound of formula 1 wherein R^1 is -NR^5R^6, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from -SR^7, -SOR^7, -SO_2R^7, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

The present invention also provides compounds of formula 1 wherein R^1 is -CO_2R^5, -$CONR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 1.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is -(C_1-C_6)alkyl; and n is 1.

Further provided is a compound of formula 1 wherein R^2 is -(C_3-C_7)cycloalkyl, or -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is -(C_1-C_6)alkyl; and n is 1.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is $-CO_2R^5$ and $-CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is $-(C_1-C_6)$alkyl; and n is 1.

Also provided is a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and n is 1.

The invention further provides a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^8$; R^2 is hydrogen; and n is 1.

The present invention further provides a compound of formula 1, wherein R^1 is $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 1.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of $-(C_3-C_7)$cycloalkyl and $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 1.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$cycloalkyl, and $-O(C_2-C_9)$heterocyclyl, optionally substituted by one

to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 1.

One embodiment of the invention is a compound of formula 1 wherein R^1 is -NR^5R^6, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 1.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from -SR^7, -SOR^7, -SO_2R^7, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 1.

The present invention also provides compounds of formula 1 wherein R^1 is -CO_2R^5, -$CONR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 1.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is hydrogen; and n is 1.

Further provided is a compound of formula 1 wherein R^2 is -(C_3-C_7)cycloalkyl, or -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is hydrogen; and n is 1.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is -CO_2R^5 and -$CONR^5R^6$ optionally substituted by one to three moieties independently

selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is hydrogen; and n is 1.

Also provided is a compound of formula 1 wherein R^1 is selected from hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and n is 2.

The invention further provides a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is $-(C_1-C_6)$alkyl; and n is 2.

The present invention further provides a compound of formula 1, wherein R^1 is $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is $-(C_1-C_6)$alkyl; and n is 2.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of $-(C_3-C_7)$cycloalkyl and $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is $-(C_1-C_6)$alkyl; and n is 2.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$cycloalkyl, and $-O(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen,

hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

One embodiment of the invention is a compound of formula 1 wherein R^1 is -NR^5R^6, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from -SR^7, -SOR^7, -SO_2R^7, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

The present invention also provides compounds of formula 1 wherein R^1 is -CO_2R^5, -$CONR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is -(C_1-C_6)alkyl; and n is 2.

Further provided is a compound of formula 1 wherein R^2 is -(C_3-C_7)cycloalkyl, or -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is -(C_1-C_6)alkyl; and n is 2.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is -CO_2R^5 and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl,

-(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is -(C_1-C_6)alkyl; and n is 2.

The invention further provides a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and -$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

The present invention further provides a compound of formula 1, wherein R^1 is -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of -(C_3-C_7)cycloalkyl and -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, and -O(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

One embodiment of the invention is a compound of formula 1 wherein R^1 is -NR^5R^6, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from -SR^7, -SOR^7, -SO_2R^7, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is -(C_1-C_6)alkyl; and n is 2.

The present invention also provides compounds of formula 1 wherein R^1 is $-CO_2R^5$, $-CONR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, or $-NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is $-(C_1-C_6)$alkyl; and n is 2.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is $-(C_1-C_6)$alkyl; and n is 2.

Further provided is a compound of formula 1 wherein R^2 is $-(C_3-C_7)$cycloalkyl, or $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is $-(C_1-C_6)$alkyl; and n is 2.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is $-CO_2R^5$ and $-CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is $-(C_1-C_6)$alkyl; and n is 2.

Also provided is a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$,

-(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and n is 2.

The invention further provides a compound of formula 1 wherein R^1 is selected from hydrogen, hydroxy, and -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and -$CONR^5R^8$; R^2 is hydrogen; and n is 2.

The present invention further provides a compound of formula 1, wherein R^1 is -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 2.

The present invention also provides a compound of formula 1 wherein R^1 is selected from the group consisting of -(C_3-C_7)cycloalkyl and -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 2.

The invention also contemplates compounds of formula 1 wherein R^1 is selected from -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, and -O(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 2.

One embodiment of the invention is a compound of formula 1 wherein R^1 is -NR^5R^6, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 2.

A further embodiment of the invention is a compound of formula 1 wherein R^1 is selected from -SR^7, -SOR^7, -SO_2R^7, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 2.

The present invention also provides compounds of formula 1 wherein R^1 is -CO_2R^5, -$CONR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three

moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen; and n is 2.

Also provided is a compound of formula 1 wherein R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is hydrogen; and n is 2.

Further provided is a compound of formula 1 wherein R^2 is -(C_3-C_7)cycloalkyl, or -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is hydrogen; and n is 2.

Another embodiment of the present invention is a compound of formula 1 wherein R^2 is -CO_2R^5 and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and -(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; R^1 is hydrogen; and n is 2.

The present invention also provides a compound of formula 1 in which R^1 and R^2 are taken together with the atom(s) to which they are attached to form a -(C_3-C_{10})cycloalkyl optionally substituted by one to three moieties selected from the group consisting of a hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O(C_1-C_6 alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R^5 groups.

The present invention further provides a compound of formula 1 in which R^1 and R^2 are taken together with the atom(s) to which they are attached to form a -(C_2-C_9)heterocyclyl optionally substituted by one to three moieties selected from the group consisting of a hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O(C_1-C_6 alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R^5 groups.

The present invention also provides a compound of formula 1 in which R^1 and R^2 are taken together with the atom(s) to which they are attached to form a -(C_3-C_{10})cycloalkyl optionally substituted by one to three moieties selected from the group consisting of a hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O(C_1-C_6 alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R^5 groups; and n is 1.

The present invention further provides a compound of formula 1 in which R^1 and R^2 are taken together with the atom(s) to which they are attached to form a -(C_2-C_9)heterocyclyl optionally substituted by one to three moieties selected from the group consisting of a hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O(C_1-C_6 alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R^5 groups; and n is 1.

The present invention also provides a compound of formula 1 wherein R^3 is hydrogen.

Preferably, R^3 is -(C_6-C_{10})aryl or -(C_1-C_9)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -$NHSO_2$(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl,

$-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, $-SO_2NR^5R^6$, and $-SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl$; wherein said $-(C_6-C_{10})$ aryl or $-(C_1-C_9)$ heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl.

Alternatively, the invention provides a compound of formula 1 wherein R^3 is $-(C_6-C_{10})aryl$, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)alkyl$, $-(C_3-C_{10})cycloalkyl$, $-NHSO_2(C_1-C_6)alkyl$, $-NHSO_2(C_3-C_6)cycloalkyl$, $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)alkyl$, $-O-SO_2(C_1-C_6)alkyl$, $-SO_2(C_1-C_6)alkyl$, $-SO_2(C_3-C_6)cycloalkyl$, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)alkyl$, $-SO_2NH(C_3-C_6)cycloalkyl$, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, and $-SO_2NR^5R^6$.

The invention also provides a compound of formula 1 wherein R^3 is $-(C_1-C_9)$heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)alkyl$, $-(C_3-C_{10})cycloalkyl$, $-NHSO_2(C_1-C_6)alkyl$, $-NHSO_2(C_3-C_6)cycloalkyl$, $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)alkyl$, $-O-SO_2(C_1-C_6)alkyl$, $-SO_2(C_1-C_6)alkyl$, $-SO_2(C_3-C_6)cycloalkyl$, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)alkyl$, $-SO_2NH(C_3-C_6)cycloalkyl$, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, and $-SO_2NR^5R^6$.

Further, the invention provides a compound in which R^3 is selected from $-(C_3-C_{10})cycloalkyl$, $-(C_2-C_9)$heterocyclyl, and $-(C_1-C_6)alkyl-(C_2-C_9)$ heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)alkyl$, $-(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)_2$, $-(C_3-C_{10})cycloalkyl$, $(C_6-C_{10})aryl$, (C_2-C_9)heterocyclyl, $-(C_1-C_9)$heteroaryl, $-NR^5R^6$, $-NSO_2(C_1-C_6)alkyl$, $-NHSO_2(C_3-C_6)cycloalkyl$, $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)alkyl$, $-O-SO_2(C_1-C_6)alkyl$, $-O-SO_2(C_1-C_6)alkyl$, $-(CO)(C_1-C_6)alkyl$, $-(CO)CF_3$, $-(CO)(C_3-C_{10})cycloalkyl$, $-(CO)(C_6-C_{10})aryl$, $-(CO)(C_2-C_9)$heterocyclyl, $-(CO)(C_1-C_9)$heteroaryl, $-(CO)O(C_1-C_6)alkyl$, $-(CO)O(C_3-C_{10})cycloalkyl$, $-(CO)O(C_6-C_{10})aryl$, $-(CO)O(C_2-C_9)$heterocyclyl, $-(CO)O(C_1-C_9)$heteroaryl, $-(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl$, $-SO_2(C_1-C_6)alkyl$, $-SO_2(C_3-C_6)cycloalkyl$, SO_2CF_3, SO_2NH_2, $SO_2NH(C_1-C_6)alkyl$, $-SO_2NH(C_3-C_6)cycloalkyl$, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, $-SO_2NR^5R^6$, and $-SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl$; wherein said $-(C_3-C_{10})cycloalkyl$, $-(C_2-C_9)$heterocyclyl, and $-(C_1-C_6)alkyl-(C_2-C_9)$ heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and R^5 and R^6 of

said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl.

Also provided is a compound in which R^3 is -(C_3-C_{10})cycloalkyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_3-C_{10})cycloalkyl, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, and -$SO_2NR^5R^6$.

The invention further provides a compound in which R^3 is -(C_2-C_9)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_3-C_{10})cycloalkyl, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, and -$SO_2NR^5R^6$.

The invention further provides a compound in which R^3 is -(C_1-C_6)alkyl-(C_2-C_9) heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_3-C_{10})cycloalkyl, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, and -$SO_2NR^5R^6$.

Moreover, the invention provides a compound of formula 1 wherein R^3 is -(C_1-C_6)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_1-C_6)alkyl is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and

-NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl.

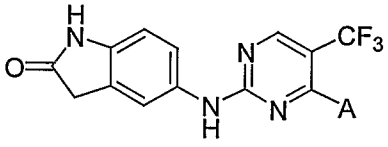
Further provided is a compound of formula 1 wherein R^3 is -(C_1-C_6)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_3-C_{10})cycloalkyl, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, -SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, and -$SO_2NR^5R^6$.

In a preferred embodiment, R^4 is a substituent selected from the group consisting of hydrogen, (C_1-C_6)alkyl, and –(C_3-C_7)cycloalkyl; wherein said -(C_1-C_6)alkyl and -(C_3-C_7)cycloalkyl is optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -(C_1-C_6)alkyl, -CN, -NR^5_2, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, and -$CONR^5R^8$; with the proviso that a heteroatom of the foregoing R^4 substituents may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^5 and R^8 of said -$CONR^5R^8$ group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl.

In a further preferred embodiment, R^4 is hydrogen.

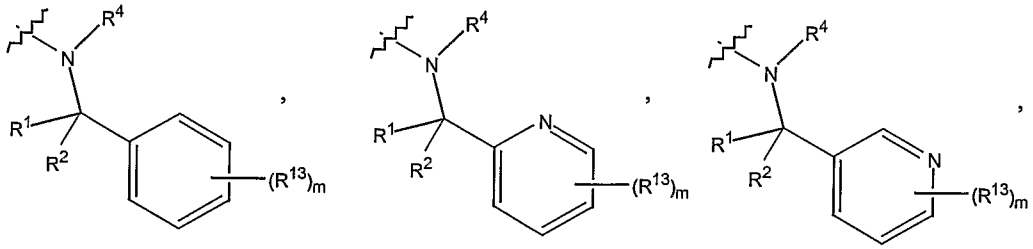
Further, the invention provides a compound of formula 1 wherein R^5 and R^6 are each substituents independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl, optionally substituted as described above.

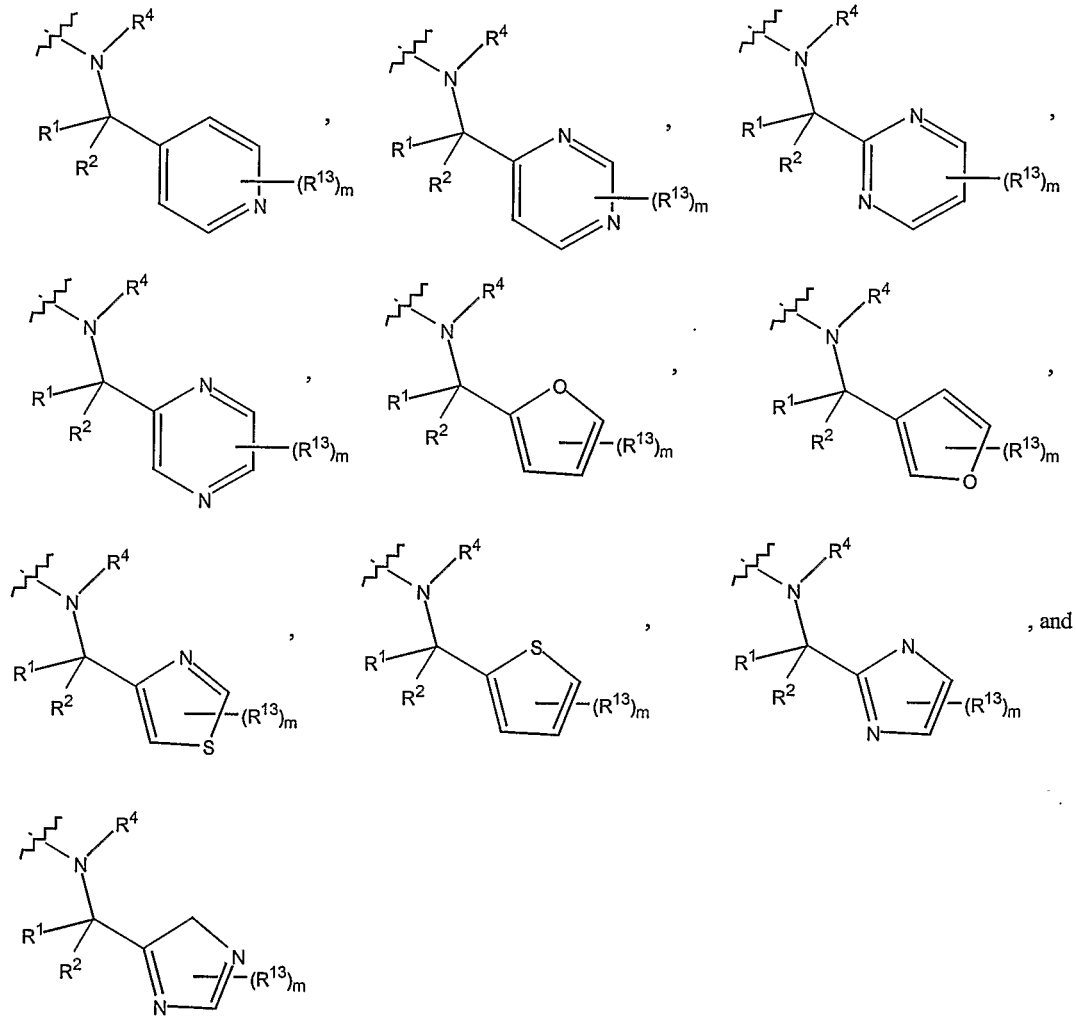
In a preferred embodiment, the present invention provides a compound of the formula **2**



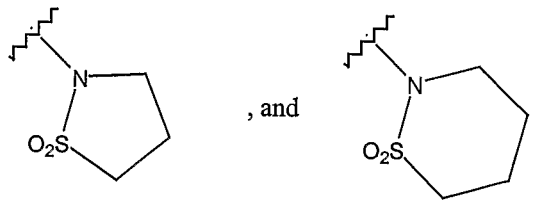
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wherein A is selected from the group consisting of:

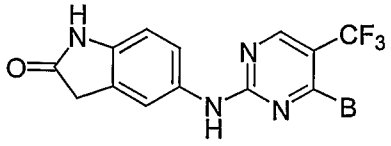




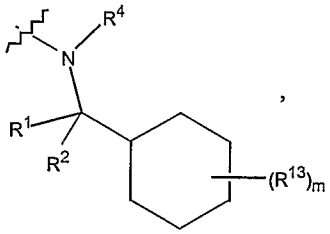
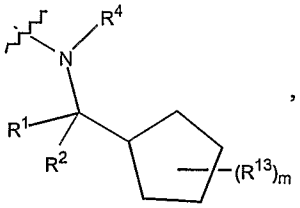
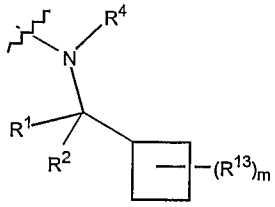
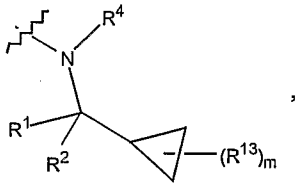
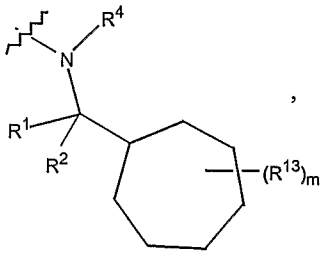
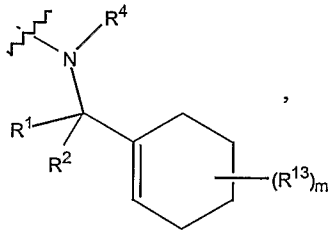
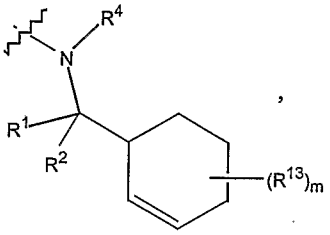
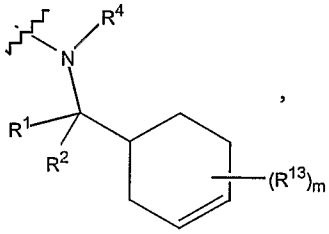
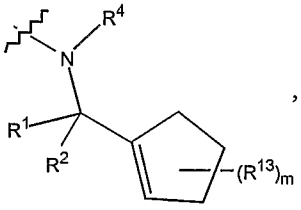
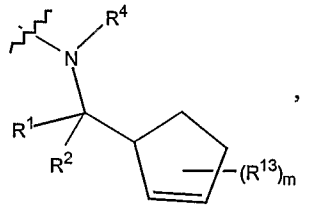
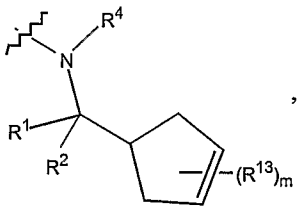
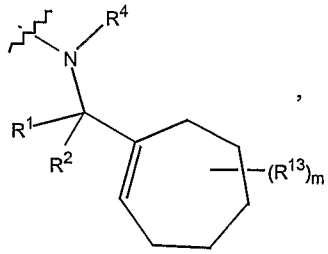
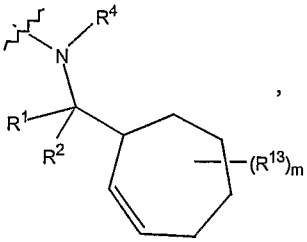
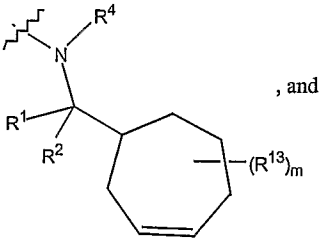
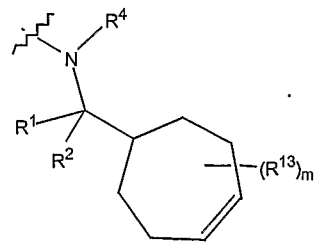
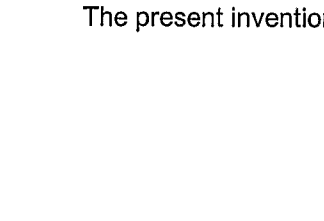
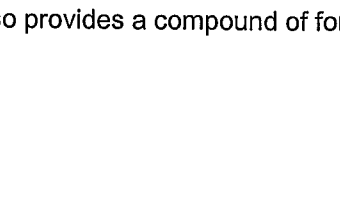
wherein m is an integer from 0-3 and R^{13} is a substituent selected from the group consisting of hydrogen, halogen, hydroxy, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_6-C_{10})-aryl, (C_1-C_9)heteroaryl, (C_2-C_9)-heterocyclyl, O-(C_1-C_6)-alkyl, O-(C_3-C_7)-cycloalkyl, SO_2-(C_1-C_6)alkyl, $SO_2(C_3-C_7)$-cycloalkyl, $NHSO_2(C_1-C_6)$alkyl, $N((C_1-C_6)alkyl)(SO_2(C_1-C_6-alkyl))$, $N((C_3-C_7)cycloalkyl)(SO_2(C_1-C_6-alkyl))$, $N(C_1-C_6-alkyl)(SO_2(C_3-C_7)cycloalkyl)$, $N((C_3-C_7)cycloalkyl)(SO_2(C_3-C_7)cycloalkyl)$, $OSO_2(C_1-C_6)$alkyl, SO_2CF_3, SO_2NH_2, $SO_2NH(C_1-C_6)$alkyl, $SO_2NH(C_3-C_7)$cycloalkyl, $SO_2NR^5R^6$, $SO_2N((C_1-C_6)alkyl)_2$, CF_3, CO-(C_1-C_6)alkyl, CO-(C_3-C_7)cycloalkyl, $COCF_3$, $CO_2(C_1-C_6)$alkyl,



Also provided is a compound of the formula 3

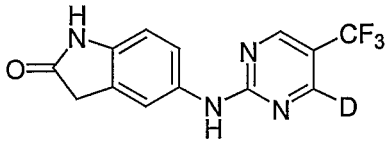


wherein B is selected from the group consisting of:

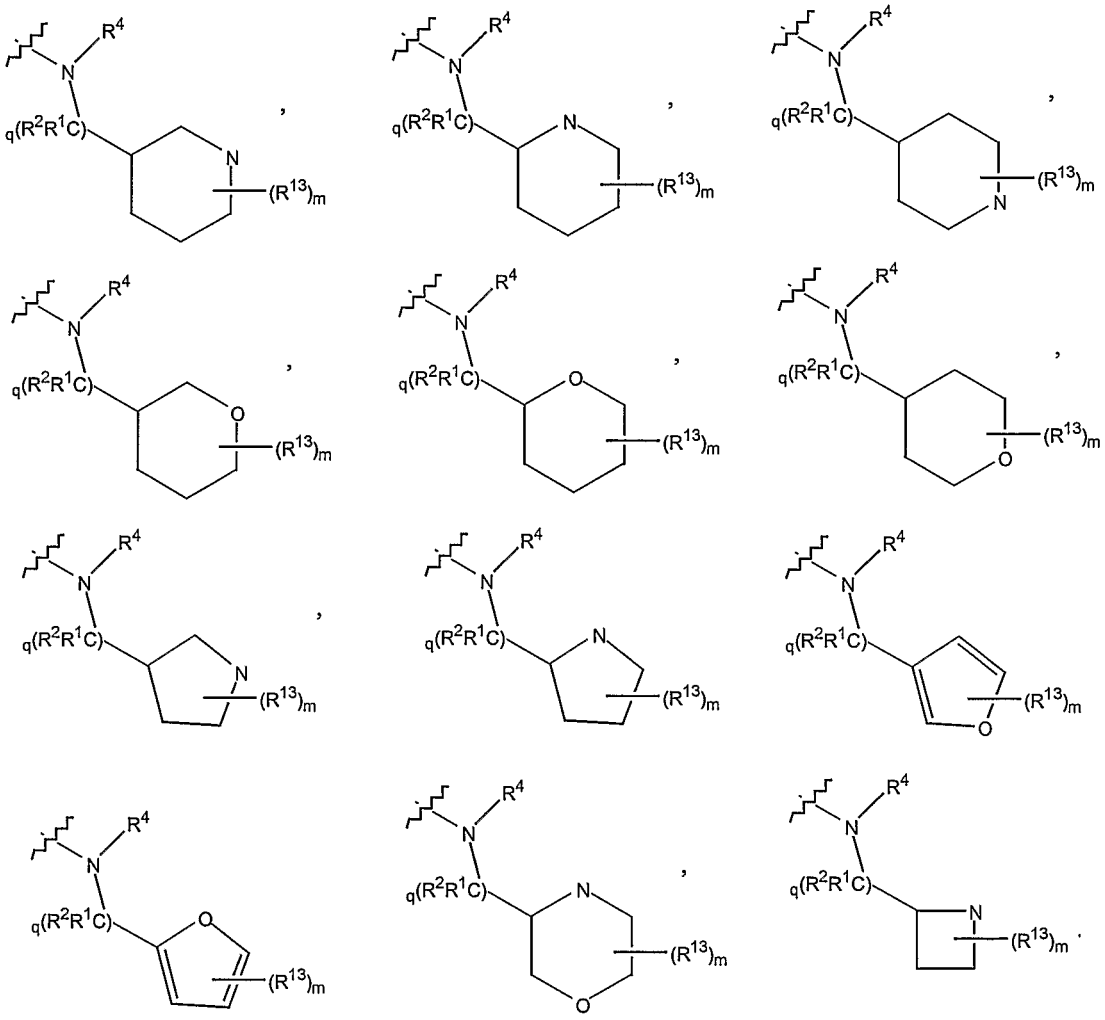

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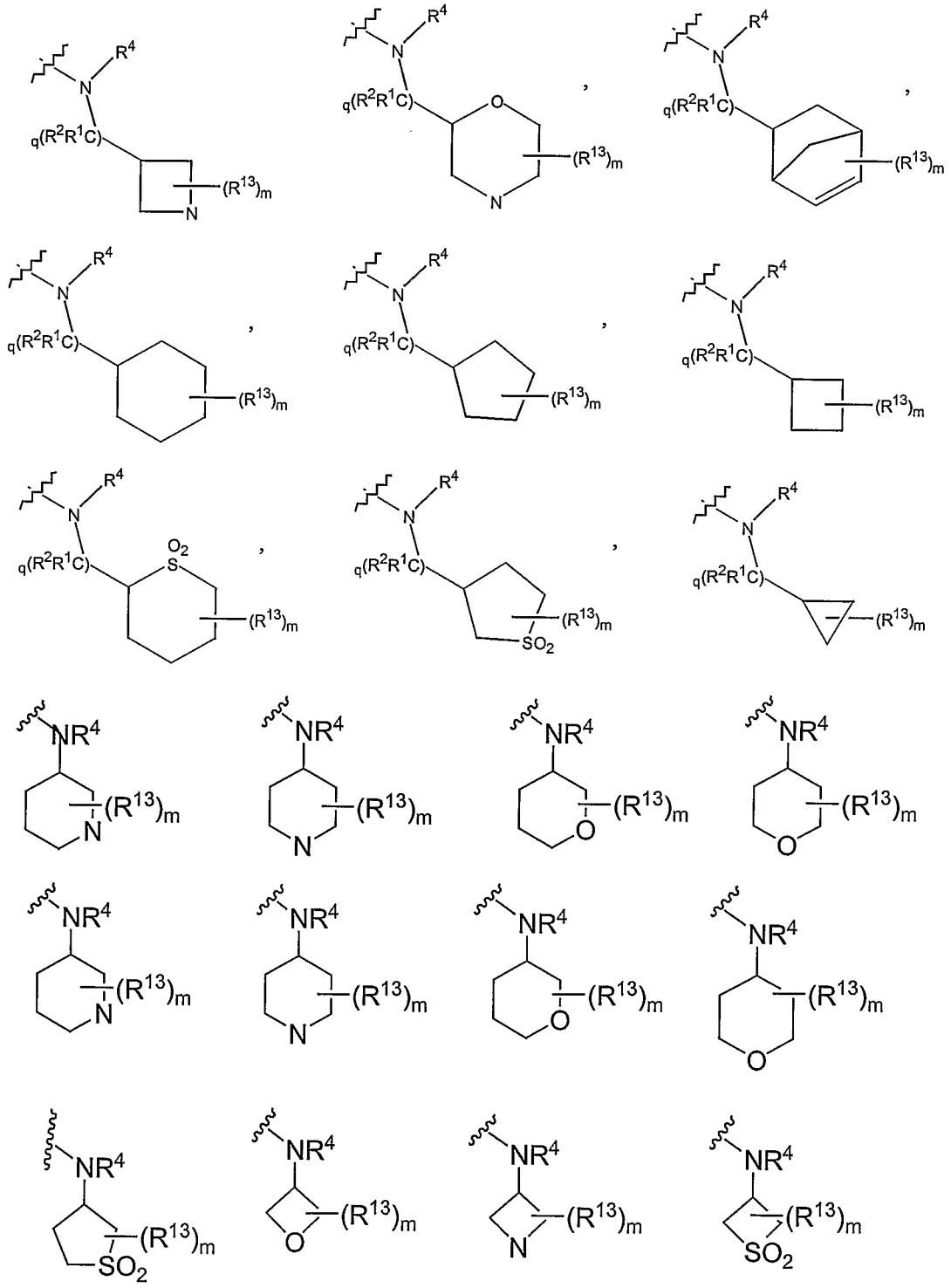
.

The present invention also provides a compound of formula 4



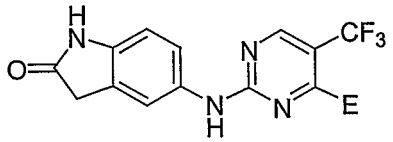
wherein D is selected from the group consisting of:



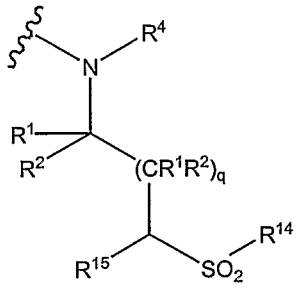


wherein q is an integer from 1-2.

Moreover, the present invention provides a compound of formula **5**:



wherein E is selected from the group consisting of:



wherein R^{14} is selected from the group consisting of (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, and (C_2-C_9)-heterocyclyl, and R^{15} is selected from the group consisting of hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, and (C_2-C_9)-heterocyclyl.

Specific embodiments of the present invention are compounds selected from

N-(1-Methyl-1-phenyl-ethyl)-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

5-{4-[3-(Trifluoro-methanesulfonyl)-benzylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

3-Oxo-3-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propionitrile;

5-{4-[3-(1,1-Dioxo-1N^6-isothiazolidin-2-yl)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-{2-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

N-{4-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-butyl}-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

Methanesulfonic acid 3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl ester;

N-{3-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(5-Oxo-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-(4-Methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(4-Trifluoroacetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-azetidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(4-methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

{2,2-Dimethyl-3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-carbamic acid tert-butyl ester;

5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Tetrahydro-pyran-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Ethyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Tetrahydro-furan-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Tetrahydro-furan-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Methoxy-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(*endo*-Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzyl)-phosphonic acid dimethyl ester;

5-[4-(3-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(2-Hydroxy-cyclohexylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(4-Ethanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-{[4-(Propane-2-sulfonyl)-morpholin-2-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-{4-[(4-Acetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Propionyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-{[4-(2,2-Dimethyl-propionyl)-morpholin-2-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-morpholine-4-carboxylic acid methyl ester;

5-{4-[(4-Methoxyacetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Ethanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-morpholin-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-morpholin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Pyrimidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Pyrazin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Isobutyryl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3,3-Dimethyl-2-oxo-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1,2-Dimethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(2-Methoxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[2-(1,1-Dioxo-1D^6-isothiazolidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methylamino-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[3-(1,1-Dioxo-1,l,6-isothiazolidin-2-yl)-benzylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(1R-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-(4-Isopropylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-(4R-sec-Butylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-(4S-sec-Butylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[4-(2-Methylamino-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1S-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(2-Methanesulfonylmethyl-thiazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-Propylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[4-(2-Hydroxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Pyridin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(1,3-Dimethyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Isopropyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-[4-(1S-Hydroxymethyl-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Cyclohexyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-[4-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(3-Methyl-thiophen-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Hydroxy-1S-phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(2-Hydroxy-1S-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1R-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1-Pyrimidin-4-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1,1-Dioxo-tetrahydro-1-thiophen-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1H-Imidazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Piperidin-2-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(Isobutyl-methyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Ethyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Isopropyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2R-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2S-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methylsulfanyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1S-Hydroxymethyl-3-methylsulfanyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(2-Hydroxy-1R-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1R-Hydroxymethyl-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Ethyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(1S-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(3,5-Dinitro-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Isopropyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-[4-(2-Hydroxy-1-phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1R-Hydroxymethyl-3-methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1S-Hydroxymethyl-3-methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(Methyl-pyridin-2-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(3-Methanesulfonyl-benzyl)-methyl-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(Methyl-pyridin-3-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-methyl-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(Methyl-pyridin-4-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-(4-Cyclopentylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[4-(2,6-Dimethoxy-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one and

5-[4-(2-Imidazol-1-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one.

Certain preferred embodiments of the invention are compounds selected from:

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Isopropyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

N-Cyclohexyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Isopropyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-Cyclopentylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

Ethanesulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide;

2,2,2-Trifluoro-N-methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-(4-Cyclobutylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-{4-[2-Hydroxy-2-(1-methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-Oxo-3-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propionitrile;

5-{4-[(1-Methanesulfonyl-piperidin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Oxo-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-{2,2-Dimethyl-3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[(1-Hydroxy-cyclopentylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Hydroxy-tetrahydro-pyran-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(2-Hydroxy-cyclohexylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propionic acid ethyl ester;

5-{4-[(1-Ethyl-5-oxo-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

2,N-Dimethyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-butyramide;

2-Methoxy-N-methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide;

5-{4-[2-(1-Acetyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Methyl-N-(4-methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzyl)-phosphonic acid dimethyl ester;

5-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Trifluoromethyl-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(3-Ethanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Pyrimidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Pyrazin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(Pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(2-Methanesulfonylmethyl-thiazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(3-Methyl-thiophen-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1H-Imidazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Imidazol-1-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-(5-Methyl-2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Isochroman-1-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(Pyridin-3-yloxy)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(6-Methyl-pyridin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(4-Methyl-1H-imidazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1H-Benzoimidazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Phenyl-4H-[1,2,4]triazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(3-Methyl-imidazo[2,1-b]thiazol-6-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-methyl-6-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-(2-Methyl-6-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-(3-Methanesulfonylamino-5-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide; and

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-pyridin-2-yl)-methanesulfonamide.

Preferred embodiment of the present invention are selected from

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

Ethanesulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide;

5-{4-[(Isochroman-1-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(Pyridin-3-yloxy)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-(2-methyl-6-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(2-Hydroxy-indan-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Hydroxy-cyclopentylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-Hydroxy-2-(1-methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one; and

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-pyridin-2-yl)-methanesulfonamide.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula **1**, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth. In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular

melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In one embodiment the method comprises comprising administering to a mammal an amount of a compound of formula 1 that is effective in treating said cancer solid tumor. In one preferred embodiment the solid tumor is breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder cancer.

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

This invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of formula **1**, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

This invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the formula **1**, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier. In one embodiment of said composition, said abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of

the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said pharmaceutical composition, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

The invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, which comprises an amount of a compound of formula **1**, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with a pharmaceutically acceptable carrier and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

This invention also relates to a method for the treatment of a disorder associated with angiogenesis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula **1**, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating said disorder. Such disorders include cancerous tumors such as melanoma; ocular disorders such as age-related macular degeneration, presumed ocular histoplasmosis syndrome, and retinal neovascularization from proliferative diabetic retinopathy; rheumatoid arthritis; bone loss disorders such as osteoporosis, particularly, post-menopausal osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, hypercalcemia from tumors metastatic to bone, and osteoporosis induced by glucocorticoid treatment; coronary restenosis; and certain microbial infections including those associated with microbial pathogens selected from adenovirus, hantaviruses, *Borrelia burgdorferi, Yersinia spp.*, *Bordetella pertussis*, and group A *Streptococcus.*

This invention also relates to a method of (and to a pharmaceutical composition for) treating abnormal cell growth in a mammal which comprise an amount of a compound of formula 1, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of formula 1 in the methods and pharmaceutical

compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are herein incorporated by reference in their entirety. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The compounds of formula **1**, and the pharmaceutically acceptable salts, solvates and prodrugs thereof, can also be used in combination with signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN™ (Genentech, Inc. of South San Francisco, California, USA).

EGFR inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998). EGFR-inhibiting agents include, but are not limited to, CI-1033 (Pfizer Inc.), the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, New Jersey, USA), and OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Massachusettes).

VEGF inhibitors, for example CP-547,632 and AG-13736 (Pfizer, Inc.), SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, California, USA), can also be combined with a compound of formula 1. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999),

United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are herein incorporated by reference in their entirety. Other examples of some specific VEGF inhibitors are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California).

ErbB2 receptor inhibitors, such as CP-724,714 (Pfizer, Inc.), GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), may be administered in combination with a compound of formula 1. Such erbB2 inhibitors include those described in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), each of which is herein incorporated by reference in its entirety. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are herein incorporated by reference in their entirety.

Other antiproliferative agents that may be used with the compounds of the present invention include inhibitors of HDI (CI-994, Pfizer Inc.), MEK (CI-1040, Pfizer Inc.), the enzyme farnesyl protein transferase and the receptor tyrosine kinase PDGFr, including the compounds disclosed and claimed in the following United States patent applications: 09/221946 (filed December 28, 1998); 09/454058 (filed December 2, 1999); 09/501163 (filed February 9, 2000); 09/539930 (filed March 31, 2000); 09/202796 (filed May 22, 1997); 09/384339 (filed August 26, 1999); and 09/383755 (filed August 26, 1999); and the compounds disclosed and claimed in the following United States provisional patent applications: 60/168207 (filed November 30, 1999); 60/170119 (filed December 10, 1999); 60/177718 (filed January 21, 2000); 60/168217 (filed November 30, 1999), and 60/200834 (filed May 1, 2000). The compounds of the invention may also be used in combination with inhibitors of topoisomerase I, e.g., irinotecan (Camptosar®) and edotecarin. Each of the

foregoing patent applications and provisional patent applications is herein incorporated by reference in their entirety.

A compound of formula **1** may also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocite antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, *supra*. Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) which is herein incorporated by reference in its entirety.

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

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

In one preferred embodiment of the present invention cancer is selected from lung cancer, bone cancer, pancreatic cancer, gastric, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, gynecological, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus,

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

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

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

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

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

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

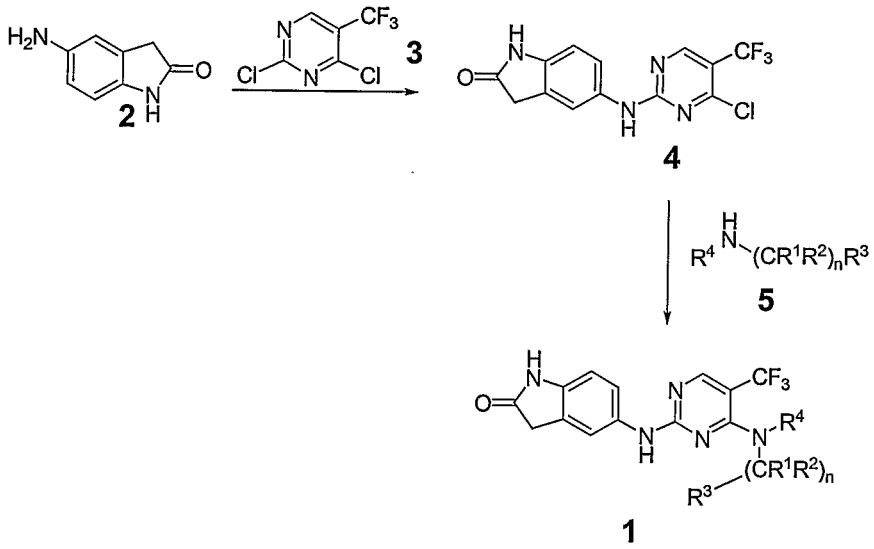
For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active

ingredient) may be in the range from 1 mg to 1 gram, preferably 1 mg to 250 mg, more preferably 10 mg to 100 mg.

The present invention also encompasses sustained release compositions.

Detailed Description of the Invention

The compounds of formula **1** can be prepared using the synthetic route outlined in Scheme 1. The substituents in Scheme 1 have the same meaning as the substituents defined for formula **1**.



Scheme 1

Compounds of formula **1** can be prepared starting from the 5-amino-oxindole (**2**) and pyrimidine (**3**). Combining **3** with an equimolar amount of a Lewis Acid at temperatures ranging from –15 to 45°C for a time period of 10-60 minutes in an inert solvent (or solvent mixture) followed by addition of **2** and a suitable base provides after the period of 1-24 h the intermediate 4-chloropyrimidine (**4**) in high yields. Examples of inert solvents include but are not limited to THF, 1,4-dioxane, n-BuOH, i-PrOH, dichloromethane and 1,2-dichloroethane. Examples of suitable bases employed may include but are not limited to (i) non-nucleophilic organic bases for example triethylamine or diisopropylethylamine (ii) inorganic bases such as potassium carbonate or cesium carbonate or (iii) resin bound bases such as MP-carbonate.

Examples of Lewis Acids include but are not limited to halide salts of magnesium, copper, zinc, tin or titanium. In the next reaction, intermediate **4** is reacted with an amine of the formula **5** either neat or in the presence of an inert solvent (or solvent mixture) at temperatures ranging from 0 to 150°C to provide the compounds of formula **1**. Optionally this reaction can be run in the presence of a suitable base. Examples of suitable solvents for this reaction include but are not limited to THF, 1,4-dioxane, DMF, N-methyl-pyrrolidinone, EtOH, n-BuOH, i-PrOH,

dichloromethane, 1,2-dichloroethane, DMSO or acetonitrile. Suitable bases are as outlined above.

Compounds of the present invention may be synthetically transformed into other compounds of the invention by techniques known to those skilled in the art. Simply for illustrative purposes and without limitation, such methods include:

a) removal of a protecting group by methods outlined in T. W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley and Sons, New York, 1991; e.g., emoval of a BOC protecting group with an acid source such as HCl or trifluoroacetic acid.

b) displacement of a leaving group (halide, mesylate, tosylate, etc) with functional groups such as but not limited to a primary or secondary amine, thiol or alcohol to form a secondary or tertiary amine, thioether or ether, respectively.

c) treatment of phenyl (or substituted phenyl) carbamates with primary of secondary amines to form the corresponding ureas as in Thavonekham, B et. al. Synthesis (1997), 10, p1189;

d) reduction of propargyl or homopropargyl alcohols or N-BOC protected primary amines to the corresponding E-allylic or E-homoallylic derivatives by treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) as in Denmark, S. E.; Jones, T. K. J. Org. Chem. (1982) 47, 4595-4597 or van Benthem, R. A. T. M.; Michels, J. J.; Speckamp, W. N. Synlett (1994), 368-370;

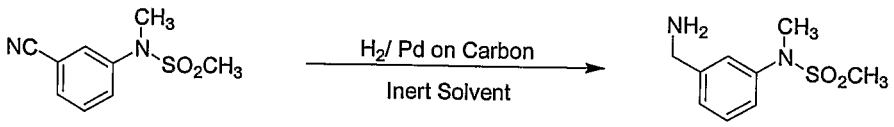
e) reduction of alkynes to the corresponding Z-alkene derivatives by treatment hydrogen gas and a Pd catalyst as in Tomassy, B. et. al. Synth. Commun. (1998), 28, p1201

f) treatment of primary and secondary amines with an isocyanate, acid chloride (or other activated carboxylic acid derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding urea, amide, carbamate or sulfonamide;

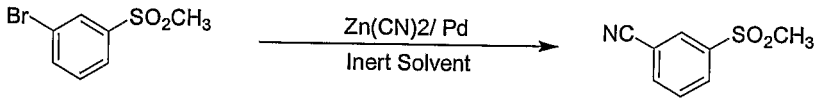
g) reductive amination of a primary or secondary amine using an aldehyde or ketone and an appropriate reducing reagent.

h) treatment of alcohols with an isocyanate, acid chloride (or other activated carboxylic acid derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding carbamate, ester, carbonate or sulfonic acid ester.

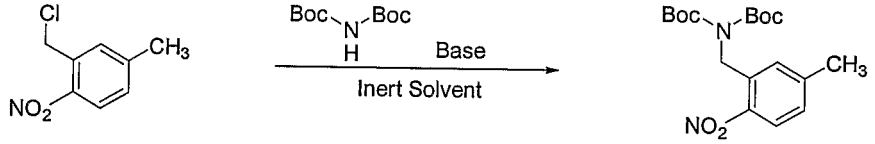
Amines of the formula **5** may be purchased and used directly or alternatively be prepared by one skilled in the art using ordinary chemical transformations. For example; arylalkylamines or heteroarylalkylamines may be prepared from the corresponding nitrile by catalytic hydrogenation using catalysts such as Pd/C or Raney Nickel or by lithium aluminum hydride reduction, (see Rylander, Catalytic Hydrogenation in Organic Synthesis, Academic Press, 1979).



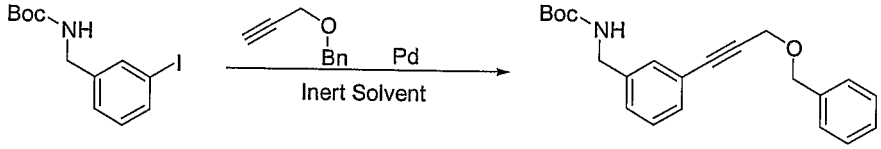
The nitrile starting materials can be either purchased or prepared from the corresponding aryl/heteroaryl bromide, iodide or triflate and Zn(CN)2 using Pd coupling conditions found in Tschaen, D. M., et. al Synthetic Communications (1994), 24, 6, pp 887-890.



Alternatively, benzylamines or heteroarylmethylamines can be prepared by reacting the appropriate arylalkyl or heteroarylalkyl halide and the potassium salt of $(BOC)_2NH$ (reference) and subsequent removal of the BOC groups with acid.

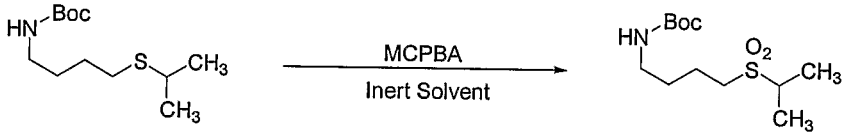


Amines, protected forms of amines, precursors to amines and precursors to the protected forms of amines of formula 5 can be prepared by combining the appropriate alkyne, or alkenyl stannane, alkenyl borane, alkenyl boronic acid, boronic ester with the appropriate aryl or heteroaryl bromide, iodide or triflate using Pd coupling conditions as found in Tsuji, J.; Palladium Reagents and Catalysis, John Wiley and Sons 1999 and references cited therein.

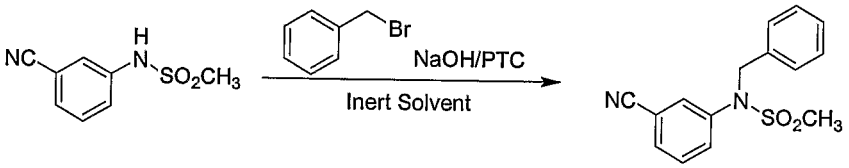


Appropriately protected amines of formula **5** may be converted to different amines of formula **5** according to methods familiar to those skilled in the art for exampleas but limited to:

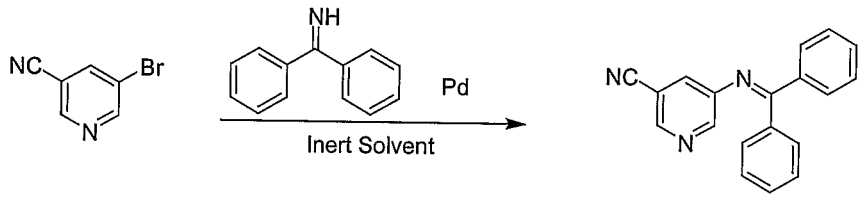
(a) oxidation of a thioether to a sulfoxide or sulfone.



(b) N-alkylation of a sulfanilide can be achieved under phase transfer using conditions described by Brehme, R. "Synthesis", (1976), pp113-114.



As understood by those skilled in the art, the chemical transformation to convert an aryl halide or triflate or heteroaryl halide or triflate to an aromatic or heteroaromatic amine may be carried out using conditions currently outlined in the literature, see Hartwig, J. F.: "Angew. Chem. Int. Ed." (1998), 37, pp. 2046-2067, Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S.L.; "Acc. Chem. Res.", (1998), 31, pp 805-818, Wolfe, J. P.; Buchwald, S.L.; "J. Org. Chem.", (2000), 65, pp 1144-1157, Muci, A. R.; Buchwald, S. L.; "Topics in Current Chemistry" (2002), pp131-209 and references cited therein. Further, as understood by those skilled in the art, these same aryl or heteroaryl aminatiion chemical transformations may alternatively be carried out on nitrile (or primary amide) precursors which provide amines of the formula **5** after nitrile (or amide) reduction. Protected amines of formula **5** may be further converted to different amines of formula **5** according to methods familiar to those skilled in the art.



The *in vitro* activity of the compounds of formula **1** may be determined by the following procedure. More particularly, the following assay provides a method to determine whether compounds of the formula **1** inhibit the tyrosine kinase activity of the catalytic construct FAK(410-689). The assay is an ELISA-based format, measuring the inhibition of poly-glu-tyr phosphorylation by FAK(410-689).

The assay protocol has three parts:

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

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

III. FAKcd Kinase ELISA

Materials:

-Ni-NTA agarose (Qiagen)

-XK-16 column (Amersham-Pharmacia)

-300 mM Imidizole

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

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

-FAKcd: Purified and activated in house

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

-BSA: Sigma #A3294

-Tween-20: Sigma #P1379

-DMSO: Sigma #D-5879

-D-PBS: Gibco #14190-037.

Reagents for Purification:

-Buffer A: 50mM HEPES pH 7.0,
500mM NaCl,
0.1mM TCEP
CompleteTM protease inhibitor cocktail tablets (Roche)
-Buffer B: 25mM HEPES pH 7.0,
400mM NaCl
0.1mM TCEP.
-Buffer C: 10mM HEPES pH 7.5,
200mM Ammonium Sulfate
0.1mM TCEP.

Reagents for Activation

-FAK(410-689): 3 tubes of frozen aliquots at 150ul/tube for a total of 450ul at 1.48 mg/ml (660ug)
-His-Src(249-524): ~0.74 mg/ml stock in 10mM HEPES, 200mM (NH4)2SO4
-Src reaction buffer (Upstate Biotech):
100 mM Tris-HCl pH7.2,
125mM MgCl2,
25 mM MnCl2,
2mM EDTA,
250 uM Na3VO4,
2 mM DTT
-Mn2+/ATP cocktail (Upstate Biotech)
75mM MnCl2
500 uM ATP
20mM MOPS pH 7.2
1mM Na3VO4
25mM □-glycerol phosphate
5mM EGTA
1mM DTT
-ATP: 150mM stock
-$MgCl_2$: 1 M Stock
-DTT: 1M stock

Reagents for FAKcd Kinase ELISA

-Phosphorylation Buffer:

50mM HEPES, pH 7.5,
125mM NaCl,
48mM MgCl2

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

-Blocking Buffer:
Tris Buffer Saline,
3% BSA,
0.05% Tween-20, filtered.

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

-ATP: 0.1M ATP in H2O or HEPES, pH7.
Note: ATP Assay Buffer:
Make up as 75 uM ATP in PBS, so that 80 ul in
120 ul reaction volume=50uM final ATP concentration.

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

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

13. Concentrate the flow-through down to 1.7 ml and load directly onto a Superdex 200 HiLoad 16/60 prep grade column equilibrated with Buffer C. The desired protein elutes between 85 - 95 ml.

14. Aliquot the FAKcd protein and store frozen at –80°C

II. FAK activation

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

30ul of 0.037 mg/ml (1uM) His-Src(249-524)

30ul of 7.5 mM ATP

12ul of 20 mM MgCl2

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

4ul of 6.7mM DTT

60ul Src Reaction Buffer (UpState Biotech.)

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

At time t_0, almost all of the FAK(410-689) is singly phosphorylated. The second phosphorylation is slow. At t_{120} (t = 120 minutes), add 10ul of 150 mM ATP.

T_0 = (Start) 90% singly phosphorylated FAK(410-689) (1 PO4)

T_{43} = (43 min) 65% singly phosphorylated (1 PO4), 35% doubly phosphorylated (2 PO4)

T_{90} = (90 min) 45% 1 PO4, 55% 2 PO4

T_{150} = 15% 1 PO4, 85% 2 PO4

T_{210} = <10% 1 PO4, >90% 2 PO4 desalted sample

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

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

III. FAKcd Kinase ELISA

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

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

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

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

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

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

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

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

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

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

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

12. Dilute phospho-tyrosine HRP-conjugated (pY20HRP) antibody to 0.250ug/ml (1:1000 of Stock) in blocking buffer. Dispense 100 ul per well, and incubate with shaking for 30min. at R.T.

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

14. Add 100 ul per well of room temperature TMB solution to initiate color development. Color development is terminated after approximately 15-30 sec. by the addition of 100ul of 0.09M H2SO4 per well.

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

16. Inhibition of tyrosine kinase activity would result in a reduced absorbance signal. The signal is typically 0.8-1.0 OD units. The values are reported as IC_{50s}, uM concentration.

FAK Inducible cell-based ELISA: Final Protocol

Materials:

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

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

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

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

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

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

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

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

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

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

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

Mifepristone InVitrogen # H110-01 @ 125 USD

CompleteTM EDTA-free Protease Inhibitor pellet Boehringer Mannheim #1873580

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

Procedure:

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

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

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

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

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

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

Additional FAK cell assays are hereby incorporated by reference from Pfizer Attorney Docket No. PC11699 entitled "INDUCIBLE FOCAL ADHESION KINASE CELL ASSAY".

In a preferred embodiment, the compounds of the present invention have an in vivo activity as determined by a kinase assay, e.g., such as that described herein, of less than 100 nM. Preferably, the compounds have an IC_{50} of less than 25 nM in the kinase assay, and more preferably less than 10 nM. In a further preferred embodiment, the compounds exhibit an IC_{50} in a FAK cell based assay, e.g., such as that described herein, of less than 1 □M, more preferably less than 100 nM, and most preferably less than 25 nM.

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the

site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

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

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

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

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

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

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

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

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

In the following examples and preparations, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, and "Bu" means butyl.

Examples

General Methods:

Preparation of 5-nitro-oxindole:

To a solution of oxindole (26 g) in 100 mL of concentrated sulfuric acid at –15oC was added fuming nitric acid (8.4 mL) dropwise. Careful attention was paid to maintain the reaction temperature at –15oC. After the addition was complete, the reaction was stirred for 30 minutes and then poured into ice water. A yellow precipitate was formed which was isolated by filtration to provide 34 grams (98%) of 5-nitro oxindole.

Preparation of 5-amino-oxindole (2):

To a solution of 5-nitro-oxindole (25 g) in 120 mL of dimethylacetamide in a Parr bottle was added 10% Pd/C (0.5 g). The mixture was hydrogenated (40 psi H2) for 16 h. The catalyst was removed by filtration and the filtrate was diluted with ether (2L) to provide 5-amino-oxindole (10.5 g; 50%).

Preparation of 2,4-dichloro-5-trifluoromethylpyrimidine (3):

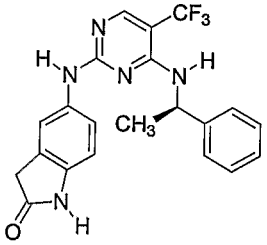
5-Trifluoromethyluracil (250g, 1.39 mol) and phosphorous oxychloride (655 mL, 6.94 mol, 5 equiv) were charged to a 3L 4-neck flask equipped with overhead stirrer, a reflux condenser, an addition funnel and an internal theromocouple. The contents were maintained under a nitrogen atmosphere as concentrated phosphoric acid (85 wt%, 9.5 mL, 0.1 equiv) was added in one portion to the slurry, resulting in a moderate exotherm. Diisopropylethylamine (245 mL, 1.39 mol, 1 equiv) was then added dropwise over 15 min at such a rate that the internal temperature of the reaction reached 85–90 °C by the end of the addition. By the end of the amine addition the reaction mixture was a homogenous light-orange solution. Heating was initiated and the orange solution was maintained at 100 °C for 20h, at which time HPLC analysis of the reaction mixture indicated that the starting material was consumed. External heating was removed and the contents of the flask were cooled to 40 °C and then added dropwise to a cooled mixture of 3N HCl (5 L, 10 equiv) and diethyl ether (2L) keeping the temperature of the quench pot between 10 and 15 °C. The layers were separated, and the aqueous layer was extracted once with ether (1L). The combined organic layers were combined, washed with water until the washes were neutral (5 × 1.5L washes), dried with $MgSO_4$ and concentrated to provide 288g (95% yield) of a light yellow-orange oil of 96% purity (HPLC). This material can be further purified by distillation (bp 109 °C at 79 mmHg).

Preparation of 5-(4-Chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one (4):

To a solution of 5-trifluoromethyl-2,4-dichloropyrimidine (214.8 g; 0.921 mol) in 1:1 DCE/tBuOH (1.240 L) was added Zinc chloride 1M solution in ether (1 eq; 0.921 L). After 0.5 hour, 5-amino-oxindole (124 g; 0.837 mol) was added followed by triethylamine (129.4 ml; 0.921 mol) keeping temperature at 25° C. The reaction was allowed to stir at room temperature overnight, then was concentrated and the product triturated from methanol as a yellow solid (224.3 g; 82%). ^{1}H NMR (DMSO-d_6, 400 MHz) □ 3.29 (s, 2H), 6.76 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 8.3 Hz), 7.51 (br s, 1H), 8.71 (s, 1H), 10.33 (s, 1H), 10.49 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) □ 177.0, 161.3, 158.7 (br), 140.7, 132.8, 126.9, 123.7 (q, J = 268 Hz), 121.0, 118.7, 111.2 (q, J = 32 Hz), 109.6, 36.7; HPLC ret. time: 5.759 min. LRMS (M+) 329.1, 331.1.

Example 1

5-[4-(R-1-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one



To a solution of 1:1 DCE/t-BuOH alcohol (1:1 ratio, 4 mL) and 5-(4-Chloro-5-trifluoromethyl-pyrimdin-2-ylamino)-1,3-dihydro-indol-2-one (0.15 g; 0.456 mmole) was added (R)(+) alpha phenethyl amine (0.071 mL; 0.547 mmole) and diisopropyl ethyl amine (0.081 mL, 0.456 mmole). The resultant solution was stirred under nitrogen and heated to 80°C for 16 hours. The reaction was cooled to room temperature, diluted with ~10 mL of a 1:1 mixture of dichloromethane and methanol followed by the addition of 0.5 g of MP-carbonate. The resultant mixture was stirred, filtered, concentrated and purified by silica gel chromatography (97:2.8:0.3 ratio of chloroform/methanol/concentrated ammonium hydroxide). The desired title compounds was obtained as a white solid (0.021 g; 11%). HPLC ret. time: 6.46 min. LRMS (M+) 413.4

The following compounds of the invention were prepared by heating chloropyrimidine (4) with an appropriate amine as in Example 1. Amines used in these reactions were either obtained commercially and used as received or alternatively they were prepared by common synthetic methods for amines known to those skilled in the art. Unless otherwise noted, compounds having chiral centers were prepared as racemic mixtures.

Table 1. Compounds Prepared by the Method of Example 1:

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
N-(1-Methyl-1-phenyl-ethyl)-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide	6.46	597.5
3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide	4.87	479.1
5-{4-[3-(Trifluoro-methanesulfonyl)-benzylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.35	532.1
5-{4-[(Piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	3.74	407.3
5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.21	485.2
N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.22	493.3
3-Oxo-3-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propionitrile	4.92	474.3
5-{4-[3-(1,1-Dioxo-1N^6-isothiazolidin-2-yl)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.89	471.1
5-[4-(2-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.53	380.3
5-{4-[(1-Methanesulfonyl-piperidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.17	485.3
N-{2-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide	4.38	431.2
N-{4-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-butyl}-methanesulfonamide	4.78	459.3
5-{4-[(1-Methanesulfonyl-piperidin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.22	485.3
N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide	4.81	445.1
Methanesulfonic acid 3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl ester	5.67	494.1
N-{3-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide	4.58	445.1
5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-	4.87	487.2

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one		
N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.29	511.1
5-{4-[(5-Oxo-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.12	423.3
N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.38	523.2
N-(4-Methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.30	507.2
5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.14	492.2
5-{4-[(4-Trifluoroacetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.64	505.1
5-{4-[(1-Methanesulfonyl-azetidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.76	457.2
N-Methyl-N-(4-methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	6.66	521.3
5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.97	471.2
N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide	5.02	459.2
5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.71	499.4
5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.68	479.1
{2,2-Dimethyl-3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-carbamic acid tert-butyl ester	7.01	495.0
5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.27	410.4
5-{4-[(1-Methyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	3.71	421.0
5-{4-[(Tetrahydro-pyran-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-	5.16	408.3

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
one		
5-[4-(2-Ethyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.95	394.3
5-{4-[(Tetrahydro-furan-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.30	394.3
5-{4-[(Tetrahydro-furan-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.30	394.3
5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.98	404.2
5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.08	471.3
5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	7.89	458.3
5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.20	473.3
5-[4-(2-Methoxy-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.87	396.3
5-{4-[(*endo*-Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.74	416.3
(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzyl)-phosphonic acid dimethyl ester	5.03	522.2
5-[4-(3-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.87	380.2
5-{4-[(2-Hydroxy-cyclohexylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.66	422.2
N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide	5.69	537.2
5-{4-[(4-Ethanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.11	501.3
5-(4-{[4-(Propane-2-sulfonyl)-morpholin-2-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	5.35	515.2
5-{4-[(4-Acetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.43	451.2
5-{4-[(4-Propionyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-	4.74	465.2

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
2-one		
5-(4-{[4-(2,2-Dimethyl-propionyl)-morpholin-2-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	5.43	493.2
2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-morpholine-4-carboxylic acid methyl ester	5.04	467.2
5-{4-[(4-Methoxyacetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.44	481.2
5-[4-(3-Ethanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.36	492.3
5-{4-[(4-Methanesulfonyl-morpholin-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.84	487.3
5-{4-[(4-Methanesulfonyl-morpholin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.86	487.3
5-{4-[(Pyrimidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.53	402.3
5-{4-[(Pyrazin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.42	402.1
N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide	5.55	523.3
5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.17	485.3
5-{4-[(4-Isobutyryl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.03	479.2
5-[4-(3,3-Dimethyl-2-oxo-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.00	408.2
5-[4-(1,2-Dimethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.65	380.3
5-[4-(2-Methoxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.57	382.3
5-{4-[2-(1,1-Dioxo-1D^6-isothiazolidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.59	457.3
5-[4-(3-Methylamino-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	3.47	381.3

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
5-{4-[(Pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.62	401.3
5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.89	479.3
5-{4-[3-(1,1-Dioxo-1,l,6-isothiazolidin-2-yl)-benzylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.45	519.2
5-[4-(1R-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.42	414.4
5-(4-Isopropylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	5.84	352.2
5-(4R-sec-Butylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	6.22	366.2
5-(4S-sec-Butylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	6.23	366.2
5-[4-(2-Methylamino-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	3.29	367.3
5-[4-(1S-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.42	414.3
5-{4-[(2-Methanesulfonylmethyl-thiazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.72	499.3
5-(4-Propylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	5.91	352.2
5-[4-(2-Hydroxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.49	368.2
5-[4-(1-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.85	382.2
5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.55	479.4
5-{4-[(Pyridin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.49	401.2
5-[4-(1,3-Dimethyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.99	394.3
N-Isopropyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide	5.12	487.3
5-[4-(1S-Hydroxymethyl-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.23	396.3
N-Cyclohexyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-	6.24	527.2

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
propyl}-methanesulfonamide		
5-[4-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	440.4	7.17
5-{4-[(1-Methanesulfonyl-pyrrolidin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.07	471.2
5-{4-[(3-Methyl-thiophen-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.18	420.4
5-{4-[(1-Methanesulfonyl-pyrrolidin-3R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.95	471.2
5-[4-(2-Hydroxy-1S-phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.28	430.3
5-[4-(2-Hydroxy-1S-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.49	368.3
5-[4-(1R-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.85	382.2
5-[4-(1-Pyrimidin-4-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.84	416.3
5-[4-(1,1-Dioxo-tetrahydro-1-thiophen-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.67	426.3
5-{4-[(1H-Imidazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	3.27	390.3
5-[4-(2-Piperidin-2-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	3.79	421.4
5-[4-(Isobutyl-methyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.82	380.3
N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.49	507.4
N-Ethyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.67	521.3
5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.47	478.2
N-Isopropyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.81	535.3
5-{4-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3-	5.79	484.3

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one		
5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.17	485.3
5-{4-[2R-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.70	499.4
5-{4-[2S-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.70	499.4
5-[4-(3-Methylsulfanyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.83	398.2
5-[4-(1S-Hydroxymethyl-3-methylsulfanyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.02	428.2
5-[4-(2-Hydroxy-1R-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.49	368.3
5-[4-(1R-Hydroxymethyl-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.23	396.4
N-Ethyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide	5.31	473.3
5-{4-[(1-Methanesulfonyl-pyrrolidin-3R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.94	471.4
5-[4-(1S-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.86	382.3
5-[4-(3,5-Dinitro-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.04	490.1
N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.84	493.1
N-Isopropyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide	5.37	473.3
5-[4-(2-Hydroxy-1-phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.29	430.3
5-[4-(1R-Hydroxymethyl-3-methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.59	410.4
5-[4-(1S-Hydroxymethyl-3-methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.59	410.4

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
5-{4-[(1-Methanesulfonyl-piperidin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.16	485.3
5-{4-[(1-Methanesulfonyl-pyrrolidin-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.08	471.3
5-[4-(Methyl-pyridin-2-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.37	415.3
5-{4-[(3-Methanesulfonyl-benzyl)-methyl-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.66	492.3
N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide	5.63	507.3
5-[4-(Methyl-pyridin-3-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.25	415.4
5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-methyl-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.69	499.4
5-[4-(Methyl-pyridin-4-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.12	415.3
5-(4-Cyclopentylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	6.47	378.3
5-[4-(2,6-Dimethoxy-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.78	460.3
5-{4-[(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.99	418.3
5-[4-(2-Imidazol-1-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	3.58	404.2
5-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.95	401.4
5-[5-Trifluoromethyl-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.57	468.2
5-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.07	415.3
5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.16	478.2
5-{4-[2-(1-Acetyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-	5.22	463.4

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
one		
5-{4-[2-(1-Propionyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.65	477.4
5-{4-[2-(1-Cyclopropanecarbonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.86	489.4
5-{4-[2-(1-Isobutyryl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.07	491.3
5-{4-[2-(1-Butyryl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.99	491.4
5-{4-[2-(1-Methoxyacetyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.19	493.4
5-{4-[2-(1-Cyclobutanecarbonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.31	503.4
N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide	4.47	423.3
N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-propionamide	4.89	437.45
Cyclopropanecarboxylic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide	5.07	449.3
N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-isobutyramide	5.24	451.3
N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-butyramide	5.25	451.4
2-Methoxy-N-methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide	4.47	453.3
Cyclobutanecarboxylic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide	5.48	463.4
2,2,N-Trimethyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-propionamide	5.80	465.3
2,N-Dimethyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-butyramide	5.55	465.3
N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-benzamide	5.38	485.3

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
Isoxazole-5-carboxylic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide	4.91	476.2
Morpholine-4-carboxylic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide	4.78	494.3
Ethanesulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide	5.29	473.3
Propane-1-sulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide	5.71	487.3
1,1,3-Trimethyl-3-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-sulfonylurea	5.53	488.3
2,2,2-Trifluoro-N-methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide	5.80	477.2
N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-acetamide	4.23	409.2
N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-propionamide	4.61	423.2
Cyclopropanecarboxylic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide	4.77	435.2
N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-isobutyramide	4.94	437.2
N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-butyramide	4.95	437.2
2-Methoxy-N-methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-acetamide	4.21	439.2
Cyclobutanecarboxylic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide	5.17	449.3
2,2,N-Trimethyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-propionamide	5.57	451.4
2,N-Dimethyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-butyramide	5.26	451.4
N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-benzamide	4.80	471.3
Isoxazole-5-carboxylic acid methyl-{2-[2-(2-oxo-	4.51	462.3

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide		
Morpholine-4-carboxylic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide	4.41	480.3
N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide	4.77	445.1
Ethanesulfonic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide	5.03	459.2
Propane-1-sulfonic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide	5.44	473.3
1,1,3-Trimethyl-3-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-sulfonylurea	5.49	474.2
2,2,2-Trifluoro-N-methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-acetamide	5.49	463.2
5-[4-(2-Hydroxy-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]- 1,3-dihydro-indol-2-one	4.05	354.3
5-(4-Cyclopropylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	5.41	350.3
5-(4-Cyclobutylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	6.01	364.3
5-[4-(1,4-Dimethyl-pentylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	7.45	408.4
5-[4-(3-Imidazol-1-yl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	3.77	418.3
5-[4-(2-Phenoxy-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]- 1,3-dihydro-indol-2-one	6.34	430.3
5-[4-(1-Cyclohexyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	7.61	420.4
5-[4-(1-Hydroxymethyl-2,2-dimethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.64	410.4
5-[4-(1-Methoxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.96	396.3
5-[4-(Indan-2-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.78	426.4
5-[4-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	7.16	440.3
5-(4-Cycloheptylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	7.21	406.3

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
5-{4-[2-(2-Oxo-imidazolidin-1-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.04	422.3
4-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-butyric acid ethyl ester	5.65	424.2
5-[4-(2-Hydroxy-1-hydroxymethyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	3.72	384.2
5-[4-(3-Hydroxy-2,2-dimethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.09	396.3
5-{4-[(Isochroman-1-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.36	456.3
5-[4-(4-Hydroxy-1,1-dioxo-tetrahydro-1&-thiophen-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.42	442.2
5-[4-(2-Methoxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.58	382.3
5-[4-(*trans*-4-Methylsulfanyl-tetrahydro-furan-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.37	426.3
5-{4-[*trans*-2-(Pyrimidin-2-ylsulfanyl)-cyclopentylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.32	488.3
5-[4-(Indan-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.86	426.3
5-{4-[2-(2-Hydroxy-ethylsulfanyl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.66	414.3
5-{4-[2-(Pyridin-3-yloxy)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.20	445.3
5-{4-[2-(6-Methyl-pyridin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.00	429.3
5-{4-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.01	458.2
5-{4-[(1-Methyl-1H-pyrazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.60	404.3
5-{4-[(4,5,6,7-Tetrahydro-benzothiazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.93	461.2
5-[4-(1-Phenyl-3-[1,2,4]triazol-1-yl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-	5.24	495.2

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
2-one		
5-(4-Isobutylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	6.12	366.4
5-[4-(2-Cyclohexyl-1-hydroxymethyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.41	450.4
2-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propionic acid methyl ester	5.26	396.3
5-(4-Cyclohexylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	6.82	392.3
5-[4-(3-Hydroxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.24	368.3
5-{4-[2-(4-Methyl-1H-imidazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	3.54	418.3
5-[4-(Tetrahydro-furan-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	4.89	380.3
5-[4-(Dicyclopropylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.59	404.3
5-{4-[2-(5-Methyl-4H-[1,2,4]triazol-3-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.00	419.3
5-[4-(2-Ethylsulfanyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.99	398.3
5-[4-(2-Phenoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]- 1,3-dihydro-indol-2-one	6.57	444.2
5-{4-[(1-Ethyl-5-oxo-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.57	435.2
5-(4-{[1-(2-Methoxy-ethyl)-5-oxo-pyrrolidin-3-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	4.44	465.2
5-[4-(Benzhydryl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	7.26	476.2
5-{4-[2-(1-Methyl-1H-pyrazol-4-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.90	418.3
5-{4-[(4-Methyl-1H-imidazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	3.40	404.2
5-{4-[(5-Cyclopropyl-1H-pyrazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.00	430.2
5-{4-[2-(4-Methyl-thiazol-5-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-	5.18	435.2

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
one		
5-{4-[2-(1H-Benzoimidazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.39	454.2
5-{4-[(5-Methyl-[1,3,4]oxadiazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.25	406.3
5-{4-[(5-Phenyl-4H-[1,2,4]triazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.92	467.3
5-{4-[(1H-Indol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.10	439.3
5-{4-[(1,5-Dimethyl-1H-pyrazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.77	418.3
5-{4-[(Benzothiazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.77	457.2
5-{4-[(3-Methyl-isoxazol-5-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.02	405.3
5-{4-[(4-Methyl-thiazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.12	421.2
5-{4-[1-(4-Methyl-thiazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.62	435.2
5-{5-Trifluoromethyl-4-[(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.95	432.2
5-{4-[1-(2-Methyl-thiazol-4-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.69	435.3
5-{4-[(3-Methyl-imidazo[2,1-b]thiazol-6-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.03	460.3
5-{4-[1-(5-Methyl-4H-[1,2,4]triazol-3-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.20	419.3
5-{4-[1-(3,5-Dimethyl-1H-pyrazol-4-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.02	432.3
5-{4-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	4.85	432.4
5-{4-[2-(4,6-Dimethyl-pyrimidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.17	444.4

Compound Name	HPLC Retention Time (min.)	MS Data (M+H)
5-{4-[2-(4-Methyl-5,6,7,8-tetrahydro-quinazolin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	5.88	484.4
5-[4-(2-Thiazol-4-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	5.18	421.3
5-(4-Dimethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one	5.60	338.3
5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one	6.17	485.4
5-[4-(Indan-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one	6.85	426.3

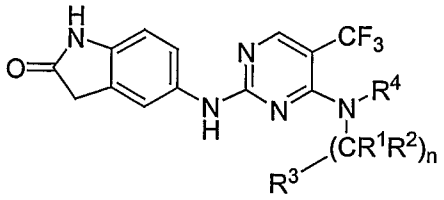
* * *

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

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

CLAIMS

1. A compound of the formula 1



1

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof,

wherein n is an integer from 1 to 3;

each R^1 is a substituent independently selected from the group consisting of hydrogen, hydroxy, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -NR^5R^6, -SR^7, -SOR^7, -SO_2R^7, -CO_2R^5, -$CONR^5R^6$, - $SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing R^1 substituents may not be bound to an sp^3 carbon atom bound to another heteroatom; and said R^1 substituents, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -NR^5R^6, -SR^7, -SOR^7, -SO_2R^7, -CO_2R^5, -$CONR^5R^6$, - $SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$ groups are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; with the proviso that a heteroatom of the foregoing optional R^1 moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

each R^2 is a substituent independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, and -$CONR^5R^6$; with the proviso that a heteroatom of any of the foregoing R^2 substituents may not be bound to an sp^3 carbon atom that is bound to another heteroatom; and said R^2 substituents, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, and -$CONR^5R^6$, are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and with the proviso that a heteroatom of the foregoing optional R^2 moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

R^1 and R^2 may be taken together with the atom(s) to which they are attached to form a cyclic group, -(C_3-C_{10})cycloalkyl or -(C_2-C_9)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R^5 groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an sp^3 carbon atom that is bound to another heteroatom;

R^3 is a substituent selected from the group consisting of:

(a) hydrogen;

(b) -(C_6-C_{10})aryl or -(C_1-C_9)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -$NHSO_2$(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_6-C_{10}) aryl or -(C_1-C_9) heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

(c) -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocyclyl, and -(C_1-C_6)alkyl-(C_2-C_9) heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6,-NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-

C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl,--SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_3-C_{10})cycloalkyl, -(C_2-C_9)heterocyclyl, and -(C_1-C_6)alkyl-(C_2-C_9) heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

(d) -(C_1-C_6)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -NSO_2(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, SO_2CF_3, SO_2NH_2, SO_2NH(C_1-C_6)alkyl, -SO_2NH(C_3-C_6)cycloalkyl, -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2N((C_3-C_6)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl; wherein said -(C_1-C_6)alkyl is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and -NR^5; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl; and wherein each R^3 (b)-(d) substituent, moiety, or element is optionally substituted by one to three radicals independently selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, -(C_1-C_9)heteroaryl, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -C=N-OH, -C=N-O(C_1-C_6 alkyl), -NR^5R^6, -SR^7, -SOR^7, -SO_2R^7, -CO_2R^5, -$CONR^5R^6$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing R^3 (b)-(d) substituents, moieties, elements or radicals may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^5 and R^6 of said -NR^5R^6, -$CONR^5R^6$, -$SO_2NR^5R^6$, and -$NR^5CONR^5R^6$ groups may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl;

R^4 is a substituent selected from the group consisting of hydrogen, (C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, and -(C_2-C_9)heterocyclyl; wherein said (C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, and -(C_2-C_9)heterocyclyl R^4 substituents are optionally substituted by one to three moieties

independently selected from the group consisting of hydrogen, halogen, -(C_1-C_6)alkyl, -CN, -NR^5_2, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, and -$CONR^5R^8$; with the proviso that a heteroatom of the foregoing R^4 substituents may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^5 and R^8 of said -$CONR^5R^8$ group may be taken together with the atoms to which they are attached to form a -(C_3-C_{10})cycloalkyl or -(C_2-C_9)heterocyclyl;

R^5 and R^6 are each substituents independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl; wherein said -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9)heteroaryl R^5 or R^6 substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -CF_3, -CN, -(C_1-C_6)alkyl, -NH(C_1-C_6)alkyl, -NH(C_3-C_7)cycloalkyl, -NH(C_2-C_9)heterocyclyl, -NH(C_6-C_{10})aryl, -NH(C_1-C_9)heteroaryl, -N((C_1-C_6)alkyl)$_2$, -N((C_3-C_7)cycloalkyl)$_2$, -N((C_2-C_9)heterocyclyl)$_2$, -N((C_6-C_{10})aryl)$_2$, -N((C_1-C_9)heteroaryl)$_2$, -O(C_1-C_6)alkyl, -O(C_3-C_7)cycloalkyl, -O(C_2-C_9)heterocyclyl, -O(C_6-C_{10})aryl, -O(C_1-C_9)heteroaryl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^7, -$CONH_2$, -$CONHR^7$, and -$CONR^7R^8$; with the proviso that a heteroatom of the foregoing R^5 or R^6 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatoms; and wherein R^7 and R^8 of said -$CONR^7R^8$ group may be taken together with the atoms to which they are attached to form a -(C_1-C_9) heteroaryl;

R^5 and R^6 may be taken together with the atom(s) to which they are attached to form a cyclic group, -(C_3-C_{10})cycloalkyl or -(C_2-C_9)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -CF_3, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R^7 groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO_2, -S-, -O-, -N-, -NH- and –NR^5, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an sp^3 carbon atom that is bound to another heteroatom;

R^7 is a substituent selected from the group consisting of –(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9) heteroaryl; wherein said -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9) heteroaryl R^7 substituents are optionally substituted by one to three moieties independently selected from

the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5_2, and -O(C_1-C_6)alkyl, with the proviso that a heteroatom of the foregoing R^7 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatom;

R^8 is a substituent selected from the group consisting of hydrogen, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9) heteroaryl; wherein said -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -(C_6-C_{10})aryl, and -(C_1-C_9) heteroaryl R^8 radicals are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NH_2, -NHR^9, -NR^9_2, OR^9, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^{10}, -$CONH_2$, -$CONHR^{10}$, and -$CONR^{10}R^{11}$; with the proviso that a heteroatom of the foregoing R^8 substituents or moieties may not be bound to an sp^3 carbon atom bound to another heteroatom; and wherein R^{10} and R^{11} of -$CONR^{10}R^{11}$ may be taken together with the atoms to which they are attached to form a -(C2-C_9)heterocyclyl;

R^9 and R^{10} are each -(C_1-C_6)alkyl and may be taken together with the atoms to which they are attached to form a -(C_2-C_9)heterocyclyl; and

R^{11} is hydrogen or -(C_1-C_6)alkyl.

2. A compound of claim 1 wherein R^1 is selected from hydrogen, hydroxy, and -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -(C_1-C_6)alkyl, -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$ and-$CONR^5R^8$; R^2 is hydrogen or -(C_1-C_6)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -NO_2, -CN, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C=N-OH, -C=N-O((C_1-C_6)alkyl), -NR^5R^6, -OR^5, -(C_3-C_7)cycloalkyl, -(C_2-C_9)heterocyclyl, -CO_2R^5, -$CONR^5R^6$, -$CONR^5R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –(C_2-C_6)alkenyl and –(C_2-C_6)alkynyl R^2 moieties may be optionally substituted by one to three R^5 groups; and n is 1.

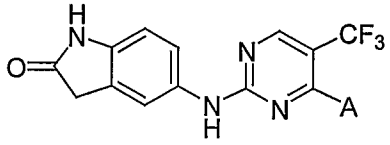
3. A compound of any of the preceding claims wherein R^3 is -(C_6-C_{10})aryl or -(C_1-C_9)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)$_2$, -(C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, -(C_1-C_9)heteroaryl, -NR^5R^6, -$NHSO_2$(C_1-C_6)alkyl, -$NHSO_2$(C_3-C_6)cycloalkyl, -N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl), -N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl), -O(C_1-C_6)alkyl, -O-SO_2(C_1-C_6)alkyl, -(CO)(C_1-C_6)alkyl, -(CO)CF_3, -(CO)(C_3-C_{10})cycloalkyl, -(CO)(C_6-C_{10})aryl, -(CO)(C_2-C_9)heterocyclyl, -(CO)(C_1-C_9)heteroaryl, -(CO)O(C_1-C_6)alkyl, -(CO)O(C_3-C_{10})cycloalkyl, -(CO)O(C_6-C_{10})aryl, -(CO)O(C_2-C_9)heterocyclyl, -(CO)O(C_1-C_9)heteroaryl, -(CO)(C_1-C_6)alkyl-O(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl,

$-SO_2(C_3-C_6)$cycloalkyl, SO_2CF_3, SO_2NH_2, $SO_2NH(C_1-C_6)$alkyl, $-SO_2NH(C_3-C_6)$cycloalkyl, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, $-SO_2NR^5R^6$, and $-SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl$; wherein said $-(C_6-C_{10})$ aryl or $-(C_1-C_9)$ heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl.

4. A compound of any of the preceding claims wherein R^3 is selected from $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocyclyl, and $-(C_1-C_6)alkyl-(C_2-C_9)$ heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)$alkyl, $-(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)_2$, $-(C_3-C_{10})$cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)heterocyclyl, $-(C_1-C_9)$heteroaryl, $-NR^5R^6$, $-NSO_2(C_1-C_6)$alkyl, $-NHSO_2(C_3-C_6)$cycloalkyl, $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)$alkyl, $-O-SO_2(C_1-C_6)$alkyl, $-O-SO_2(C_1-C_6)$alkyl, $-(CO)(C_1-C_6)$alkyl, $-(CO)CF_3$, $-(CO)(C_3-C_{10})$cycloalkyl, $-(CO)(C_6-C_{10})$aryl, $-(CO)(C_2-C_9)$heterocyclyl, $-(CO)(C_1-C_9)$heteroaryl, $-(CO)O(C_1-C_6)$alkyl, $-(CO)O(C_3-C_{10})$cycloalkyl, $-(CO)O(C_6-C_{10})$aryl, $-(CO)O(C_2-C_9)$heterocyclyl, $-(CO)O(C_1-C_9)$heteroaryl, $-(CO)(C_1-C_6)alkyl-O(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_3-C_6)$cycloalkyl, SO_2CF_3, SO_2NH_2, $SO_2NH(C_1-C_6)$alkyl, $-SO_2NH(C_3-C_6)$cycloalkyl, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, $-SO_2NR^5R^6$, and $-SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl$; wherein said $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocyclyl, and $-(C_1-C_6)alkyl-(C_2-C_9)$ heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and R^5 and R^6 of said NR^5R^6 R^3(b) group may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl.

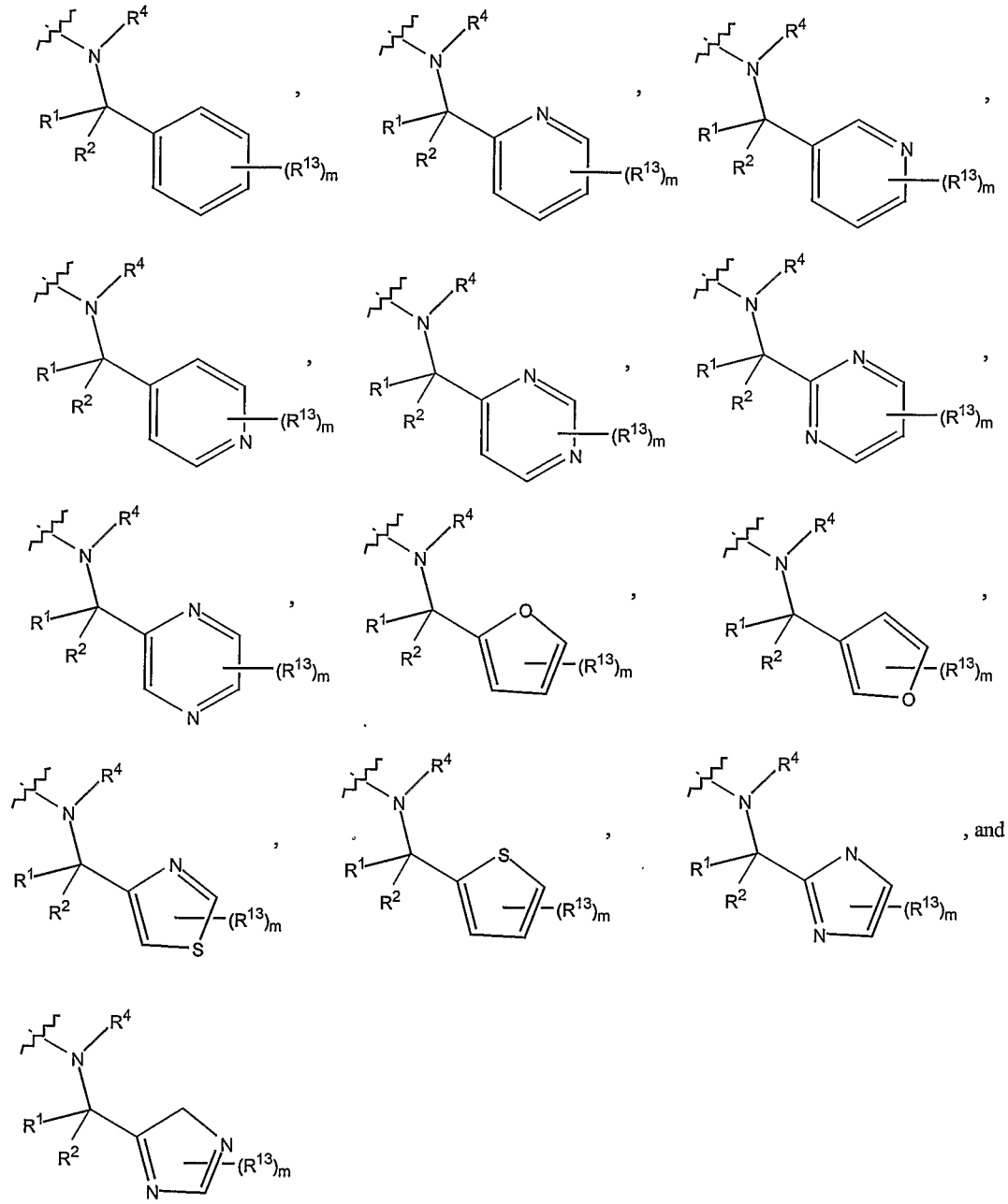
5. A compound of any of the preceding claims wherein R^3 is $-(C_1-C_6)$alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)$alkyl, $-(C_3-C_{10})$cycloalkyl, $-NSO_2(C_1-C_6)$alkyl, $-NHSO_2(C_3-C_6)$cycloalkyl, $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)$alkyl, $-O-SO_2(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_3-C_6)$cycloalkyl, $-SO_2NH_2$, $SO_2NH(C_1-C_6)$alkyl, $-SO_2NH(C_3-C_6)$cycloalkyl, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, and $-SO_2NR^5R^6$.

6. A compound according to any of the preceding claims of the formula **2**

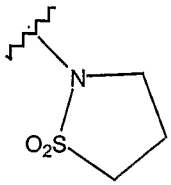


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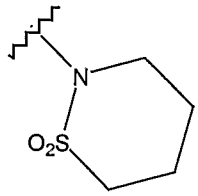
wherein A is selected from the group consisting of:



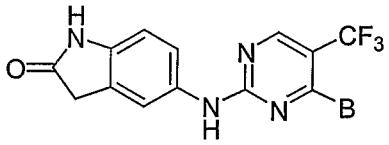
wherein m is an integer from 0-3 and R^{13} is a substituent selected from the group consisting of hydrogen, halogen, hydroxy, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_7)$-cycloalkyl, $(C_6\text{-}C_{10})$-aryl, $(C_1\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$-heterocyclyl, O-$(C_1\text{-}C_6)$-alkyl, O-$(C_3\text{-}C_7)$-cycloalkyl, SO_2-$(C_1\text{-}C_6)$alkyl, $SO_2(C_3\text{-}C_7)$-cycloalkyl, $NHSO_2(C_1\text{-}C_6)$alkyl, $N((C_1\text{-}C_6)alkyl)(SO_2(C_1\text{-}C_6\text{-}alkyl))$, $N((C_3\text{-}C_7)cycloalkyl)(SO_2(C_1\text{-}C_6\text{-}alkyl))$, $N(C_1\text{-}C_6\text{-}alkyl)(SO_2(C_3\text{-}C_7)cycloalkyl)$, $N((C_3\text{-}C_7)cycloalkyl)(SO_2(C_3\text{-}C_7)cycloalkyl)$, $OSO_2(C_1\text{-}C_6)alkyl$, SO_2CF_3, SO_2NH_2, $SO_2NH(C_1\text{-}C_6)alkyl$, $SO_2NH(C_3\text{-}C_7)cycloalkyl$, $SO_2NR^5R^6$, $SO_2N((C_1\text{-}C_6)alkyl)_2$, CF_3, CO-$(C_1\text{-}C_6)$alkyl, CO-$(C_3\text{-}C_7)$cycloalkyl, $COCF_3$, $CO_2(C_1\text{-}C_6)alkyl$,



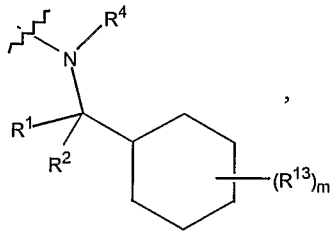
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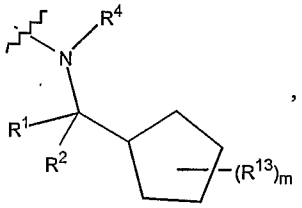
7. A compound according to any of the preceding claims of the formula 3



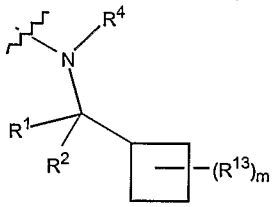
wherein B is selected from the group consisting of:



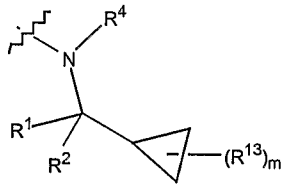
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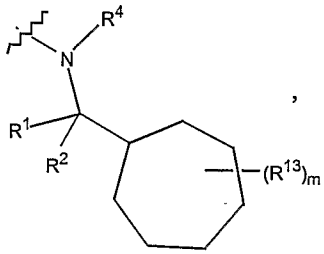
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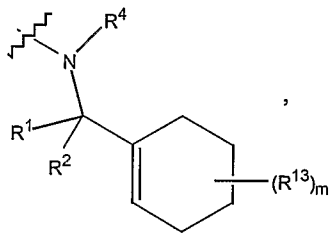
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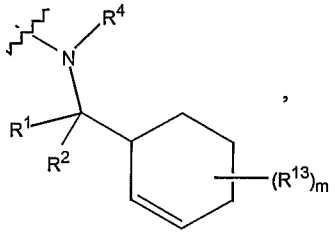
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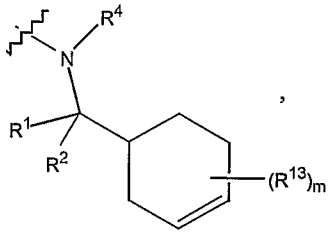
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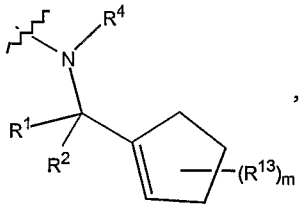
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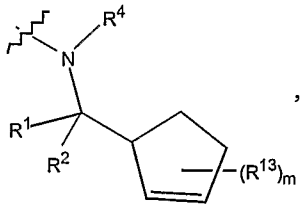
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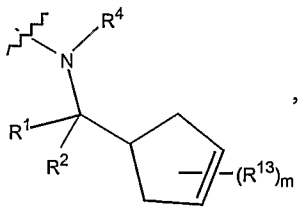
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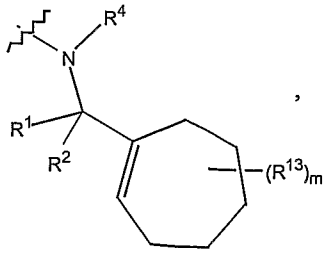
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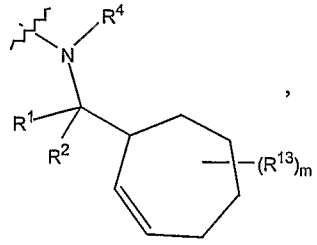
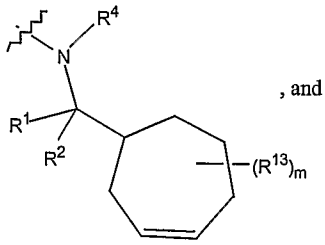
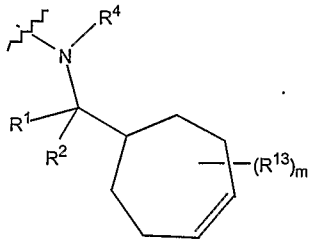
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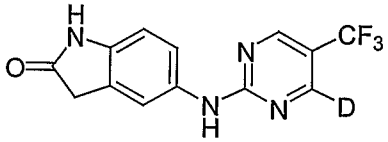
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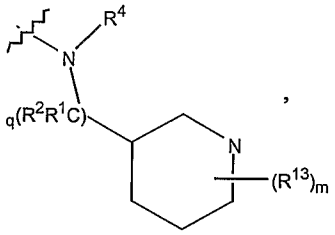
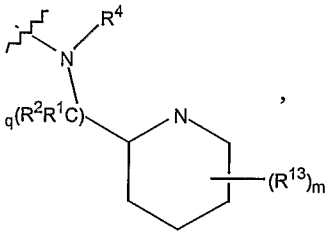
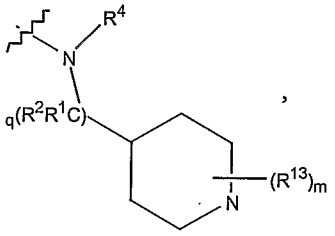
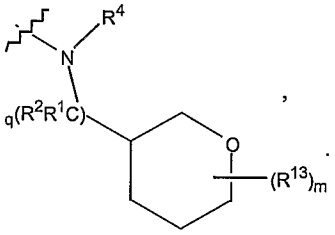
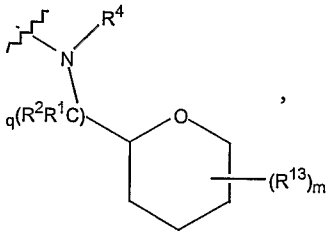
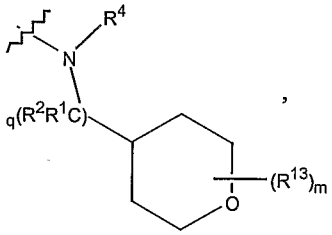
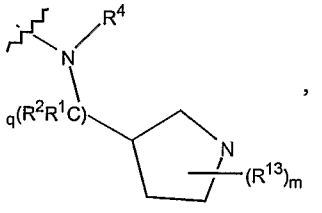
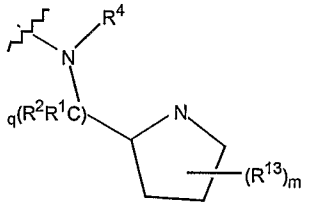
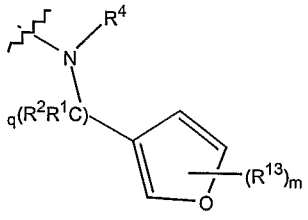
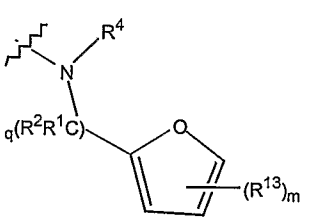
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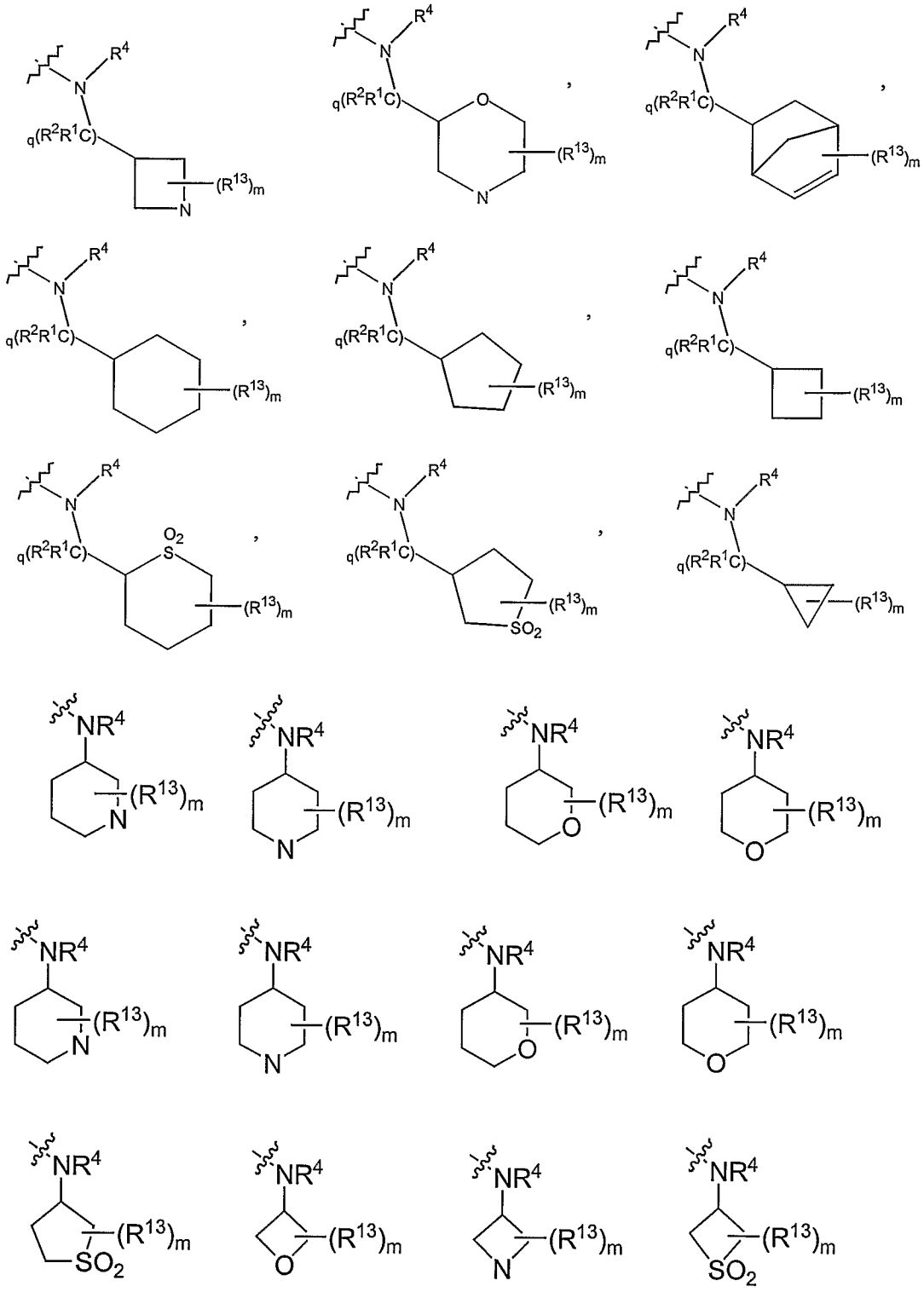
8. A compound according to any of the preceding claims of formula 4



wherein D is selected from the group consisting of:

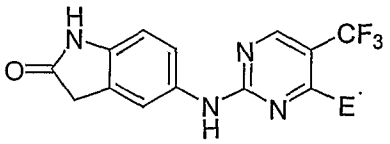

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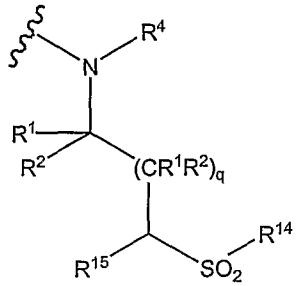


wherein q is an integer from 1-2.

9. A compound according to any of the preceding claims of formula **5**:



wherein E is selected from the group consisting of:



wherein R^{14} is selected from the group consisting of (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, and (C_2-C_9)-heterocyclyl, and R^{15} is selected from the group consisting of hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, and (C_2-C_9)-heterocyclyl.

10. A compound selected from the group consisting of:

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

Ethanesulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide;

5-{4-[(Isochroman-1-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(Pyridin-3-yloxy)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-(2-methyl-6-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(2-Hydroxy-indan-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Hydroxy-cyclopentylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-Hydroxy-2-(1-methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one; and

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-pyridin-2-yl)-methanesulfonamide.

11. A method for the treatment of abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth.

12. A pharmaceutical composition for the treatment of abnormal cell growth in a mammal comprising an amount of a compound of claim 1 that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier.