Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2265672 C 2008/12/02

(11)(21) 2 265 672

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 1997/09/15
(87) Date publication PCT/PCT Publication Date: 1998/03/19
(45) Date de délivrance/Issue Date: 2008/12/02
(85) Entrée phase nationale/National Entry: 1999/03/12
(86) N° demande PCT/PCT Application No.: US 1997/016252
(87) N° publication PCT/PCT Publication No.: 1998/011075
(30) Priorité/Priority: 1996/09/16 (US60/026,373)

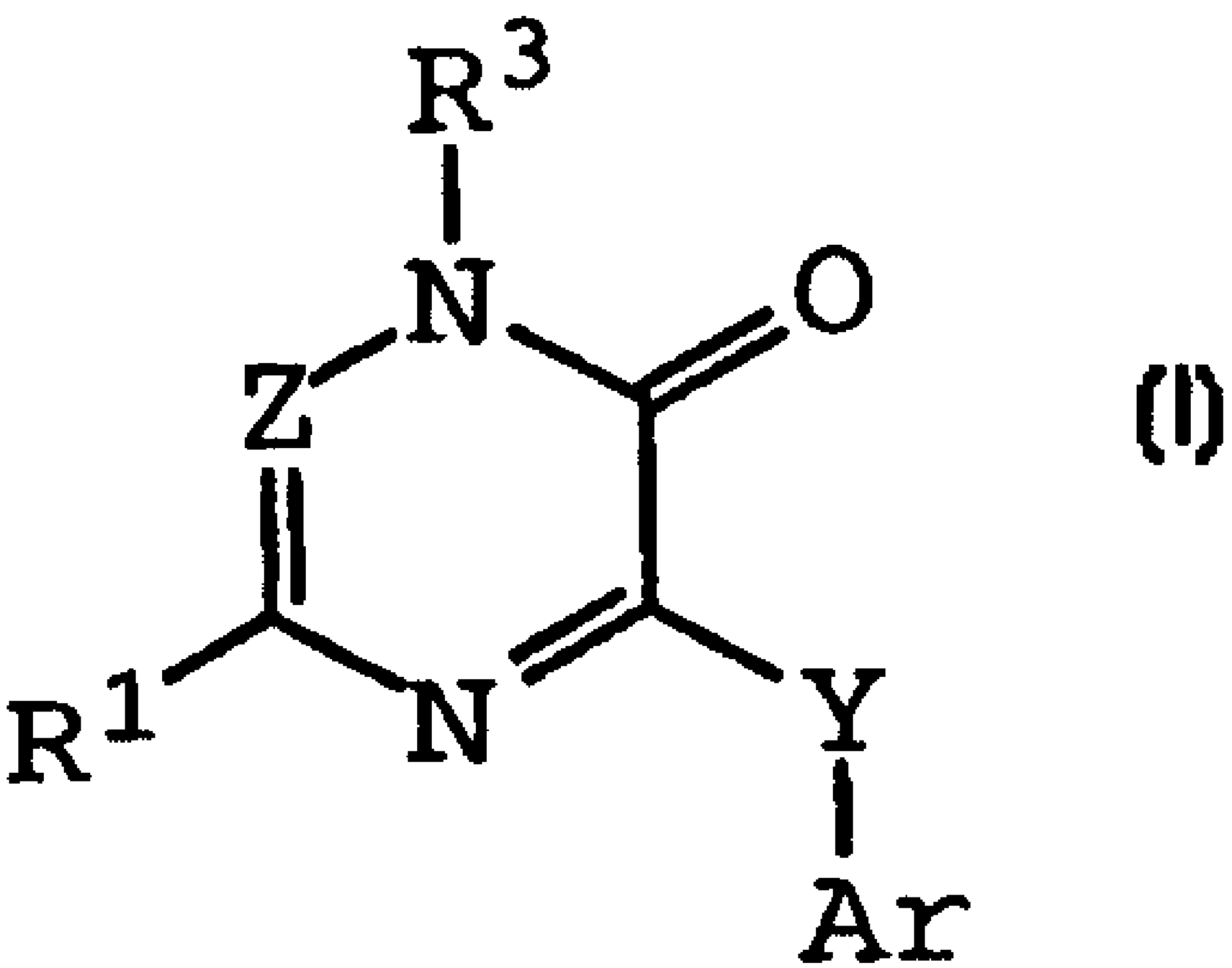
(51) Cl.Int./Int.Cl. *C07D 241/20* (2006.01), *A61K 31/4965* (2006.01), *A61K 31/53* (2006.01), *C07D 241/18* (2006.01), *C07D 253/07* (2006.01)

(72) Inventeurs/Inventors:
ARVANITIS, ARGYRIOS GEORGIOS, US;
OLSON, RICHARD E., US;
ARNOLD, CHARLES R., III, US;
FRIETZE, WILLIAM E., US

(73) Propriétaire/Owner:
BRISTOL-MYERS SQUIBB PHARMA COMPANY, US

(74) Agent: DIMOCK STRATTON LLP

(54) Titre : PYRAZINONES ET TRIAZINONES AINSI QUE LEURS DERIVES
(54) Title: PYRAZINONES AND TRIAZINONES AND THEIR DERIVATIVES THEREOF



(I)

(57) Abrégé/Abstract:
Corticotropin releasing factor (CRF) antagonists of Formula (I), and their use in treating psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorders, supranuclear palsy and eating disorders.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 241/20, A61K 31/495, C07D 401/12, 405/12, 253/07, 241/18	A1	(11) International Publication Number: WO 98/11075
		(43) International Publication Date: 19 March 1998 (19.03.98)

(21) International Application Number: PCT/US97/16252

(22) International Filing Date: 15 September 1997 (15.09.97)

(30) Priority Data:
60/026,373 16 September 1996 (16.09.96) US

(71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

(72) Inventors: ARVANITIS, Argyrios, Georgios; 101 Willow Glen Road, Kennett Square, PA 19348 (US). OLSON, Richard, Eric; 600 Silverside Road, Wilmington, DE 19809 (US). ARNOLD, Charles, R., III; 96 East Violette, New Castle, DE 19720 (US). FRIETZE, William, E.; 900 Merrybell Lane, Kennett Square, PA 19348 (US).

(74) Agent: LARSEN, Scott, K.; The du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

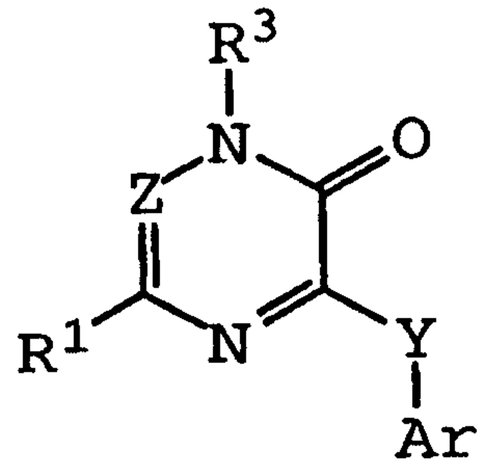
(81) Designated States: AM, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PYRAZINONES AND TRIAZINONES AND THEIR DERIVATIVES THEREOF

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of Formula (I), and their use in treating psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorders, supranuclear palsy and eating disorders.



(I)

TITLE

PYRAZINONES AND TRIAZINONES AND THEIR DERIVATIVES THEREOF

FIELD OF THE INVENTION

This invention relates to novel compounds and pharmaceutical compositions, and to methods of using same in the treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorders, supranuclear palsy and eating disorders.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin(POMC)-derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (**1983**); W. Vale et al., *Science* 213:1394 (**1981**)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (**1983**); G.F. Koob, *Persp. Behav. Med.* 2:39 (**1985**); E.B. De Souza et al., *J. Neurosci.* 5:3189 (**1985**)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (**1989**); J.E. Morley, *Life Sci.* 41:527 (**1987**)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and eating disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's

disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (**1988**)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (**1984**); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (**1987**); R.D. France et al., *Biol. Psychiatry* 28:86 (**1988**); M. Arato et al., *Biol Psychiatry* 25:355 (**1989**)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (**1988**)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (**1984**); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (**1984**); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (**1986**)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (**1989**)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (**1989**)].

There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (**1982**); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (**1986**)]. Preliminary studies using the putative CRF receptor

antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (**1987**), *Brain Research Reviews* 15:71 (**1990**)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders.

Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (**1985**); K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (**1986**)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (a-helical CRF_{9-41}) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

DuPont Merck PCT application WO95/10506 describes corticotropin releasing factor antagonist compounds

and their use to treat psychiatric disorders and neurological diseases.

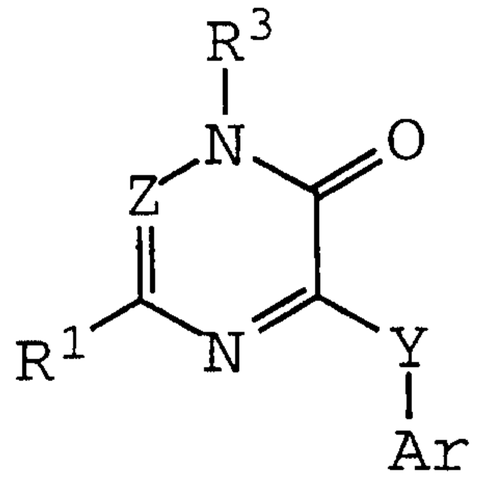
European patent application 0 576 350 A1 by Elf Sanofi describes corticotropin releasing factor antagonist compounds useful in the treatment of CNS and stress disorders.

Pfizer patent applications WO 94/13676, WO 94/13677, WO 94/13661, WO 95/33750, WO 95/34563, WO 95/33727 describe corticotropin releasing factor antagonist compounds useful in the treatment of CNS and stress disorders.

The compounds and the methods of the present invention provide for the production of compounds capable of inhibiting the action of CRF at its receptor protein in the brain. These compounds would be useful in the treatment of a variety of neurodegenerative, neuropsychiatric and stress-related disorders such as affective disorders, anxiety, depression, post-traumatic stress disorders, supranuclear palsy, seizure disorders, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders and fertility problems. It is further asserted that this invention may provide compounds and pharmaceutical compositions suitable for use in such a method.

SUMMARY OF THE INVENTION

This invention is a class of novel compounds which are CRF receptor antagonists and which can be represented by Formula (I):



(I)

or a pharmaceutically acceptable salt form thereof, wherein

Z is CR^2 or N;

when Z is CR^2:

Y is NR^4, O or $S(O)_n$;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, indolinyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, benzothiazolyl, indazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 4 R^5 groups; wherein Ar is attached to Y through an unsaturated carbon;

R^1 is H, halo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CONR^6R^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl;

R^2 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, halo, -CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-OR^{11}$, -SH or $-S(O)_nR^{12}$;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, $-S(O)_2R^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$,
wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl,
with the proviso that when R^3 is aryl, Ar is not imidazolyl;

R^4 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_2-C_6 alkenyl or C_2-C_6 alkynyl is optionally substituted with C_1-C_4 alkyl or C_3-C_6 cycloalkyl and wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, heterocyclyl, $-NO_2$, halo, -CN, C_1-C_4 haloalkyl, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, -SH, and $-S(O)_nR^{13}$,
wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$ and $-S(O)_nR^{13}$;

R^6 and R^7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-,

morpholinoethyl, morpholinopropyl and morpholinobutyl; or $-NR^6R^7$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl, biphenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^{15}$, -SH, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-OC(O)R^{14}$, $-NO_2$, $-NR^8COR^{15}$, $-N(COR^{15})_2$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, $-NR^{15}R^{16}$ and $-CONR^{15}R^{16}$;

heterocyclyl is 5- to 10- membered heterocyclic ring which may be saturated, partially unsaturated or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, wherein the heterocyclic ring is substituted with 0 to 3 substituents

independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^{15}$, -SH, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-OC(O)R^{14}$, $-NR^8COR^{15}$, $-N(COR^{15})_2$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, $-NR^{15}R^{16}$, and $-CONR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2;

and wherein, when Z is N:

Y is NR^4, O or $S(O)_n$;

Ar, R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, aryl, heterocyclyl, heterocyclyl and n are as defined above, but

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-S(O)_2R^{13}$, $-CO_2R^7$, $-COR^7$ or $-CONR^6R^7$,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl,

with the proviso that when R^3 is aryl, Ar is not imidazolyl.

[3] Preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is CR^2;

Y is NR^4 or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_4 alkyl, cyclopropyl, C_1-C_4 haloalkyl, -CN, $-NR^6R^7$, $-CONR^6R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$ or $-S(O)_nR^{13}$,

wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and aryl;

R^2 is H, C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, $-S(O)_2R^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, aryl and heterocyclyl;

R^4 is H, C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_8 cycloalkylalkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, CO_2R^7 and $-S(O)_nR^{13}$,

wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_4-C_8 cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7 and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-

C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or $-NR^6R^7$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$ and $-NR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$,

$-S(O)_nR^{14}$, $-CO_2R^{15}$, $-NO_2$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

[4] More preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is CR^2;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_4 alkyl, cyclopropyl, C_1-C_3 haloalkyl, -CN, $-NR^6R^7$, $-CONR^6R^7$, $-COR^7$, $-CO_2R^7$, $-OR^7$ or $-S(O)_nR^{13}$ wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_3-C_4 cycloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^6R^7$;

R^2 is H;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl or aryl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and aryl;

R^4 is H, allyl, or C_1-C_4 alkyl, wherein C_1-C_4 alkyl is optionally substituted with C_1-C_4 alkyl, $-OR^7$, $-S(O)_2R^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, $-CO_2R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_6 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$,

halo, -CN, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7 and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_2-C_8 alkoxyalkyl;

wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8, R^9 and R^{10} are independently at each occurrence H or C_1-C_4 alkyl;

R^{12} and R^{13} are independently at each occurrence C_1-C_4 alkyl or $-NR^6R^7$;

R^{14} is C_1-C_4 alkyl or $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$ and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

[5] Even more preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is CR^2;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 2 to 4 R^5 groups;

R^1 is H, Cl, Br, methyl, ethyl, cyclopropyl, or -CN,

R^2 is H;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl or aryl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each

occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -CF_3, halo, -CN, -OR^7, and aryl;

R^4 is H, methyl, ethyl, i-propyl, n-propyl, n-butyl, i-butyl, s-butyl, n-butyl, or allyl;

R^5 is independently selected at each occurrence from methyl, ethyl, i-propyl, n-propyl, aryl, -CF_3, halo, -CN, -$N(CH_3)_2$, -$C(=O)CH_3$, -OCH_3, -OCH_2CH_3, -OCF_3, and -$S(O)_2CH_3$;

R^{14} is C_1-C_4 alkyl or -$NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

[6] Specifically preferred compounds of this invention are compounds of Formula (I), pharmaceutically acceptable salts and pro-drug forms thereof, which are:

3-[(2,4-Dibromophenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2,4-Dibromophenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Chloro-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4,6-Dimethyl-2-iodophenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Bromo-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Acetyl-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4,6-Dimethyl-2-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4,6-Dimethyl-2-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Chloro-2-iodo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-phenyl-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dibromophenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4-Dichloro-6-methylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4-Dichloro-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4-Dibromo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(2-methoxyethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-(2-methoxy-1-methylethyl)-2(1H)-pyrazinone;

(+/-)3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-(2-methoxy-1-methylethyl)-2(1H)-pyrazinone;

(+/-)3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(ethoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-(2-ethoxy-1-methylethyl)-2(1H)-pyrazinone; and

(+/-)3-[(4-Bromo-2,6-difluorophenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Bromo-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-(N,N-dimethylamino)phenyl)-amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dichloro-6-methylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Chloro-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4,6-Dimethyl-2-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone; and

3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-(1-ethylpropyl)-2(1H)-pyrazinone.

[7] A second embodiment of preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is CR^2;

Y is NR^4 or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CONR^6R^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl;

R^2 is H, C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl;

R^3 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl and $-NR^6R^7$,

wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4

haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and $-CONR^6R^7$;

R^4 is H, C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, heterocyclyl, $-NO_2$, halo, -CN, C_1-C_4 haloalkyl, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$ and $-S(O)_nR^{13}$;

R^6 and R^7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl (C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or $-NR^6R^7$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$ and $-NR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-CO_2R^{15}$, $-NO_2$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

[8] More preferred compounds of the second embodiment of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is CR^2;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, aryl,

heterocyclyl, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -$CONR^6R^7$, -CO_2R^7 or -NR^6R^7,

wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^7, -SH, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -$OC(O)R^{13}$, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7, -$CONR^6R^7$, aryl and heterocyclyl;

R^2 is H;

R^3 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl and -NR^6R^7,

wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7 and -$CONR^6R^7$;

R^4 is H, allyl, or C_1-C_4 alkyl, wherein C_1-C_4 alkyl is optionally substituted with C_1-C_4 alkyl, -OR^7, -$S(O)_2R^{12}$, -CO_2R^7, -NR^6R^7 or -NR^9COR^{10};

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, -NO_2, -NR^6R^7, -COR^7, -OR^7, -$CONR^6R^7$, -$CON(OR^9)R^7$, -CO_2R^7 and -$S(O)_nR^{13}$, wherein C_1-C_6 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, -NO_2, halo, -CN, -NR^6R^7, COR^7, -OR^7, -$CONR^6R^7$, CO_2R^7 and -$S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_2-C_8 alkoxyalkyl;

wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8, R^9 and R^{10} are independently at each occurrence H or C_1-C_4 alkyl;

R^{12} and R^{13} are independently at each occurrence C_1-C_4 alkyl or $-NR^6R^7$;
R^{14} is C_1-C_4 alkyl or $-NR^{15}R^{16}$;
R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;
aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, $-CN$, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$ and $-NR^{15}R^{16}$; and
n is independently at each occurrence 0, 1 or 2.

[10] A third embodiment of preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is N;
Y is NR^4 or O;
Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;
R^1 is H, halo, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, aryl, $-CN$, C_1-C_4 haloalkyl, $-NR^6R^7$, $-CONR^6R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$ or $-S(O)_nR^{13}$,
wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_3 alkyl, C_3-C_6 cycloalkyl, halo, $-CN$, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and aryl;
R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, $-CN$, $-S(O)_2R^{13}$, $-COR^7$, $-CO_2R^7$ or $-CONR^6R^7$,
wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, $-CN$, $-OR^7$, $-S(O)_nR^{13}$, $-CO_2R^7$,

$-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, aryl and heterocyclyl;

R^4 is H, C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_8 cycloalkylalkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, CO_2R^7 and $-S(O)_nR^{13}$,
wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_4-C_8 cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7 and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or $-NR^6R^7$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$ and $-NR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-CO_2R^{15}$, $-NO_2$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

[11] More preferred compounds of the third embodiment of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is N;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_4 alkyl, C_1-C_3 haloalkyl, cyclopropyl, -CN, $-NR^6R^7$, $-CONR^6R^7$, $-COR^7$, $-CO_2R^7$, $-OR^7$ or $-S(O)_nR^{13}$

wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_3-C_4 cycloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^6R^7$;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl or aryl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and aryl;

R^4 is H, allyl, or C_1-C_4 alkyl, wherein C_1-C_4 alkyl is optionally substituted with C_1-C_4 alkyl, $-OR^7$, $-S(O)_2R^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, $-CO_2R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_6 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7 and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_2-C_8 alkoxyalkyl;
wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8, R^9 and R^{10} are independently at each occurrence H or C_1-C_4 alkyl;

R^{12} and R^{13} are independently at each occurrence C_1-C_4 alkyl or $-NR^6R^7$;

R^{14} is C_1-C_4 alkyl or $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

[12] Even more preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is N;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 2 to 4 R^5 groups;

R^1 is H, methyl, ethyl, cyclopropyl, -CF_3, or -$N(CH_3)_2$;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl or aryl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -CF_3, halo, -CN, -OR^7, and aryl;

R^4 is H, methyl, ethyl, i-propyl, n-propyl, n-butyl, i-butyl, s-butyl, n-butyl, or allyl;

R^5 is independently selected at each occurrence from methyl, ethyl, i-propyl, n-propyl, aryl, -CF_3, halo, -CN, -$N(CH_3)_2$, -$C(=O)CH_3$, -OCH_3, -OCH_2CH_3, -OCF_3, and -$S(O)_2CH_3$;

R^{14} is C_1-C_4 alkyl or -$NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

[13] A fourth embodiment of preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is N;

Y is NR^4 or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CONR^6R^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl;

R^3 is C_1-C_4 alkyl, -CN, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-OR^7$, $-COR^7$, $-CO_2R^7$ or $-CONR^6R^7$,

wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and $-CONR^6R^7$;

R^4 is H, C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, heterocyclyl, $-NO_2$, halo, -CN, C_1-C_4 haloalkyl,

$-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, $-CN$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$ and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or NR^6R^7 taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a

whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 , -NR^8COR^{15}, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$ and -$NR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -CO_2R^{15}, -NO_2 , -NR^8COR^{15}, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$, and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

[14] More preferred compounds of the fourth embodiment of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is N;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -$CONR^6R^7$, -CO_2R^7 or -NR^6R^7,

wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^7, -SH, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -$OC(O)R^{13}$, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7, -$CONR^6R^7$, aryl and heterocyclyl;

R^3 is C_1-C_4 alkyl, -CN, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-OR^7$, $-COR^7$ or $-CO_2R^7$,
wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^6R^7$ and $-CONR^6R^7$;

R^4 is H, allyl, or C_1-C_4 alkyl, wherein C_1-C_4 alkyl is optionally substituted with C_1-C_4 alkyl, $-OR^7$, $-S(O)_2R^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, $-CO_2R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_6 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7 and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_2-C_8 alkoxyalkyl;
wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8, R^9 and R^{10} are independently at each occurrence H or C_1-C_4 alkyl;

R^{12} and R^{13} are independently at each occurrence C_1-C_4 alkyl or $-NR^6R^7$;

R^{14} is C_1-C_4 alkyl or $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$ and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

A fifth embodiment of this invention is the method of treating affective disorders, anxiety, depression, post-traumatic stress disorders, supranuclear palsy, seizure disorders, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, or fertility problems in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of Formula I.

A sixth embodiment of this invention are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I.

This invention also includes intermediate compounds useful in preparation of the CRF antagonist compounds and processes for making those intermediates, as described in the following description and claims.

The CRF antagonist compounds provided by this invention (and especially labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

DETAILED DESCRIPTION OF INVENTION

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting

materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. For example, the term "C_1-C_{10} alkyl" denotes alkyl having 1 to 10 carbon atoms; thus, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl, wherein, for example, butyl can be $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$ or $-CH(CH_3)_3$.

The term "alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain. For example, the term "C_2-C_{10} alkenyl" denotes alkenyl having 2 to 10 carbon atoms; thus, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl and decenyl, such as allyl, propargyl, 1-buten-4-yl, 2-buten-4-yl and the like, wherein, for example, butenyl can be, but is not limited to, $-CH=CH_2CH_2CH_3$, $-CH_2CH=CHCH_3$, $-CH_2CH_2CH=CH_2$, $-CH=C(CH_3)_2$ or $-CH=CHCH=CH_2$.

The term "alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain. The term "C_2-C_{10} alkynyl" denotes alkynyl having 2 to 10 carbon atoms; thus, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl and decynyl.

The term "haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted independently with 1 or more halogen, such as, but not limited to, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CF_2Br$, $-CH_2CF_3$, $-CF_2CF_3$, $-CH(CF_3)_2$ and the like.

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

The term "cycloalkyl" is intended to include saturated ring groups having the specified number of carbon atoms, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl (c-Pr), cyclobutyl (c-Bu), cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, [3.3.0]bicyclooctyl, [2.2.2]bicyclooctyl and so forth.

As used herein, the term "heterocyclyl" or "heterocyclic" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which may be saturated, partially unsaturated, or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, isoxazolinyl, isoxazolyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6*H*-1,2,5-thiadiazinyl, 2*H*,6*H*-1,5,2-dithiazinyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolinyl, isoxazolyl, oxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl,

indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, 1*H*-indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolinyl, quinolinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazole, carbazole, ß-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzothienyl, 2,3-dihydrobenzofuranyl or 2,3-dihydrobenzothienyl.

The term "halo" or "halogen" includes fluoro, chloro, bromo and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of formula (I). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount

of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I); and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

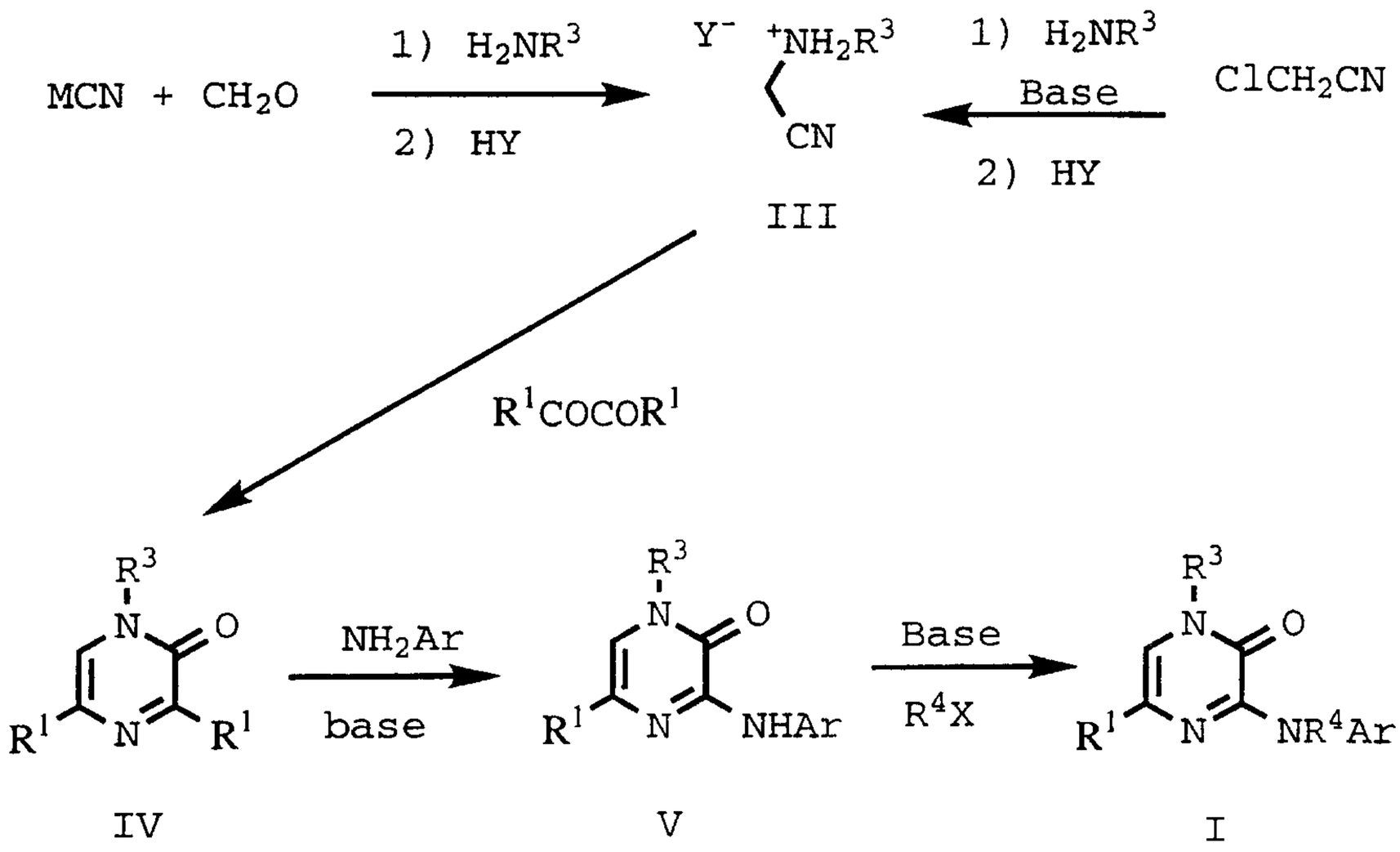
Synthesis

The pyrazinones and triazinones of this invention can be prepared by one of the general schemes outlined below (Scheme 1-6).

Compounds of the Formula (I) wherein Z = CH, Y = NR^4, R^1 = halogen and R^2 = H can be prepared as shown in Scheme 1. Compounds wherein R^2 is a substituent other than H as defined in the broad scope of the invention can also be prepared as shown in Scheme 1 by using the corresponding

R^2COH substituted aldehydes or $ClCHR^2CN$ substituted haloacetonitriles.

Scheme 1



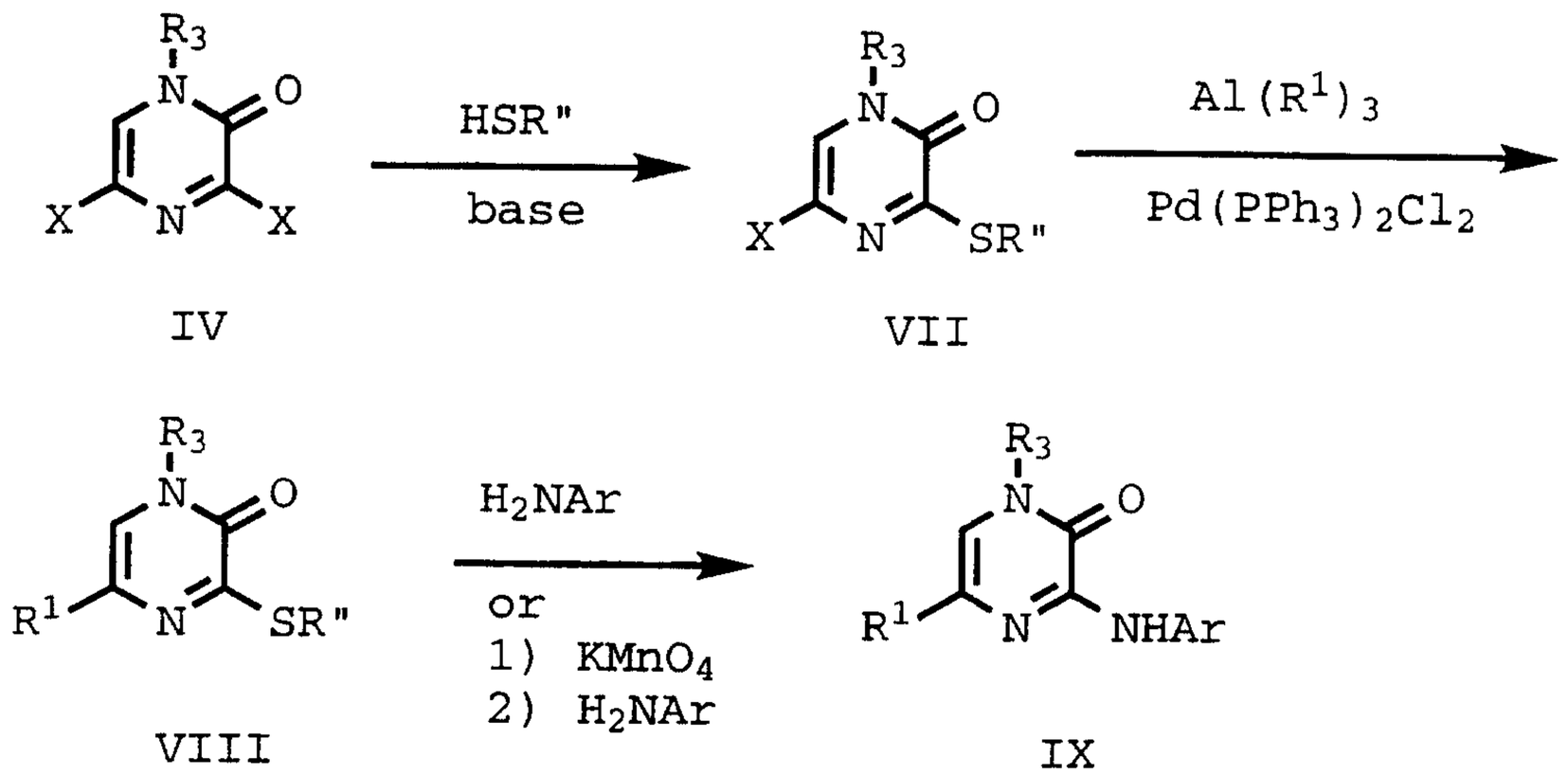
Wherein R^1 = halogen

Reaction of a cyanide salt with formaldehyde and the appropriate substituted amine afforded the corresponding aminoacetonitrile which was purified as the hydrochloride salt of Formula (III). Alternatively the same compounds of Formula (III) can be synthesized by reaction of the amine H_2NR^3 with a haloacetonitrile, such as chloroacetonitrile, in the presence of a base such as a tertiary amine or an inorganic base such as K_2CO_3 in an organic solvent and isolated as a salt of an inorganic acid by treatment with that acid. Amine salt of Formula (III) was treated with an oxalyl halide, R^1COCOR^1, such as oxalyl chloride or bromide to afford the dihalo compound Formula (IV), as described in Vekemans, J.; Pollers-Wieers, C.; Hoornaert, G. *J. Heterocyclic Chem.* 20, 919, **(1982)**. Compound Formula (IV) can be coupled with an aryl amine H_2NAr thermally, in the presence of a strong base such as NaH, $KN(SiMe_3)_2$, $LiN(SiMe_3)_2$ or $NaN(SiMe_3)_2$ in an aprotic organic solvent,

or under acid catalysis to give compounds of Formula (V). Compounds of Formula (V) can be alkylated with an alkyl halide R^4X to afford compounds of Formula (I).

Compounds where R^1 = alkyl or substituted alkyl can be prepared according to Scheme 2.

Scheme 2

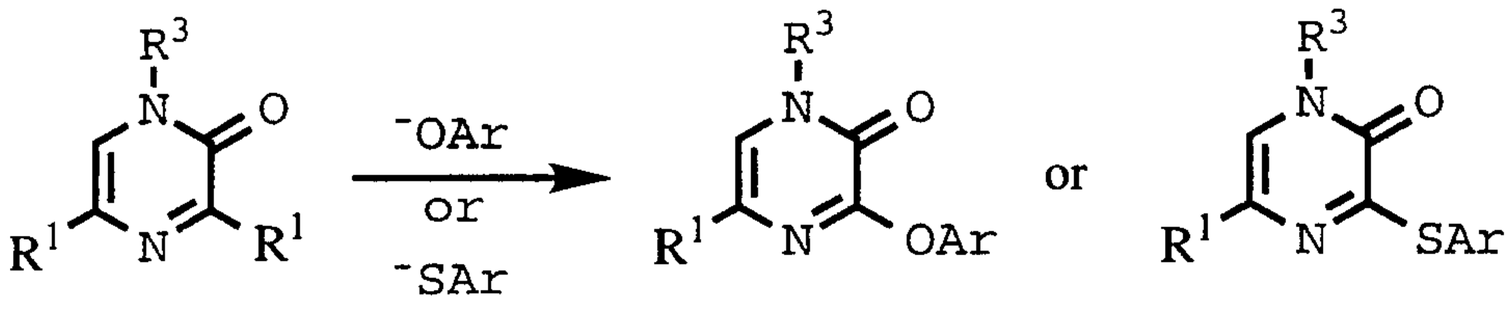


Reaction of the intermediate of Formula (IV) in Scheme 1, wherein R^1 = X = halogen in Scheme 2, with an alkyl or aryl thiol, HSR", in the presence of base such as NaH affords the adduct of Formula (VII), which may then be treated with a trialkylaluminum as described in Hirota, K.; Kitade, Y.; Kanbe, Y.; Maki, Y.; *J. Org. Chem.* 57, 5268, **(1992)**, in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$, to give compounds of Formula (VIII). Condensation of compounds of Formula (VIII) with an aryl amine H_2NAr under thermal, base, or acid catalyzed conditions gives compounds of Formula (IX). Alternatively (VIII) may be oxidized to the corresponding sulfones with an oxidant such as $KMnO_4$ and then condensed with the arylamines of formula H_2NAr to give (IX). The use of appropriately substituted aluminum alkyls, or simple transformations of those substituted alkyls can give access to compounds of Formula (I), where R^1 is a substituted alkyl; see Ratovelomanana,

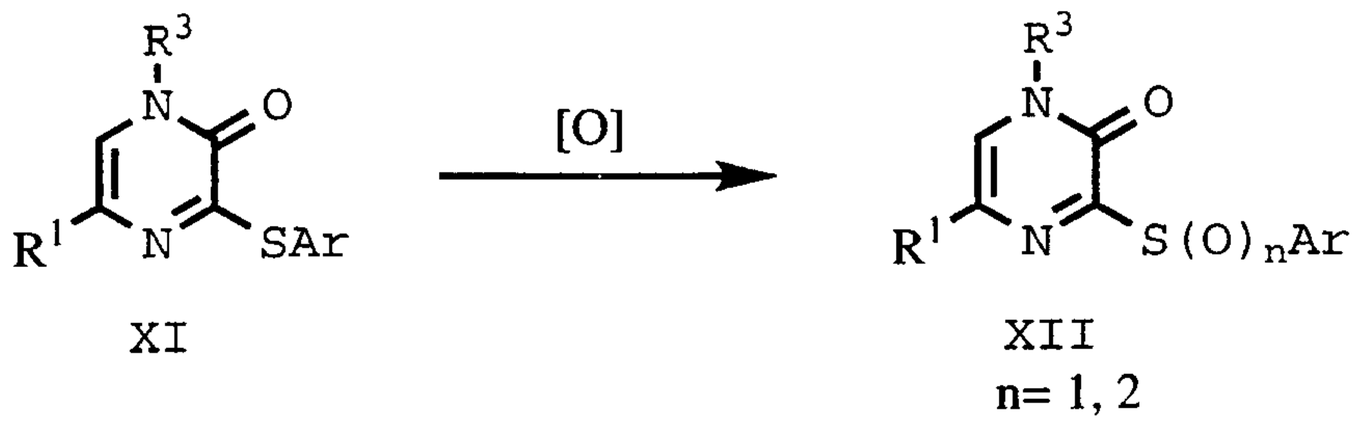
V.;Linstrumelle, G.; *Tet. Letters* 52, 6001 (**1984**) and references cited therein.

Compounds of the Formula (I) wherein Z = CH, Y = O or $S(O)_n$ and R^1 = halogen can be prepared as shown in Scheme 3.

Scheme 3



Wherein R^1 = halogen

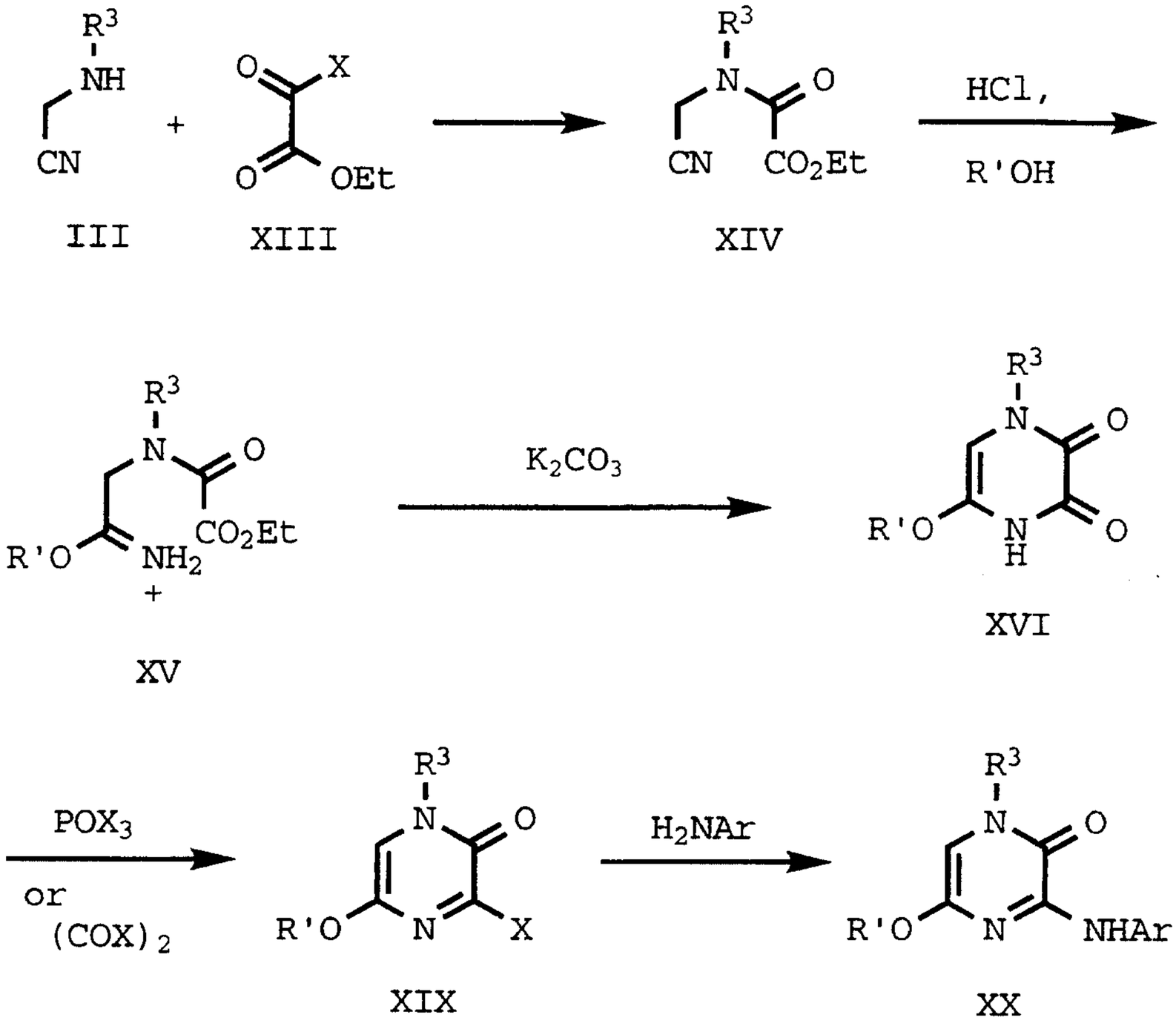


Reaction of the dihalo intermediate (IV) from Scheme 1 with a phenoxide or thiophenoxide, formed by treatment of the corresponding phenol or thiophenol with an appropriate base, such as NaH in an aprotic solvent, gives the adduct of Formula (X) or (XI). Adduct (XI) may be further oxidized to the sulfoxide or sulfone of Formula (XII), by treatment with the appropriate oxidant, such as a peroxide, NaIO4 or KMnO4.

Compounds of Formula (I) where R^1 = OR, SR and $S(O)_nR$ and Z= CH can be introduced on compounds of Formula (V) by copper or copper salt-catalyzed coupling of the corresponding anions RO^- and RS^- with the pyrazinone bromide. Keegstra, M.A.; Peters, T.H.A.; Brandsma, L.; *Tetrahedron*, 48, 3633 (**1992**) describes the addition of phenoxide anions by this method; alternatively, the same conditions can be used for the addition of thiophenoxide

anions. Alternatively the same compounds can be synthesized by Scheme 4.

Scheme 4



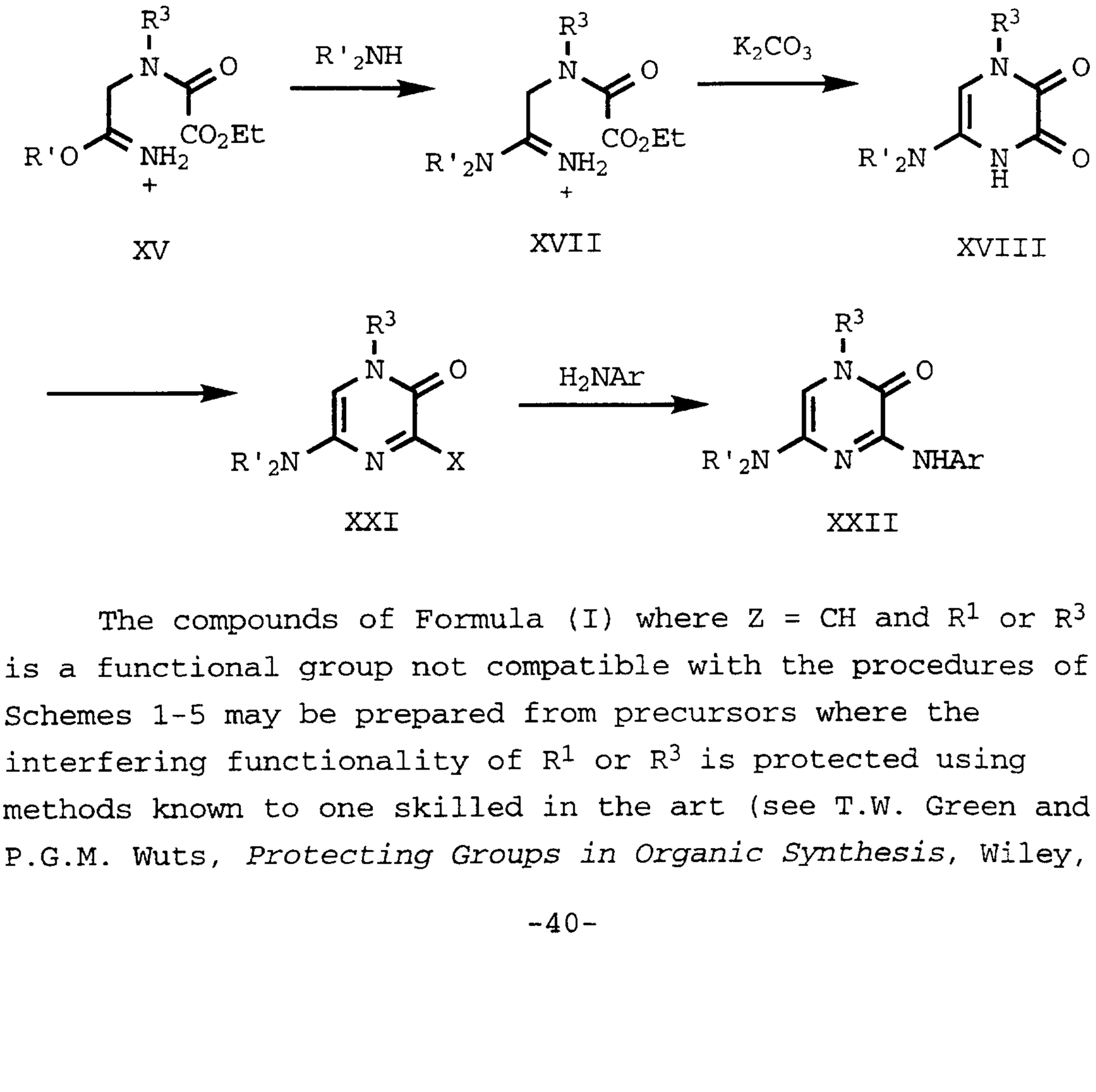
In Scheme 4, reaction of an aminoacetonitrile salt (III), described in Scheme 1, with an oxalyl halide ester (XIII) gives the corresponding amide (XIV), which in turn can be converted to the corresponding imidate salt (XV). This can be cyclized under treatment with a base, such as K_2CO_3 or Et_3N to the pyrazinedione of Formula (XVI). This can be converted to the corresponding halide (XIX), using a halogenating agent such as POX_3, oxalyl halide or SOX_2. Alternatively, (XVI) can be converted to the corresponding mesylate, tosylate or triflate, by treatment with the corresponding mesyl, tosyl, or triflic anhydride. Subsequently, (XIX) can be coupled with an aniline to the corresponding adduct of Formula (XX), under the conditions described in Scheme 1, or (XIX) can be coupled with a

phenoxide or thiophenoxide as described in Scheme 3 to yield compounds of Formula (I) wherein Y = O or $S(O)_n$.

Compounds of Formula (I) wherein R^1 = substituted N and Z = CH can be introduced on compounds of Formula (XV) by reaction with an amine to form the corresponding amidate (XVII) according to Scheme 5. Subsequently, (XVII) can be cyclized, halogenated, and substituted with the appropriate aniline, phenoxide or thiophenoxide as described in Scheme 4 above.

Compounds of Formula I wherein Z = CH and R^1 = COR^7 or CO_2R^7 can be synthesized from compounds of Formula (VII) by coupling with the appropriate vinyl aluminum or boron reagent in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$, and further transformations of the vinyl group, using methods known to one skilled in the art.

Scheme 5



XV XVII XVIII

XXI XXII

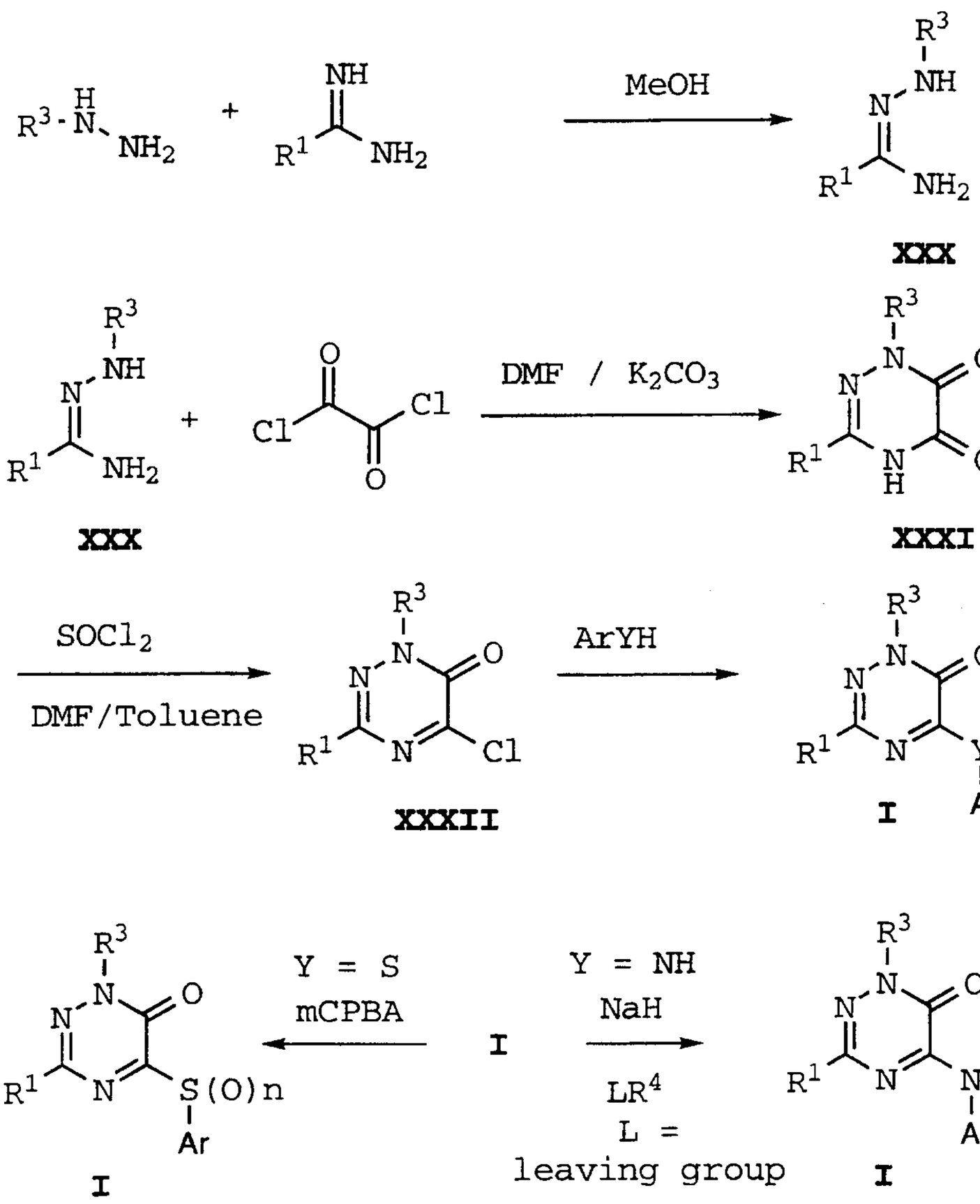
The compounds of Formula (I) where Z = CH and R^1 or R^3 is a functional group not compatible with the procedures of Schemes 1-5 may be prepared from precursors where the interfering functionality of R^1 or R^3 is protected using methods known to one skilled in the art (see T.W. Green and P.G.M. Wuts, *Protecting Groups in Organic Synthesis*, Wiley,

New York, 1991); or from precursors bearing R^1 or R^3 groups amenable to later conversion into the desired functionality using standard methods (see J. March, *Advanced Organic Chemistry*, Wiley, New York, 1992).

Triazinones of Formula (I) wherein Z = N and Y = NR^4, O or $S(O)_n$ can be prepared by the synthetic route shown in Scheme 6.

Condensation of a substituted hydrazine with acetamidines or imidates provides amidrazones of Formula (XXX) (Khrustalev, V. A., Zelenin, K. N. Zhurnal Organicheskoi Khimii, Vol. 15, No. 11, 1979, 2280). Cyclization of (XXX) with oxalyl derivatives such as oxalyl chloride provides diones of Formula (XXXI). Treatment of (XXXI) with chlorodehydrating agents such as thionyl chloride, oxalyl chloride or phosphorous oxychloride provides chlorotriazinones of Formula (XXXII), which may be treated with phenols, thiophenols, anilines and their heterocyclic analogs under basic, acidic or thermal conditions to provide compounds of Formula (I) where Z = N and Y = O, S or NH, respectively. In the preceding instance where Y = NH, alkylation of the nitrogen atom with e.g. alkyl iodides provides the related compounds of Formula (I) where Z = N and Y = NR^4. In the preceding instance where Y = S, oxidation with e.g. mCPBA provides the compounds of Formula (I) where Z = N and Y = S(O) and $S(O)_2$. The compounds of Formula (I) where Z = N and R^1 or R^3 is a functional group not compatible with the procedures of Scheme 4 may be prepared from precursors such as amidrazones of Formula (XXX) or substituted hydrazines where the

Scheme 6

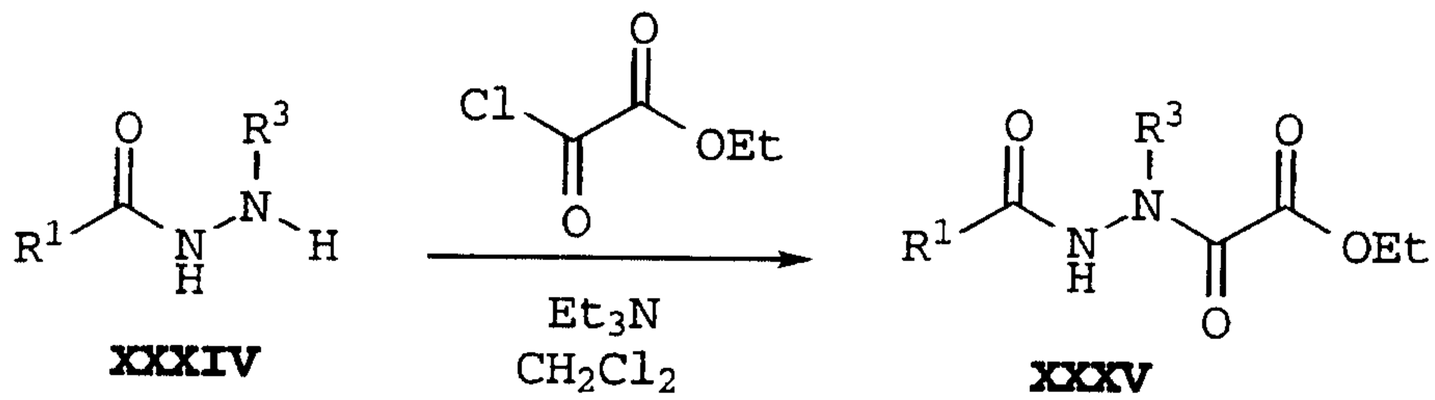


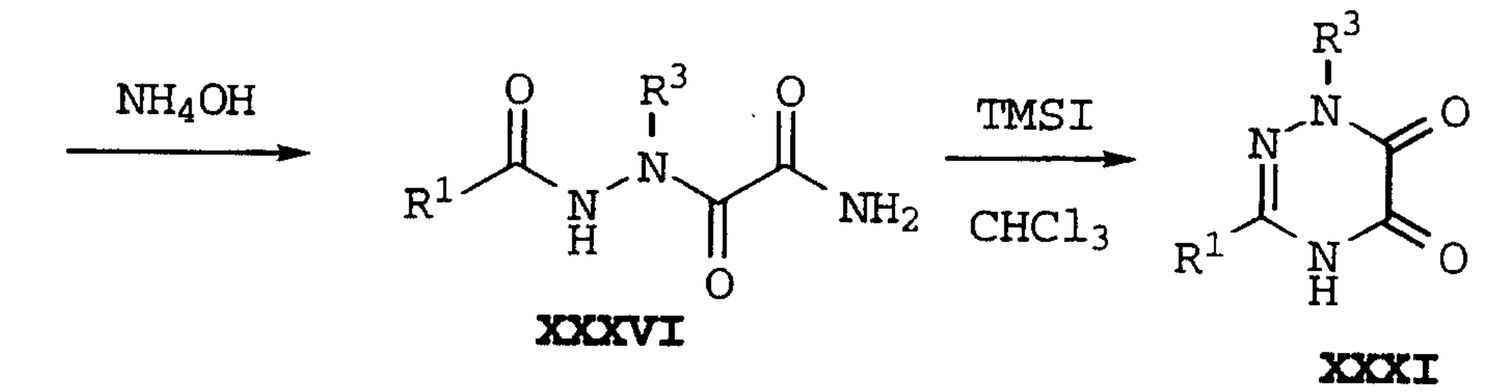
XXX XXXI XXXII I I I I

interfering functionality of R^1 or R^3 is protected using methods known to one skilled in the art (see T.W. Green and P.G.M. Wuts, *Protecting Groups in Organic Synthesis*, Wiley, New York, 1991); or from precursors bearing R^1 or R^3 groups amenable to later conversion into the desired functionality using standard methods (see J. March, *Advanced Organic Chemistry*, Wiley, New York, 1992).

Triazinones of Formula (I) wherein Z = N and Y = NR^4, O or $S(O)_n$ can also be prepared by the synthetic route shown in Scheme 7

Scheme 7





Reaction of ethyl oxalyl chloride with acylated hydrazines of Formula (XXXIV) provides the ethyl oxalyl acylhydrazine derviatives of Formula (XXXV). Compounds of Formula (XXXIV) may be arrived at via condensation of an appropriate ketone or aldehyde with an acylated hydrazide to give acylated hydrazones which may then be reduced under catalytic hydrogenation conditions or by other reducing agents to give the compounds of Formula (XXXIV). The abovementioned acylated hydrazones may also be produced by acylation of a hydrazone made from hydrazine and an appropriate ketone or aldehyde using methods known to one skilled in the art of organic synthesis. Alternatively, compounds of Formula (XXXIV) may also be produced by acylation of an appropriate hydrazine using methods known to one skilled in the art of organic synthesis.

The ethyl esters of compound (XXXV) may then be converted to the primary amide derivatives of Formula (XXXVI) by treatment with an ammonia source such as ammonium

hydroxide. Cyclization of (XXXVI) to produce the diones of Formula (XXXI) may be achieved by treatment with, for example, iodotrimethylsilane (TMSI) or $POCl_3$, or by heating in the presence of a Lewis acid such as $ZnCl_2$. The oxo group in the 5 position of the 1,2,4-triazin-5,6-diones of Formula (XXXI) may then be converted to a leaving group using reagents such as trifluoromethanesulfonic anhydride under basic conditions to yield compounds of Formula (XXXVII) which may then be treated with phenols, thiophenols, anilines and their heterocyclic analogs under basic conditions to provide compounds of Formula (I)

Additional 1,2,4-triazinone syntheses are disclosed in the literature (A. R. Katritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, New York, Vol. 3, 1984, p. 385) and can be prepared by one skilled in the art.

Intermediates, for example ArYH, H_2NAr, HOAr or HSAr, in the synthesis of compounds of Formula (I) in Schemes 1-6 may be prepared using standard methods known to one skilled in the art (see, D. Barton and W. D. Ollis, *Comprehensive Organic Chemistry*, Pergamon Press, New York, Vol. 1-6, 1979; A. R. Katritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, New York, Vol. 1-8, 1984; B. Trost and I. Fleming, *Comprehensive Organic Synthesis*, Pergamon Press, New York, Vol. 1-9, 1991; and DuPont Merck PCT application WO95/10506).

Example 1

3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

Part A: Hydrogen chloride (12M, aq., 3.8 mL), methanol (33 mL), water (30 mL), potassium cyanide (3 g), 1-ethylpropylamine (4 g), and formaldehyde (37% w/v, 3.7

mL) were stirred 18 hours at room temperature. Water (200 mL) was added, and the mixture was extracted with 2 x 200 mL methylene chloride, which was dried over MgSO4 and concentrated to a light oil (5.57 g). The oil was dissolved in ether and 1N HCl was added. The precipitate was collected on paper and dried to give N-(1-ethylpropyl)-aminoacetonitrile hydrochloride as an off-white solid (6.70g).

Part B: The product from part A (2 g), chloroform (20 mL), and oxalyl chloride (4.68 g) were heated at reflux for 12 hours. The reaction was concentrated to remove excess oxalyl chloride and solvent, and the crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent to afford 3,5-dichloro-1-(1-ethylpropyl)-2(1H)-pyrazinone as a white solid (2.09 g).

Part C: The product from part B (0.68 g) and 2-bromo-4-isopropylaniline (1.24g) were heated at 140°C for 5 hours. After cooling, methylene chloride (20 mL)was added, filtered, and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:9) as eluent to afford the title compound. 639 mg. mp 118.5 - 119.5°C. Elemental analysis: calcd. for $C_{18}H_{23}N_3OBrCl$: C, 52.38; H, 5.626; N, 10.18; Br, 19.36; Cl, 8.599. Found: C, 52.62; H, 5.43; N, 10.13; Br, 19.53; Cl, 8.97.

Example 2

3-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

The product from Example 1 (198 mg), N,N-dimethyl-formamide (5 mL), and sodium hydride (60% in oil, 96 mg) were stirred at room temperature 20 minutes. Iodoethane (112 mg) was added and the reaction was stirred overnight at room temperature and quenched with water (10 mL) and saturated sodium chloride (aq., 10 mL). The mixture was extracted with methylene chloride which was dried and

concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:19) as eluent to afford the title compound (125 mg). CI-HRMS calcd. for $C_{20}H_{28}N_3OClBr$ $(M+H)^+$: 440.110427. Found: 440.107480.

Example 3

3-[(2,4-Dibromophenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

2,4-Dibromoaniline (500 mg), toluene (8 mL), and sodium hydride (60% in oil, 398 mg) were stirred for 10 minutes at room temperature and then 3,5-dichloro-1-(1-ethylpropyl)-2(1H)-pyrazinone (468 mg, Example 1, part B) was added. The reaction was heated at reflux 3 hours, cooled, and quenched with water (50 mL). The mixture was extracted with ethyl acetate (100 mL), which was washed with brine, then dried and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:19) affording 400 mg of material, which was crystallized from ether/hexane to give the title compound (240 mg). Elemental analysis: calcd. for $C_{15}H_{16}N_3OClBr_2$: C, 40.07; H, 3.597; N, 9.356; Cl, 7.895; Br, 35.55. Found: C, 40.41; H, 3.49; N, 9.34; Cl, 8.27; Br, 35.71.

Example 4

3-[(2,4-Dibromophenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 2. Elemental analysis calcd. for $C_{17}H_{20}N_3OClBr_2$: C,42.75; H,4.22; N, 8.807. Found: C, 42.82; H, 4.14; N, 8.67.

Example 5

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{18}H_{24}N_3OCl$: C, 64.76; H, 7.256; N, 12.59. Found: C, 64.69; H, 7.03; N, 12.55.

Example 6

3-[(2,4,6-Trimethylphenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 2. Elemental analysis calcd. for $C_{20}H_{28}N_3OCl$: C, 66.37; H, 7.808; N, 11.61. Found: C, 66.50; H, 7.69; N, 11.51.

Example 7

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{18}H_{24}N_3O_2Cl$: C, 61.80; H, 6.91; N, 12.01; Cl, 10.13. Found: C, 61.69; H, 7.00; N, 11.93; Cl, 9.87.

Example 8

3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{17}H_{21}N_3O_3BrCl$: C, 47.40; H, 4.91; N, 9.765. Found: C, 47.06; H, 4.61; N, 9.56.

Example 9

3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

Part A: 3-[(2-Iodo-4,6-dimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone was prepared in a manner similar to Example 3.

Part B: The product from part A (460 mg), N,N-dimethylformamide (8 mL), cuprous cyanide (97 mg), and sodium cyanide were heated at 120°C for 18 hours and then at 130°C for 3 hours. After cooling, ethyl acetate (100 mL) was added to the reaction which was then washed with water (50 mL) and brine (50 mL), dried, and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent. The product was then crystallized from methylene chloride/hexane to afford the title compound (235 mg). Elemental analysis calcd. for $C_{18}H_{21}N_4OCl$: C, 62.69; H, 6.148; N, 16.25; Cl, 10.28. Found: C, 62.29; H, 6.27; N, 15.99; Cl, 10.20.

Example 10

(+/-)-3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{17}H_{21}N_3O_4BrCl$: C, 45.71; H, 4.748; N, 9.416. Found: C, 45.86; H, 4.43; N, 9.26.

Example 12

(+/-)-3-[(2-Iodo-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

Part A: Chloroacetonitrile (3.2 mL), 2-amino-1-methoxybutane (10.32 g), and deuterochloroform (50mL) were stirred and heated at reflux for 48 h. Methylene chloride (100 mL) and sodium hydroxide (aq., 1N, 100 mL) were added to the reaction, the layers separated, and the organic layer concentrated to an oil (3.4 g). The oil was dissolved in ether (100 mL) and HCl/ether (1N, 100 mL) was added. The precipitate was collected on paper affording N-

[(1-methoxymethyl)propyl]aminoacetonitrile hydrochloride (6.86 g).

Part B: The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{17}H_{21}N_3O_2ClI$: C, 44.22; H, 4.58; N, 9.10. Found: C, 44.26; H, 4.60; N, 9.83.

Example 15

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

To (+/-)-3,5-dichloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone (300 mg) and 4-bromo-2,6-dimethylaniline (238 mg) in THF (anhydrous, 9.4 mL) at 0°C was added sodium bis(trimethylsilyl)amide (1.0 M/THF, 2.6 mL). The mixture was stirred at 0°C for 10 minutes. Ethyl acetate (100mL) was added and washed with water (25 mL) and brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated and the crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent. The product was then crystallized from ethyl acetate/hexane to afford the title compound (419 mg). Elemental analysis calcd. for $C_{17}H_{21}N_3O_2BrCl$: C, 49.23; H, 5.10; N, 10.13. Found: C, 49.33; H, 5.05; N, 10.09.

Example 16

(+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

To the product of Example 15 (250 mg), bis(triphenylphosphine)palladium(II) chloride (11 mg), and tetrakis(triphenylphosphine)palladium(0) (17 mg) in a dry flask under nitrogen was added toluene (1.5 mL) and 1-ethoxyvinyl tributyl tin (260 mg). The reaction was heated at reflux 18 hours, and then concentrated *in vacuo*. The residue was taken up in ether (15 mL) and saturated aqueous potassium fluoride (15 mL), and filtered. The layers were

separated, and the ether layer was stirred with 1N HCl (aq., 15 mL). The layers were separated and the ether layer was dried over $MgSO_4$ and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (3:7) as eluent to afford the title compound (90 mg). Elemental analysis calcd. for $C_{19}H_{24}N_3O_3Cl$: C, 60.39; H, 6.40; N, 11.12. Found: C, 60.51; H, 6.31; N, 11.00.

Example 16a

(+/-)-3-[(4-Acetyl-2-methoxy-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 16. Elemental analysis calcd. for $C_{19}H_{24}N_3O_4Cl$: C, 57.94; H, 6.14; N, 10.67. Found: C, 57.70; H, 5.98; N, 10.41.

Example 20

(+/-)-3-[(4-Chloro-2-iodo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{16}H_{18}N_3O_2Cl_2I$: C, 39.86; H, 3.76; N, 8.725. Found: C, 40.00; H, 3.69; N, 8.64.

Example 21

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

Part A: To serinol (9.90 g) in DMF (200 mL) was added triethyl amine (14.6 mL) and then chlorotriphenylmethane (24.3 g). The reaction mixture was stirred at room temperature for 18 hours. Toluene (800 mL) was added and washed with water (500 mL and 250 mL) and brine (250 mL),

and then dried over K_2CO_3 and concentrated to dryness. The product was crytallized from benzene/hexane (1:1) to afford product (14.57 g).

Part B: The product from part A (14.57 g), sodium hydroxide (17.5 g), and iodomethane (8.8 mL) were stirred overnight in DMSO (220 mL) at room temperature. Water (500 mL) was added and extracted with ethyl acetate (3 X 250 mL). The extracts were washed with water (2 X 250 mL) and brine (200 mL), dried over K_2CO_3, and concentrated to give product (14.46 g).

Part C: The product from part B (14.46 g) and hydrogen chloride (1M/Et_2O, 84 mL) were stirred in methanol (300 mL) at room temperature for 6 hours. The solution was washed with hexane (3 X 300 mL), concentrated, and co-evaporated with ethanol affording 2-amino-1,3-methoxypropane (5.69 g).

Part D: The title compound was prepared in a manner similar the product of Example 3. Elemental analysis calcd. for $C_{18}H_{24}N_3O_3Cl$: C, 59.09; H, 6.61; N, 11.49. Found: C, 59.27; H, 6.53; N, 11.47.

Example 30a

(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 84. Elemental analysis calcd. for C18H24N3O2Cl: C, 61.80; H, 6.91; N, 12.01. Found: C, 61.70; H, 6.94; N, 11.56.

Example 36

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd.

for $C_{19}H_{26}N_3O_3Cl$: C, 60.07; H, 6.908; N, 11.06. Found: C, 60.22; H, 7.16; N, 10.92.

Example 36a

3-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{18}H_{23}N_3O_4ClBr$: C, 46.92; H, 5.03; N, 9.129. Found: C, 47.29; H, 5.03; N, 8.98.

Example 45a

3-[(2-Bromo-6-flouro-4-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{16}H_{18}N_3O_3FClBr$: C, 44.21; H, 4.17; N, 9.67. Found: C, 44.35; H, 4.25; N, 9.41.

Example 46a

3-[(2-Chloro-4-methoxy-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{17}H_{20}N_3O_4Cl_2$: C, 50.89; H, 5.02; N, 10.47. Found: C, 50.72; H, 5.33; N, 10.37.

Example 49

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{18}H_{23}N_3O_3ClBr$: C, 48.61; H, 5.21; N, 9.457. Found: C, 48.59; H, 5.32; N, 9.45.

Example 53

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{17}H_{21}N_3O_3ClBr$: C, 47.40; H, 4.91; N, 9.765. Found: C, 47.52; H, 4.99; N, 9.72.

Example 54

3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{17}H_{21}N_3O_3Cl_2$: C, 52.86; H, 5.489; N, 10.88. Found: C, 52.89; H, 5.44; N, 10.72.

Example 77

(+/-)-3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{18}H_{24}N_3O_2ClS$: C, 56.62; H, 6.33; N, 11.00; S, 8.405. Found: C, 56.66; H, 6.19; N, 10.89; S, 8.45.

Example 79

(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{17}H_{21}N_3O_2Cl_2$: C, 55.14; H, 5.726; N, 11.35. Found: C, 55.27; H, 5.70; N, 11.25.

Example 80

(+/-)-3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{17}H_{21}N_3O_3BrCl$: C, 47.40; H, 4.91; N, 9.765. Found: C, 47.91; H, 4.95; N, 9.74.

Example 81

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{18}H_{24}N_3O_3ClS$: C, 54.33; H, 6.08; N, 10.56; S, 8.06. Found: C, 54.48; H, 6.01; N, 10.46; S, 7.86.

Example 83

3-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for $C_{17}H_{21}N_3O_4ClBr$: C, 45.71; H, 4.748; N, 9.416. Found: C, 45.80; H, 4.70; N, 9.39.

Example 84

3-[(2,4,6-Trimethylphenyl)amino]-1-(1-ethylpropyl)-5-methyl-2(1H)-pyrazinone

Part A: N-(1-ethylpropyl)aminoacetonitrile hydrochloride (1.41 g) and oxalyl bromide (2.0 M/CH_2Cl_2, 13 mL) were heated at reflux for 18 hours. The reaction was concentrated to remove excess oxalyl bromide and solvent, and the crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent to afford 3,5-dibromo-1-(1-ethylpropyl)-2(1H)-pyrazinone as a white solid (1.19 g).

Part B: The product from part A (133 mg) and sodium thiomethoxide (29 mg) were combined in THF (1.5 mL) and stirred at 25 °C 4 hours. More sodium thiomethoxide (29 mg) was added and the reaction was stirred for 2 hours more at room temperature. Water (20 mL) was added and extracted with CH_2Cl_2 (2 X 20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexanes (1:4) as eluent to afford 5-bromo-1-(1-ethylpropyl)-3-thiomethyl-2(1H)-pyrazinone (78 mg).

Part C: The product from part B (200 mg) and $Pd(PPh_3)_2Cl_2$ (40 mg) were combined in dry THF (6 mL) under inert atmosphere (N_2). To that a 2M solution $AlMe_3$ in hexanes (0.5 mL) was added and the reaction was heated at reflux for one hour. The excess $AlMe_3$ was quenched with water at 0 °C and the mixture was partitioned between ethyl acetate (50 mL) and water (30 mL). The water was separated and extracted with ethyl acetate (50 mL), and the combined EtOAc extracts were washed with brine, dried ($MgSO_4$) and stripped *in vacuo*. The crude product was chromatographed on silica gel using ethyl acetate/hexanes as eluent (1:9) to give 1-(1-ethylpropyl)-5-methyl-3-thiomethyl-2(1H)-pyrazinone (100 mg).

Part D: The product from part B (50 mg) and 2,4,6-trimethylaniline (40 mg) were combined in dry THF (2 mL)

under inert atmosphere (N_2), and cooled to 0 °C. To that a 1M solution $NaN(SiMe_3)_2$ in THF (0.5 mL) was added dropwise and the reaction was stirred at 0 °C for 20 min. Then an additional $NaN(SiMe_3)_2$ in THF (0.3 mL) was added and the reaction was stirred at 0 °C for 30 min and at 25 °C for one hour. Then it was quenched with water (30 mL) and extracted with ethyl acetate (80 mL). The ethyl acetate was washed with brine, dried ($MgSO_4$) and stripped *in vacuo*. The crude product was chromatographed on silica gel using ethyl acetate/hexanes as eluent (1:9) to give 3-[(2,4,6-trimethylphenyl)amino]-1-(1-ethylpropyl)-5-methyl-2(1H)-pyrazinone (40 mg). mp. 109°C.

Example 84a

3-[(2-Chloro-4,6-dimethylphenyl)amino]-1-(1-ethylpropyl)-5-methyl-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 84. Elemental analysis calcd. for $C_{18}H_{24}N_3OCl$: C, 64.76; H, 7.256; N, 12.59. Found: C, 65.12; H, 7.28; N, 12.33.

Example 84b

3-[(2-Chloro-4-methoxy-6-methylphenyl)amino]-1-(1-ethylpropyl)-5-methyl-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 84. Elemental analysis calcd. for $C_{18}H_{24}N_3O_2Cl$: C, 61.80; H, 6.91; N, 12.01. Found: C, 61.72; H, 6.96; N, 11.83.

Example 84c

3-[(2,4,6-Trimethylphenyl)amino]-1-(1-ethylpropyl)-5-ethyl-2(1H)-pyrazinone

Part A: 5-bromo-1-(1-ethylpropyl)-3-thiomethyl-2(1H)-pyrazinone was prepared in a manner similar to Example 84, parts A and B.

Part B: To the product of part A (2.14 g) and bis(triphenylphosphine)palladium(II) chloride (258 mg) in anhydrous THF (60 mL) under inert atmosphere was added triethyl aluminum (1 M/THF, 14.7 mL). The reaction was heated at reflux 3 hours and then cooled and quenched with water. Ethyl Acetate (200 mL) was added and washed with water and saturated aqueous sodium chloride. The ethyl acetate was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed on silica gel using ethyl acetate/hexane (3:17) as eluent to afford 5-ethyl-1-(1-ethylpropyl)-3-thiomethyl-2(1H)-pyrazinone (809 mg).

Part C: The title compound was prepared in a manner similar to the product of Example 84 using the procuct from part B. Elemental analysis calcd. for $C_{20}H_{29}N_3O$: C, 73.36; H, 8.936; N, 12.83. Found: C, 73.01; H, 8.55; N, 12.69.

Example 84d

3-[(2-Chloro-4,6-dimethylphenyl)amino]-1-(1-ethylpropyl)-5-ethyl-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 84c. Elemental analysis calcd. for $C_{19}H_{26}N_3OCl$: C, 65.60; H, 7.53; N, 12.08. Found: C, 65.53; H, 7.33; N, 11.92.

Example 85

3-[(2,4,6-Trimethylphenyl)amino]-5-bromo-1-(1-ethylpropyl)-2(1H)-pyrazinone

Part A: N-(1-ethylpropyl)-aminoacetonitrile hydrochloride (1.41 g) and oxalyl bromide (2.0 M, CH_2Cl_2, 13 mL) were heated at reflux for 18 hours. The reaction was concentrated to remove excess oxalyl bromide and

solvent, and the crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent to afford 3,5-dibromo-1-(1-ethylpropyl)-2(1H)-pyrazinone as a white solid (1.19 g).

Part B: Using the product of part A, the title compound was prepared in a manner similar to the product of Example 3. MS m/z 378, $(m+H)^+$, 100%.

Example 204

5-[(2,4,6-Trimethylphenyl)amino]-3-methyl-1-(1-ethylpropyl)-1,2,4-triazine-6(1H)-one

Part A: 3-Pentanone (18.56 g, 0.215 mol), acetic hydrazide (14.8 g, 0.2 mol), and 200mL of absolute ethanol were placed in a 500mL flask. The reaction mixture was reluxed for 18hr and then evaporated to dryness to afford the desired hydrazone of suitable purity.

The hydrazone was then dissolved in 200mL of glacial acetic acid containing 1.0 g of PtO_2 and hydrogenated at 50 psi hydrogen pressure for 14 hr. The mixture was decanted from the catalyst and evaporated to dryness to afford 23.9 g of a colorless oil (83% yield for the two steps).

Part B: The 1-acetyl-2-(1-ethylpropyl)hydrazine product from Part A (23.9 g, 0.166 mol) was dissolved in CH_2Cl_2 (200mL) and to the stirring solution was added triethylamine (27.9 mL, 0.2 mol) and ethyl oxalyl chloride (19 mL, 0.17 mol). After stirring at room temperature for 3 hr, the reaction mixture was poured into water and the organic layer was separated, dried (Na_2SO_4), filtered and evaporated *in vacuo*. To the resultant oil was added ammonium hydroxide (250mL), THF (100mL), and ethanol (50mL). The flask containing the mixture was sealed with a rubber septum and stirred for 18 hr at room temperature. The mixture was then concentrated *in vacuo* until the reduced volume of solvent remaining was approximately 100mL, and a white precipitate had formed. The flask was then placed in the refrigerator for 1 hr. The precipitate was collected by

vacuum filtration and washed with small volumes of cold water. 26.3 g of a white solid was collected (73% yield). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.78 (s, 1H); 6.74 (br s, 1H); 5.6 (br s, 1H); 4.25 (m, 1H); 2.04 (s, 1H); 1.5 (m, 4H); 0.95 (t, 6H, J = 7.3 Hz).

Part C: The 1-oxamyl-1-(3-pentyl)-2-acetylhydrazine product from Part B (2 g, 9.3 mmol) was suspended in chloroform (50mL) and 2 mL of iodotrimethylsilane was added dropwise. The mixture was allowed to stir at room temperature for 12 hr. The reaction mixture was then partitioned between CH_2Cl_2 and 1N NaOH. The aqueous layer was separated and made acidic by addition of conc. HCl and then extracted with CH_2Cl_2. This organic layer was dried (Na_2SO_4), filtered and evaporated *in vacuo* to yield 1.2 g of an off-white solid of suitable purity (65% yield). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.85 (br s, 1H); 4.61 (m, 1H); 2.35 (s, 3H); 1.73 (m, 4H); 0.83 (t, 6H, J = 7.3 Hz).

Part D: To a solution of the triazine dione product from above (198 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added trifluoromethanesulfonic anhydride (0.19 mL, 1.1 mmol) and 2,4,6-collidine (0.15 mL, 1.1 mmol). The resulting reaction mixture was stirred at room temperature for 30 min., then 2,4,6-trimethylaniline (162 mg, 1.2 mmol) in 5 mL of THF was added followed by addition of 2,4,6-collidine (0.15 mL, 1.1 mmol). The resulting reaction mixture was stirred at room temperature for 1 hr, at which time TLC showed complete reaction. The reaction mixture was partitioned between water and CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel using EtOAc / hexane (1:9) to afford 260 mg of the title compound (83% yield). mp = 133 - 135°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.89 (br s, 1H); 6.94 (s, 2H); 4.72 (m, 1H); 2.31 (s, 3H); 2.19 (s, 9H); 1.9 - 1.7 (m, 4H); 0.85 (t, 6H, J = 7.32 Hz). Mass Spec. (NH_3-CI): Calc. (M+H)+ = 315, Obs. (M+H)+ = 315.

Example 703

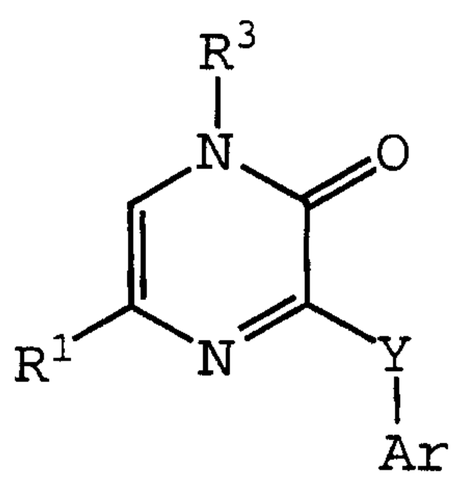
(+/-)-5-Chloro-1-[1-(methoxymethyl)propyl]-3-(2,4,6-trimethylphenoxy)-2(1H)-pyrazinone

Part A: (+/-)-3,5-dichloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone was prepared in a manner similar to Example 12, part A, and Example 1, part B.

Part B: 2,4,6-Trimethylphenol (59 mg) and potassium t-butoxide (48 mg) were added to pyridine (2 mL) at 0°C. The mixture was warmed to ambient temperature and (+/-)-3,5-dichloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone (98 mg) and copper (I) iodide (19 mg) were added. The reaction mixture was stirred at ambient temperature for three hours and then heated at reflux for three hours and then cooled to 0°C. Ethyl acetate (50 mL) and saturated ammonium chloride (50 mL) were added and the mixture was stirred overnight at ambient temperature. The layers were separated, and the organic layer was washed with 1M ammonium hydroxide (2 x 50 mL), 1N sodium hydroxide (2 x 50mL), 1N hydrochloric acid (2 x 50mL), and saturated sodium chloride (50 mL). The ethyl acetate was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent to afford the title compound (66 mg). mp = 116°C. Elemental analysis calcd. for $C_{18}H_{23}N_2O_3Cl$: C, 61.62; H, 6.618; N, 7.98. Found: C, 61.45; H, 6.44; N, 7.77.

Various analogs synthesized using Schemes 1, 2 and 3 are listed in Table 1.

Table 1



Ex No	R^1	R^3	Y	Ar	mp/°C
1	Cl	Et_2CH	NH	2-Br-4-iPr-phenyl	118.5
2	Cl	Et_2CH	NEt	2-Br-4-iPr-phenyl	MS = 440
3	Cl	Et_2CH	NH	2,4-Br_2-phenyl	155.5
4	Cl	Et_2CH	NEt	2,4-Br_2-phenyl	88.1
5	Cl	Et_2CH	NH	2,4,6-Me_3-phenyl	180.8
6	Cl	Et_2CH	NEt	2,4,6-Me_3-phenyl	93.8
7	Cl	$MeOCH_2(Et)CH$	NH	2,4,6-Me_3-phenyl	153.8
8	Cl	Et_2CH	NH	2-Br-4,6-$(MeO)_2$-phenyl	181.3
9	Cl	Et_2CH	NH	2-CN-4,6-Me_2-phenyl	174.0
10	Cl	$MeOCH_2(Et)CH$	NH	2-Br-4,6-$(MeO)_2$-phenyl	175.8
11	Cl	$MeOCH_2(Et)CH$	NH	2-Cl-4,6-$(MeO)_2$-phenyl	
12	Cl	$MeOCH_2(Et)CH$	NH	2-I-4,6-Me_2-phenyl	109.4
13	Cl	$MeOCH_2(Et)CH$	NH	2-CN-4,6-Me_2-phenyl	
14	Cl	$MeOCH_2(Et)CH$	NH	2-Br-4,6-Me_2-phenyl	
15	Cl	$MeOCH_2(Et)CH$	NH	4-Br-2,6-Me_2-phenyl	152.8
16	Cl	$MeOCH_2(Et)CH$	NH	4-MeCO-2,6-Me_2-phenyl	127.1
16a	Cl	$MeOCH_2(Et)CH$	NH	4-MeCO-2-OMe-6-Me-phenyl	179.8
17	Cl	$MeOCH_2(Et)CH$	NH	2-MeCO-4,6-Me_2-phenyl	
18	Cl	$MeOCH_2(Et)CH$	NH	4,6-Me_2-2-SMe-phenyl	

19	Cl	$MeOCH_2(Et)CH$	NH	$4,6\text{-}Me_2\text{-}2\text{-}SO_2Me$-phenyl	
20	Cl	$MeOCH_2(Et)CH$	NH	4-Cl-2-I-6-Me-phenyl	121.8
21	Cl	$(MeOCH_2)_2CH$	NH	$2,4,6\text{-}Me_3$-phenyl	127.2
22	Cl	phenyl	NH	$2,4,6\text{-}Me_3$-phenyl	
23	CN	$MeOCH_2(Et)CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
24	$CONH_2$	$MeOCH_2(Et)CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
25	COOH	$MeOCH_2(Et)CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
26	CHO	$MeOCH_2(Et)CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
27	CH_2OH	$MeOCH_2(Et)CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
28	CH_3	$MeOCH_2(Et)CH$	NH	$2,4\text{-}Br_2$-phenyl	
29	CH_3	$MeOCH_2(Et)CH$	NH	2-Br-4-iPr-phenyl	
30	CH_3	$MeOCH_2(Et)CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
30a	CH_3	$MeOCH_2(Et)CH$	NH	$2\text{-}Cl\text{-}4,6\text{-}Me_2$-phenyl	117.9
31	CH_3	$(MeOCH_2)_2CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
32	CH_3	$(MeOCH_2)_2CH$	NH	$2,4\text{-}Cl_2\text{-}6\text{-}Me$-phenyl	
33	Cl	$(MeOCH_2)_2CH$	NH	$2,4\text{-}Cl_2\text{-}6\text{-}Me$-phenyl	
34	Cl	$(MeOCH_2)_2CH$	NH	$2,4\text{-}Br_2\text{-}6\text{-}Me$-phenyl	
35	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
36	Cl	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4,6\text{-}Me_3$-phenyl	120.0
36a	Cl	$MeOC_2H_4(MeOCH_2)CH$	NH	4-Br-2-OMe-6-Me-phenyl	130.9
37	Cl	$(MeOC_2H_4)_2CH$	NH	$2,4,6\text{-}Me_3$-phenyl	
38	Cl	$MeOCH_2(Et)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeO$-phenyl	
39	Cl	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeO$-phenyl	
40	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeO$-phenyl	
41	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$4\text{-}Br\text{-}2,6\text{-}Me_2$-phenyl	
42	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2\text{-}Cl\text{-}4,6\text{-}Me_2$-phenyl	
43	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeOCH_2$-phenyl	
44	CH_3	$(MeOCH_2)_2CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeO$-phenyl	
45	CH_3	$(MeOCH_2)_2CH$	NH	$4\text{-}Br\text{-}2,6\text{-}Me_2$-phenyl	
45a	CH_3	$(MeOCH_2)_2CH$	NH	2-Br-6-F-4-Me-phenyl	138.9
46	CH_3	$(MeOCH_2)_2CH$	NH	$2\text{-}Cl\text{-}4,6\text{-}Me_2$-phenyl	
46a	CH_3	$(MeOCH_2)_2CH$	NH	2-Cl-4-OMe-6-Me-phenyl	128.3
47	CH_3	$(MeOCH_2)_2CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeOCH_2$-phenyl	

48	Cl	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeO\text{-}$phenyl	
49	Cl	$MeOC_2H_4(MeOCH_2)CH$	NH	$4\text{-}Br\text{-}2,6\text{-}Me_2\text{-}$phenyl	138.6
50	Cl	$MeOC_2H_4(MeOCH_2)CH$	NH	$2\text{-}Cl\text{-}4,6\text{-}Me_2\text{-}$phenyl	
51	Cl	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeOCH_2\text{-}$phenyl	
52	Cl	$(MeOCH_2)_2CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeO\text{-}$phenyl	
53	Cl	$(MeOCH_2)_2CH$	NH	$4\text{-}Br\text{-}2,6\text{-}Me_2\text{-}$phenyl	152.1
54	Cl	$(MeOCH_2)_2CH$	NH	$2\text{-}Cl\text{-}4,6\text{-}Me_2\text{-}$phenyl	132.8
55	Cl	$(MeOCH_2)_2CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeOCH_2\text{-}$phenyl	
56	Cl	$MeOCH_2(Me)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}MeO\text{-}$phenyl	
57	Cl	$MeOCH_2(Me)CH$	NH	$4\text{-}Br\text{-}2,6\text{-}Me_2\text{-}$phenyl	
58	Cl	$EtOCH_2(Et)CH$	NH	$4\text{-}Br\text{-}2,6\text{-}Me_2\text{-}$phenyl	
59	Cl	$EtOCH_2(Me)CH$	NH	$4\text{-}Br\text{-}2,6\text{-}Me_2\text{-}$phenyl	
60	Cl	$MeOCH_2(Et)CH$	NH	$4\text{-}Br\text{-}2,6\text{-}F_2\text{-}$phenyl	
61	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2\text{-}Br\text{-}4,6\text{-}Me_2\text{-}$phenyl	
62	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}SMe\text{-}$phenyl	
63	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4\text{-}Me_2\text{-}6\text{-}SO_2Me\text{-}$phenyl	
64	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$4\text{-}NMe_2\text{-}2,6\text{-}Me_2\text{-}$phenyl	
65	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,4\text{-}Cl_2\text{-}6\text{-}Me\text{-}$phenyl	
66	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$4\text{-}Cl\text{-}2,6\text{-}Me_2\text{-}$phenyl	
67	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,6\text{-}Me_2\text{-}4\text{-}SMe\text{-}$phenyl	
68	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,6\text{-}Me_2\text{-}4\text{-}OMe\text{-}$phenyl	
69	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$2,6\text{-}Me_2\text{-}4\text{-}SO_2Me\text{-}$phenyl	
70	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	$4\text{-}MeC(O)\text{-}2,6\text{-}Me_2\text{-}$phenyl	
71	CH_3	$(MeOCH_2)_2CH$	NH	$4\text{-}Br\text{-}2,6\text{-}Me_2\text{-}$phenyl	
72	CH_3	$(MeOCH_2)_2CH$	NH	$4\text{-}MeC(O)\text{-}2,6\text{-}Me_2\text{-}$phenyl	
73	CH_3	$(MeOCH_2)_2CH$	NH	$2,6\text{-}Me_2\text{-}4\text{-}SMe\text{-}$phenyl	
74	CH_3	$(MeOCH_2)_2CH$	NH	$2,6\text{-}Me_2\text{-}4\text{-}SO_2Me\text{-}$phenyl	
75	CH_3	$(MeOCH_2)_2CH$	NH	$4\text{-}NMe_2\text{-}2,6\text{-}Me_2\text{-}$phenyl	
76	CH_3	$(MeOCH_2)_2CH$	NH	$2\text{-}NMe_2\text{-}4,6\text{-}Me_2\text{-}$phenyl	
77	Cl	$MeOCH_2(Et)CH$	NH	$2,6\text{-}Me_2\text{-}4\text{-}SMe\text{-}$phenyl	104.9
78	Cl	$MeOCH_2(Et)CH$	NH	$2,6\text{-}Me_2\text{-}4\text{-}SO_2Me\text{-}$phenyl	

79	Cl	$MeOCH_2(Et)CH$	NH	2-Cl-4,6-Me_2-phenyl	116.7
80	Cl	$MeOCH_2(Et)CH$	NH	4-Br-6-OMe-2-Me-phenyl	147.8
81	Cl	$(MeOCH_2)_2CH$	NH	2,6-Me_2-4-SMe-phenyl	158.9
82	Cl	$(MeOCH_2)_2CH$	NH	2,6-Me_2-4-SO_2Me-phenyl	
83	Cl	$(MeOCH_2)_2CH$	NH	4-Br-6-OMe-2-Me-phenyl	175.5
84	CH_3	Et_2CH	NH	2,4,6-Me_3-phenyl	109
84a	CH_3	Et_2CH	NH	2-Cl-4,6-Me_2-phenyl	133.8
84b	CH_3	Et_2CH	NH	2-Cl-4-OMe-6-Me-phenyl	121.9
84c	CH_2CH_3	Et_2CH	NH	2,4,6-Me_3-phenyl	79.3
84d	CH_2CH_3	Et_2CH	NH	2-Cl-4,6-Me_2-phenyl	95.6
85	Br	Et_2CH	NH	2,4,6-Me_3-phenyl	MS = 378
86	Br	Et_2CH	NH	2-Br-4-iPr-phenyl	
87	Br	Et_2CH	NEt	2-Br-4-iPr-phenyl	
88	Br	Et_2CH	NH	2,4-Br_2-phenyl	
89	Br	Et_2CH	NEt	2,4-Br_2-phenyl	
90	Br	Et_2CH	NEt	2,4,6-Me_3-phenyl	
91	Br	Et_2CH	NEt	2,4,6-Me_3-phenyl	
92	Br	$MeOCH_2(Et)CH$	NH	2,4,6-Me_3-phenyl	
93	Br	Et_2CH	NH	2-Br-4,6-$(MeO)_2$-phenyl	
94	Br	Et_2CH	NH	2-CN-4,6-Me_2-phenyl	
95	Br	$MeOCH_2(Et)CH$	NH	2-Br-4,6-$(MeO)_2$-phenyl	
96	Br	$MeOCH_2(Et)CH$	NH	2-I-4,6-Me_2-phenyl	
97	Br	$MeOCH_2(Et)CH$	NH	2,6-Me_2-4-Br-phenyl	
98	Br	$MeOCH_2(Et)CH$	NH	2-I-4-Cl-6-Me-phenyl	
99	Br	$(MeOCH_2)_2CH$	NH	2,4,6-Me_3-phenyl	
100	Br	$MeOCH_2(Et)CH$	NH	2,6-Me_2-4-SMe-phenyl	
101	Br	$MeOCH_2(Et)CH$	NH	2,6-Me_2-4-SO_2Me-phenyl	
102	Br	$MeOCH_2(Et)CH$	NH	2-Cl-4,6-Me_2-phenyl	
103	Br	$MeOCH_2(Et)CH$	NH	2-Me-4-Br-6-OMe-phenyl	
104	CH_3	Et_2CH	NH	2,4,6-Me_3-pyrid-3-yl	
105	CH_3	Et_2CH	NH	4,6-Me_2-pyrid-3-yl	
106	CH_3	Et_2CH	NH	2-Br-6-Me-pyrid-3-yl	

107	CH_3	Et_2CH	NH	2-Br-6-OMe-pyrid-3-yl
108	CH_3	Et_2CH	NH	2,6-Me_2-pyrid-3-yl
109	CH_3	Et_2CH	NH	2-Cl-6-Me-pyrid-3-yl
110	CH_3	Et_2CH	NH	2-Cl-6-OMe-pyrid-3-yl
111	CH_3	$MeOCH_2(Et)CH$	NH	2,4,6-Me_3-pyrid-3-yl
112	CH_3	$MeOCH_2(Et)CH$	NH	4,6-Me_2-pyrid-3-yl
113	CH_3	$MeOCH_2(Et)CH$	NH	2-Br-6-Me-pyrid-3-yl
114	CH_3	$(MeOCH_2)_2CH$	NH	2-Br-6-OMe-pyrid-3-yl
115	CH_3	$(MeOCH_2)_2CH$	NH	2,6-Me_2-pyrid-3-yl
116	CH_3	$(MeOCH_2)_2CH$	NH	2-Cl-6-Me-pyrid-3-yl
117	CH_3	$(MeOCH_2)_2CH$	NH	2-Cl-6-OMe-pyrid-3-yl
118	CH_3	$MeOCH_2(Et)CH$	NH	2-Br-6-OMe-pyrid-3-yl
119	CH_3	$MeOCH_2(Et)CH$	NH	2,6-Me_2-pyrid-3-yl
120	CH_3	$MeOCH_2(Et)CH$	NH	2-Cl-6-Me-pyrid-3-yl
121	CH_3	$MeOCH_2(Et)CH$	NH	2-Cl-6-OMe-pyrid-3-yl
120	CH_3	$(MeOCH_2)_2CH$	NH	2,4,6-Me_3-pyrid-3-yl
123	CH_3	$(MeOCH_2)_2CH$	NH	4,6-Me_2-pyrid-3-yl
124	CH_3	$(MeOCH_2)_2CH$	NH	2-Br-6-Me-pyrid-3-yl
125	Cl	Et_2CH	NH	2-Br-6-OMe-pyrid-3-yl
124	Cl	Et_2CH	NH	2,6-Me_2-pyrid-3-yl
127	Cl	Et_2CH	NH	2-Cl-6-Me-pyrid-3-yl
128	Cl	Et_2CH	NH	2-Cl-6-OMe-pyrid-3-yl
129	Cl	$MeOCH_2(Et)CH$	NH	2,4,6-Me_3-pyrid-3-yl
130	Cl	$MeOCH_2(Et)CH$	NH	4,6-Me_2-pyrid-3-yl
131	Cl	$MeOCH_2(Et)CH$	NH	2-Br-6-Me-pyrid-3-yl
132	Cl	Et_2CH	NH	2,4,6-Me_3-pyrid-3-yl
133	Cl	Et_2CH	NH	4,6-Me_2-pyrid-3-yl
134	Cl	Et_2CH	NH	2-Br-6-Me-pyrid-3-yl
135	Cl	$MeOCH_2(Et)CH$	NH	2-Br-6-OMe-pyrid-3-yl
136	Cl	$MeOCH_2(Et)CH$	NH	2,6-Me_2-pyrid-3-yl
137	Cl	$MeOCH_2(Et)CH$	NH	2-Cl-6-Me-pyrid-3-yl
138	Cl	$MeOCH_2(Et)CH$	NH	2-Cl-6-OMe-pyrid-3-yl
139	Cl	$(MeOCH_2)_2CH$	NH	2-Br-6-OMe-pyrid-3-yl
140	Cl	$(MeOCH_2)_2CH$	NH	2,6-Me_2-pyrid-3-yl
141	Cl	$(MeOCH_2)_2CH$	NH	2-Cl-6-Me-pyrid-3-yl
142	Cl	$(MeOCH_2)_2CH$	NH	2-Cl-6-OMe-pyrid-3-yl
143	Cl	$(MeOCH_2)_2CH$	NH	2,4,6-Me_3-pyrid-3-yl

144	Cl	$(MeOCH_2)_2CH$	NH	4,6-Me_2-pyrid-3-yl
145	Cl	$(MeOCH_2)_2CH$	NH	2-Br-6-Me-pyrid-3-yl
146	Et_2CH	CH_3	NH	2,4,6-Me_3-phenyl
147	Et_2CH	CH_3	NH	2,6-Me_2-4-Br-phenyl
148	Et_2CH	CH_3	NH	2-Br-4-iPr-phenyl
149	$MeOCH_2(Et)CH$	CH_3	NH	2,4,6-Me_3-phenyl
150	$MeOCH_2(Et)CH$	CH_3	NH	2,6-Me_2-4-Br-phenyl
151	$MeOCH_2(Et)CH$	CH_3	NH	2-Cl-4,6-Me_2-phenyl
152	$(MeOCH_2)_2CH$	CH_3	NH	2,4,6-Me_3-phenyl
153	$(MeOCH_2)_2CH$	CH_3	NH	2,6-Me_2-4-Br-phenyl
154	$(MeOCH_2)_2CH$	CH_3	NH	2-Cl-4,6-Me_2-phenyl
155	Et_2CH	CH_3	NH	2-Br-4,6-$(MeO)_2$-phenyl
156	Et_2CH	CH_3	NH	2-Cl-4,6-Me_2-phenyl
400	CH_3	Me(Et)CH	NH	2,4,6-Me_3-phenyl
401	CH_3	Me(Et)CH	NH	2-Cl-4,6-Me_2-phenyl
402	CH_3	Me(Et)CH	NH	2,4-Cl_2-6-Me-phenyl
403	CH_3	Me(Et)CH	NH	2,4,6-Cl_3-phenyl
404	CH_3	Me(Et)CH	NH	2-Me-4-MeO-phenyl
405	CH_3	Me(Et)CH	NH	2-Cl-4-MeO-phenyl
406	CH_3	Me(Et)CH	NH	2,4,6-Me_3-5-F-phenyl
407	CH_3	Me(Et)CH	NH	2,5-Me_2-4-MeO-phenyl
408	CH_3	Me(Et)CH	NH	2,4-Me_2-6-MeO-phenyl
409	CH_3	Me(Et)CH	NH	2,6-Cl_2-4-Me-phenyl
410	CH_3	Me(Et)CH	NH	2,4-Cl_2-phenyl
411	CH_3	Me(Et)CH	NH	2-Cl-4-Me-phenyl
412	CH_3	Me(Et)CH	NH	2-Me-4-Cl-phenyl
413	CH_3	Me(Et)CH	NH	2-NMe_2-6-Me-pyrid-5-yl
414	CH_3	Me(Et)CH	NH	2-NMe_2-4-Me-pyrid-5-yl
415	CH_3	Me(Et)CH	NH	2-Cl-4-MeO-6-Me-phenyl
416	CH_3	Me(Et)CH	NH	2-Cl-4,6-Me_2-5-F-phenyl
417	CH_3	Me(Et)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
418	CH_3	Me(Et)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl

419	CH_3	Me(n-Pr)CH	NH	2,4,6-Me_3-phenyl
420	CH_3	Me(n-Pr)CH	NH	2-Cl-4,6-Me_2-phenyl
421	CH_3	Me(n-Pr)CH	NH	2,4-Cl_2-6-Me-phenyl
422	CH_3	Me(n-Pr)CH	NH	2,4,6-Cl_3-phenyl
423	CH_3	Me(n-Pr)CH	NH	2-Me-4-MeO-phenyl
424	CH_3	Me(n-Pr)CH	NH	2-Cl-4-MeO-phenyl
425	CH_3	Me(n-Pr)CH	NH	2,4,6-Me_3-5-F-phenyl
426	CH_3	Me(n-Pr)CH	NH	2,5-Me_2-4-MeO-phenyl
427	CH_3	Me(n-Pr)CH	NH	2,4-Me_2-6-MeO-phenyl
428	CH_3	Me(n-Pr)CH	NH	2,6-Cl_2-4-Me-phenyl
429	CH_3	Me(n-Pr)CH	NH	2,4-Cl_2-phenyl
430	CH_3	Me(n-Pr)CH	NH	2-Cl-4-Me-phenyl
431	CH_3	Me(n-Pr)CH	NH	2-Me-4-Cl-phenyl
432	CH_3	Me(n-Pr)CH	NH	2-NMe_2-6-Me-pyrid-5-yl
433	CH_3	Me(n-Pr)CH	NH	2-NMe_2-4-Me-pyrid-5-yl
434	CH_3	Me(n-Pr)CH	NH	2-Cl-4-MeO-6-Me-phenyl
435	CH_3	Me(n-Pr)CH	NH	2-Cl-4,6-Me_2-5-F-phenyl
436	CH_3	Me(n-Pr)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
437	CH_3	Me(n-Pr)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
438	CH_3	Et_2CH	NH	2,4-Cl_2-6-Me-phenyl
439	CH_3	Et_2CH	NH	2,4,6-Cl_3-phenyl
440	CH_3	Et_2CH	NH	2-Me-4-MeO-phenyl
441	CH_3	Et_2CH	NH	2-Cl-4-MeO-phenyl
442	CH_3	Et_2CH	NH	2,4,6-Me_3-5-F-phenyl
443	CH_3	Et_2CH	NH	2,5-Me_2-4-MeO-phenyl
444	CH_3	Et_2CH	NH	2,4-Me_2-6-MeO-phenyl
445	CH_3	Et_2CH	NH	2,6-Cl_2-4-Me-phenyl
446	CH_3	Et_2CH	NH	2,4-Cl_2-phenyl
447	CH_3	Et_2CH	NH	2-Cl-4-Me-phenyl
448	CH_3	Et_2CH	NH	2-Me-4-Cl-phenyl
449	CH_3	Et_2CH	NH	2-NMe_2-6-Me-pyrid-5-yl
450	CH_3	Et_2CH	NH	2-NMe_2-4-Me-pyrid-5-yl
451	CH_3	Et_2CH	NH	2-Cl-4,6-Me_2-5-F-phenyl

452	CH_3	Et_2CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
453	CH_3	Et_2CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
454	CH_3	$(c\text{-}Pr)_2CH$	NH	2,4,6-Me_3-phenyl
455	CH_3	$(c\text{-}Pr)_2CH$	NH	2-Cl-4,6-Me_2-phenyl
456	CH_3	$(c\text{-}Pr)_2CH$	NH	2,4-Cl_2-6-Me-phenyl
457	CH_3	$(c\text{-}Pr)_2CH$	NH	2,4,6-Cl_3-phenyl
458	CH_3	$(c\text{-}Pr)_2CH$	NH	2-Me-4-MeO-phenyl
459	CH_3	$(c\text{-}Pr)_2CH$	NH	2-Cl-4-MeO-phenyl
460	CH_3	$(c\text{-}Pr)_2CH$	NH	2,4,6-Me_3-5-F-phenyl
461	CH_3	$(c\text{-}Pr)_2CH$	NH	2,5-Me_2-4-MeO-phenyl
462	CH_3	$(c\text{-}Pr)_2CH$	NH	2,4-Me_2-6-MeO-phenyl
463	CH_3	$(c\text{-}Pr)_2CH$	NH	2,6-Cl_2-4-Me-phenyl
464	CH_3	$(c\text{-}Pr)_2CH$	NH	2,4-Cl_2-phenyl
465	CH_3	$(c\text{-}Pr)_2CH$	NH	2-Cl-4-Me-phenyl
466	CH_3	$(c\text{-}Pr)_2CH$	NH	2-Me-4-Cl-phenyl
467	CH_3	$(c\text{-}Pr)_2CH$	NH	2-NMe_2-6-Me-pyrid-5-yl
468	CH_3	$(c\text{-}Pr)_2CH$	NH	2-NMe_2-4-Me-pyrid-5-yl
469	CH_3	$(c\text{-}Pr)_2CH$	NH	2-Cl-4-MeO-6-Me-phenyl
470	CH_3	$(c\text{-}Pr)_2CH$	NH	2-Cl-4,6-Me_2-5-F-phenyl
471	CH_3	$(c\text{-}Pr)_2CH$	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
472	CH_3	$(c\text{-}Pr)_2CH$	NH	6-Me-2,3-dihydro-benzofuran-5-yl
473	CH_3	c-Pr(Me)CH	NH	2,4,6-Me_3-phenyl
474	CH_3	c-Pr(Me)CH	NH	2-Cl-4,6-Me_2-phenyl
475	CH_3	c-Pr(Me)CH	NH	2,4-Cl_2-6-Me-phenyl
476	CH_3	c-Pr(Me)CH	NH	2,4,6-Cl_3-phenyl
477	CH_3	c-Pr(Me)CH	NH	2-Me-4-MeO-phenyl
478	CH_3	c-Pr(Me)CH	NH	2-Cl-4-MeO-phenyl
479	CH_3	c-Pr(Me)CH	NH	2,4,6-Me_3-5-F-phenyl
480	CH_3	c-Pr(Me)CH	NH	2,5-Me_2-4-MeO-phenyl
481	CH_3	c-Pr(Me)CH	NH	2,4-Me_2-6-MeO-phenyl
482	CH_3	c-Pr(Me)CH	NH	2,6-Cl_2-4-Me-phenyl
483	CH_3	c-Pr(Me)CH	NH	2,4-Cl_2-phenyl

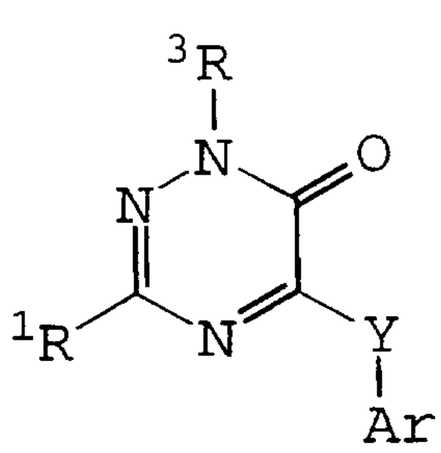
484	CH_3	c-Pr(Me)CH	NH	2-Cl-4-Me-phenyl
485	CH_3	c-Pr(Me)CH	NH	2-Me-4-Cl-phenyl
486	CH_3	c-Pr(Me)CH	NH	2-NMe_2-6-Me-pyrid-5-yl
487	CH_3	c-Pr(Me)CH	NH	2-NMe_2-4-Me-pyrid-5-yl
488	CH_3	c-Pr(Me)CH	NH	2-Cl-4-MeO-6-Me-phenyl
489	CH_3	c-Pr(Me)CH	NH	2-Cl-4,6-Me_2-5-F-phenyl
490	CH_3	c-Pr(Me)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
491	CH_3	c-Pr(Me)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
492	CH_3	c-Pr(Et)CH	NH	2,4,6-Me_3-phenyl
493	CH_3	c-Pr(Et)CH	NH	2-Cl-4,6-Me_2-phenyl
494	CH_3	c-Pr(Et)CH	NH	2,4-Cl_2-6-Me-phenyl
495	CH_3	c-Pr(Et)CH	NH	2,4,6-Cl_3-phenyl
496	CH_3	c-Pr(Et)CH	NH	2-Me-4-MeO-phenyl
497	CH_3	c-Pr(Et)CH	NH	2-Cl-4-MeO-phenyl
498	CH_3	c-Pr(Et)CH	NH	2,4,6-Me_3-5-F-phenyl
499	CH_3	c-Pr(Et)CH	NH	2,5-Me_2-4-MeO-phenyl
500	CH_3	c-Pr(Et)CH	NH	2,4-Me_2-6-MeO-phenyl
501	CH_3	c-Pr(Et)CH	NH	2,6-Cl_2-4-Me-phenyl
502	CH_3	c-Pr(Et)CH	NH	2,4-Cl_2-phenyl
503	CH_3	c-Pr(Et)CH	NH	2-Cl-4-Me-phenyl
504	CH_3	c-Pr(Et)CH	NH	2-Me-4-Cl-phenyl
505	CH_3	c-Pr(Et)CH	NH	2-NMe_2-6-Me-pyrid-5-yl
506	CH_3	c-Pr(Et)CH	NH	2-NMe_2-4-Me-pyrid-5-yl
507	CH_3	c-Pr(Et)CH	NH	2-Cl-4-MeO-6-Me-phenyl
508	CH_3	c-Pr(Et)CH	NH	2-Cl-4,6-Me_2-5-F-phenyl
509	CH_3	c-Pr(Et)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
510	CH_3	c-Pr(Et)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
511	CH_3	c-Pr(n-Pr)CH	NH	2,4,6-Me_3-phenyl
512	CH_3	c-Pr(n-Pr)CH	NH	2-Cl-4,6-Me_2-phenyl
513	CH_3	c-Pr(n-Pr)CH	NH	2,4-Cl_2-6-Me-phenyl
514	CH_3	c-Pr(n-Pr)CH	NH	2,4,6-Cl_3-phenyl

515	CH_3	c-Pr(n-Pr)CH	NH	2-Me-4-MeO-phenyl
516	CH_3	c-Pr(n-Pr)CH	NH	2-Cl-4-MeO-phenyl
517	CH_3	c-Pr(n-Pr)CH	NH	2,4,6-Me_3-5-F-phenyl
518	CH_3	c-Pr(n-Pr)CH	NH	2,5-Me_2-4-MeO-phenyl
519	CH_3	c-Pr(n-Pr)CH	NH	2,4-Me_2-6-MeO-phenyl
520	CH_3	c-Pr(n-Pr)CH	NH	2,6-Cl_2-4-Me-phenyl
521	CH_3	c-Pr(n-Pr)CH	NH	2,4-Cl_2-phenyl
522	CH_3	c-Pr(n-Pr)CH	NH	2-Cl-4-Me-phenyl
523	CH_3	c-Pr(n-Pr)CH	NH	2-Me-4-Cl-phenyl
524	CH_3	c-Pr(n-Pr)CH	NH	2-NMe_2-6-Me-pyrid-5-yl
525	CH_3	c-Pr(n-Pr)CH	NH	2-NMe_2-4-Me-pyrid-5-yl
526	CH_3	c-Pr(n-Pr)CH	NH	2-Cl-4-MeO-6-Me-phenyl
527	CH_3	c-Pr(n-Pr)CH	NH	2-Cl-4,6-Me_2-5-F-phenyl
528	CH_3	c-Pr(n-Pr)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
529	CH_3	c-Pr(n-Pr)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
530	CH_3	c-Pr(n-Bu)CH	NH	2,4,6-Me_3-phenyl
531	CH_3	c-Pr(n-Bu)CH	NH	2-Cl-4,6-Me_2-phenyl
532	CH_3	c-Pr(n-Bu)CH	NH	2,4-Cl_2-6-Me-phenyl
533	CH_3	c-Pr(n-Bu)CH	NH	2,4,6-Cl_3-phenyl
534	CH_3	c-Pr(n-Bu)CH	NH	2-Me-4-MeO-phenyl
535	CH_3	c-Pr(n-Bu)CH	NH	2-Cl-4-MeO-phenyl
536	CH_3	c-Pr(n-Bu)CH	NH	2,4,6-Me_3-5-F-phenyl
537	CH_3	c-Pr(n-Bu)CH	NH	2,5-Me_2-4-MeO-phenyl
538	CH_3	c-Pr(n-Bu)CH	NH	2,4-Me_2-6-MeO-phenyl
539	CH_3	c-Pr(n-Bu)CH	NH	2,6-Cl_2-4-Me-phenyl
540	CH_3	c-Pr(n-Bu)CH	NH	2,4-Cl_2-phenyl
541	CH_3	c-Pr(n-Bu)CH	NH	2-Cl-4-Me-phenyl
542	CH_3	c-Pr(n-Bu)CH	NH	2-Me-4-Cl-phenyl
543	CH_3	c-Pr(n-Bu)CH	NH	2-NMe_2-6-Me-pyrid-5-yl
544	CH_3	c-Pr(n-Bu)CH	NH	2-NMe_2-4-Me-pyrid-5-yl
545	CH_3	c-Pr(n-Bu)CH	NH	2-Cl-4-MeO-6-Me-phenyl
546	CH_3	c-Pr(n-Bu)CH	NH	2-Cl-4,6-Me_2-5-F-phenyl

547	CH_3	c-Pr(n-Bu)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
548	CH_3	c-Pr(n-Bu)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
549	CH_3	c-PrCH_2(Et)CH	NH	2,4,6-Me_3-phenyl
550	CH_3	c-PrCH_2(Et)CH	NH	2-Cl-4,6-Me_2-phenyl
551	CH_3	c-PrCH_2(Et)CH	NH	2,4-Cl_2-6-Me-phenyl
552	CH_3	c-PrCH_2(Et)CH	NH	2,4,6-Cl_3-phenyl
553	CH_3	c-PrCH_2(Et)CH	NH	2-Me-4-MeO-phenyl
554	CH_3	c-PrCH_2(Et)CH	NH	2-Cl-4-MeO-phenyl
555	CH_3	c-PrCH_2(Et)CH	NH	2,4,6-Me_3-5-F-phenyl
556	CH_3	c-PrCH_2(Et)CH	NH	2,5-Me_2-4-MeO-phenyl
557	CH_3	c-PrCH_2(Et)CH	NH	2,4-Me_2-6-MeO-phenyl
558	CH_3	c-PrCH_2(Et)CH	NH	2,6-Cl_2-4-Me-phenyl
559	CH_3	c-PrCH_2(Et)CH	NH	2,4-Cl_2-phenyl
560	CH_3	c-PrCH_2(Et)CH	NH	2-Cl-4-Me-phenyl
561	CH_3	c-PrCH_2(Et)CH	NH	2-Me-4-Cl-phenyl
562	CH_3	c-PrCH_2(Et)CH	NH	2-NMe_2-6-Me-pyrid-5-yl
563	CH_3	c-PrCH_2(Et)CH	NH	2-NMe_2-4-Me-pyrid-5-yl
564	CH_3	c-PrCH_2(Et)CH	NH	2-Cl-4-MeO-6-Me-phenyl
565	CH_3	c-PrCH_2(Et)CH	NH	2-Cl-4,6-Me_2-5-F-phenyl
566	CH_3	c-PrCH_2(Et)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
567	CH_3	c-PrCH_2(Et)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl

Compounds that can be synthesized using synthetic Scheme 6 or Scheme 7 are listed in Table 2

Table 2



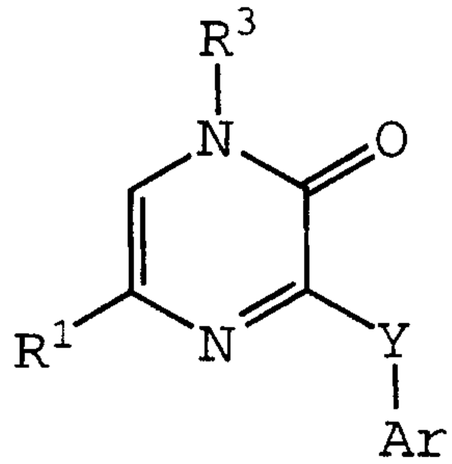
Ex. No.	R^1	R^3	Y	Ar	mp
200	CH_3	Et_2CH	NH	2,4-Br_2-phenyl	
201	CH_3	Et_2CH	NH	2-Br-4-iPr-phenyl	
202	CH_3	Et_2CH	NEt	2,4-Br_2-phenyl	
203	CH_3	Et_2CH	NEt	2-Br-4-iPr-phenyl	
204	CH_3	Et_2CH	NH	2,4,6-Me_3-phenyl	133
205	CH_3	Et_2CH	NEt	2,4,6-Me_3-phenyl	
206	CH_3	$MeOCH_2(Et)CH$	NH	2,4,6-Me_3-phenyl	
207	CH_3	Et_2CH	NH	2-Br-4,6-$(MeO)_2$-phenyl	
208	CH_3	$MeOCH_2(Et)CH$	NH	2-Br-4,6-$(MeO)_2$-phenyl	
209	CH_3	$MeOCH_2(Et)CH$	NH	2-Cl-4,6-$(MeO)_2$-phenyl	
210	CH_3	$MeOCH_2(Et)CH$	NH	2,4-Me_2-6-I-phenyl	
211	CH_3	$MeOCH_2(Et)CH$	NH	2-CN-4,6-Me_2-phenyl	
212	CH_3	$MeOCH_2(Et)CH$	NH	2-Br-4,6-Me_2-phenyl	
213	CH_3	$MeOCH_2(Et)CH$	NH	4-Br-2,6-Me_2-phenyl	
214	CH_3	$MeOCH_2(Et)CH$	NH	4-MeC(O)-2,6-Me_2-phenyl	
215	CH_3	$MeOCH_2(Et)CH$	NH	2-MeC(O)-4,6-Me_2-phenyl	
216	CH_3	$MeOCH_2(Et)CH$	NH	2,4-Me_2-6-SMe-phenyl	
217	CH_3	$MeOCH_2(Et)CH$	NH	2,4-Me_2-6-SO_2Me-phenyl	
218	CH_3	$MeOCH_2(Et)CH$	NH	4-Cl-2-I-6-Me-phenyl	
219	CH_3	$(MeOCH_2)_2CH$	NH	2,4,6-Me_3-phenyl	
220	CH_3	Et_2CH	NH	2,4,6-Me_3-phenyl	
221	CH_3	$(MeOCH_2)_2CH$	NH	2,4-Cl_2-6-Me-phenyl	
222	CH_3	$(MeOCH_2)_2CH$	NH	2,4-Br_2-6-Me-phenyl	
223	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	2,4,6-Me_3-phenyl	

224	CH_3	$(MeOC_2H_4)_2CH$	NH	2,4,6-Me_3-phenyl
225	CH_3	$MeOCH_2(Et)CH$	NH	2,4-Me_2-6-MeO-phenyl
226	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	2,4-Me_2-6-MeO-phenyl
227	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	2-Br-4,6-Me_2-phenyl
228	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	2-Cl-4,6-Me_2-phenyl
229	CH_3	$MeOC_2H_4(MeOCH_2)CH$	NH	2,4-Me_2-6-$MeOCH_2$-phenyl
230	CH_3	$(MeOCH_2)_2CH$	NH	2,4-Me_2-6-MeO-phenyl
231	CH_3	$(MeOCH_2)_2CH$	NH	4-Br-2,6-Me_2-phenyl
232	CH_3	$(MeOCH_2)_2CH$	NH	2-Cl-4,6-Me_2-phenyl
233	CH_3	$(MeOCH_2)_2CH$	NH	2,4-Me_2-6-$MeOCH_2$-phenyl
234	CH_3	$MeOCH_2(Me)CH$	NH	2,4-Me_2-6-MeO-phenyl
235	CH_3	$MeOCH_2(Me)CH$	NH	2-Br-4,6-Me_2-phenyl
236	CH_3	$EtOCH_2(Et)CH$	NH	2-Br-4,6-Me_2-phenyl
237	CH_3	$EtOCH_2(Me)CH$	NH	2-Br-4,6-Me_2-phenyl
238	CH_3	$MeOCH_2(Et)CH$	NH	2-Br-4,6-F_2-phenyl
239	Et_2CH	CH_3	NH	2,4,6-Me_3-phenyl
240	Et_2CH	CH_3	NH	4-Br-2,6-Me_2-phenyl
241	Et_2CH	CH_3	NH	2-Br-4-iPr-phenyl
242	$MeOCH_2(Et)CH$	CH_3	NH	2,4,6-Me_3-phenyl
243	$MeOCH_2(Et)CH$	CH_3	NH	4-Br-2,6-Me_2-phenyl
244	$MeOCH_2(Et)CH$	CH_3	NH	2-Cl-4,6-Me_2-phenyl
245	$(MeOCH_2)_2CH$	CH_3	NH	2,4,6-Me_3-phenyl
246	$(MeOCH_2)_2CH$	CH_3	NH	4-Br-2,6-Me_2-phenyl
247	$(MeOCH_2)_2CH$	CH_3	NH	2-Cl-4,6-Me_2-phenyl
248	Et_2CH	CH_3	NH	2-Br-4,6-$(MeO)_2$-phenyl
249	Et_2CH	CH_3	NH	2-Cl-4,6-Me_2-phenyl
250	CH_3	Et_2CH	NH	2-Cl-4,6-Me_2-phenyl
251	CH_3	Et_2CH	NH	2,4-Cl_2-6-Me-phenyl
252	CH_3	Et_2CH	NH	2,4,6-Cl_3-phenyl
253	CH_3	Et_2CH	NH	2-Me-4-MeO-phenyl
254	CH_3	Et_2CH	NH	2-Cl-4-MeO-phenyl
255	CH_3	Et_2CH	NH	2,4,6-Me_3-5-F-phenyl
256	CH_3	Et_2CH	NH	2,5-Me_2-4-MeO-phenyl
257	CH_3	Et_2CH	NH	2,4-Me_2-6-MeO-phenyl
258	CH_3	Et_2CH	NH	2,6-Cl_2-4-Me-phenyl

259	CH_3	Et_2CH	NH	2,4-Cl_2-phenyl
260	CH_3	Et_2CH	NH	2-Cl-4-Me-phenyl
261	CH_3	Et_2CH	NH	2-Me-4-Cl-phenyl
262	CH_3	Et_2CH	NH	2-NMe_2-6-Me-pyrid-5-yl
263	CH_3	Et_2CH	NH	2-NMe_2-4-Me-pyrid-5-yl
264	CH_3	Et_2CH	NH	2-Cl-4-MeO-6-Me-phenyl
265	CH_3	Et_2CH	NH	2-Cl-4,6-Me_2-5-F-phenyl
266	CH_3	Et_2CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
267	CH_3	Et_2CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
268	CH_3	$MeOCH_2(Et)CH$	NH	2-Cl-4,6-Me_2-phenyl
269	CH_3	$MeOCH_2(Et)CH$	NH	2,4-Cl_2-6-Me-phenyl
270	CH_3	$MeOCH_2(Et)CH$	NH	2,4,6-Cl_3-phenyl
271	CH_3	$MeOCH_2(Et)CH$	NH	2-Me-4-MeO-phenyl
272	CH_3	$MeOCH_2(Et)CH$	NH	2-Cl-4-MeO-phenyl
273	CH_3	$MeOCH_2(Et)CH$	NH	2,4,6-Me_3-5-F-phenyl
274	CH_3	$MeOCH_2(Et)CH$	NH	2,5-Me_2-4-MeO-phenyl
275	CH_3	$MeOCH_2(Et)CH$	NH	2,6-Cl_2-4-Me-phenyl
276	CH_3	$MeOCH_2(Et)CH$	NH	2,4-Cl_2-phenyl
277	CH_3	$MeOCH_2(Et)CH$	NH	2-Cl-4-Me-phenyl
278	CH_3	$MeOCH_2(Et)CH$	NH	2-Me-4-Cl-phenyl
279	CH_3	$MeOCH_2(Et)CH$	NH	2-NMe_2-6-Me-pyrid-5-yl
280	CH_3	$MeOCH_2(Et)CH$	NH	2-NMe_2-4-Me-pyrid-5-yl
281	CH_3	$MeOCH_2(Et)CH$	NH	2-Cl-4-MeO-6-Me-phenyl
282	CH_3	$MeOCH_2(Et)CH$	NH	2-Cl-4,6-Me_2-5-F-phenyl
283	CH_3	$MeOCH_2(Et)CH$	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
284	CH_3	$MeOCH_2(Et)CH$	NH	6-Me-2,3-dihydro-benzofuran-5-yl

Compounds wherein Y = Oxygen that can be synthesized using synthetic Scheme 3 are listed in Table 3

Table 3



Ex No	R^1	R^3	Y	Ar	mp/°C
700	Cl	Et_2CH	O	2-Br-4-iPr-phenyl	
701	Cl	Et_2CH	O	2,4-Br_2-phenyl	
702	Cl	Et_2CH	O	2,4,6-Me_3-phenyl	
703	Cl	$MeOCH_2(Et)CH$	O	2,4,6-Me_3-phenyl	116
704	Cl	Et_2CH	O	2-Br-4,6-$(MeO)_2$-phenyl	
705	Cl	Et_2CH	O	2-CN-4,6-Me_2-phenyl	
706	Cl	$MeOCH_2(Et)CH$	O	2-Br-4,6-$(MeO)_2$-phenyl	
707	Cl	$MeOCH_2(Et)CH$	O	2-Cl-4,6-$(MeO)_2$-phenyl	
708	Cl	$MeOCH_2(Et)CH$	O	2-I-4,6-Me_2-phenyl	
709	Cl	$MeOCH_2(Et)CH$	O	2-CN-4,6-Me_2-phenyl	
710	Cl	$MeOCH_2(Et)CH$	O	2-Br-4,6-Me_2-phenyl	
711	Cl	$MeOCH_2(Et)CH$	O	4-Br-2,6-Me_2-phenyl	
712	Cl	$MeOCH_2(Et)CH$	O	4-MeCO-2,6-Me_2-phenyl	
713	Cl	$MeOCH_2(Et)CH$	O	4-MeCO-2-OMe-6-Me-phenyl	
714	Cl	$MeOCH_2(Et)CH$	O	2-MeCO-4,6-Me_2-phenyl	
715	Cl	$MeOCH_2(Et)CH$	O	4,6-Me_2-2-SMe-phenyl	
716	Cl	$MeOCH_2(Et)CH$	O	4,6-Me_2-2-SO_2Me-phenyl	
717	Cl	$MeOCH_2(Et)CH$	O	4-Cl-2-I-6-Me-phenyl	
718	Cl	$(MeOCH_2)_2CH$	O	2,4,6-Me_3-phenyl	

719	Cl	phenyl	O	2,4,6-Me_3-phenyl
720	CH_3	$MeOCH_2$(Et)CH	O	2,4-Br_2-phenyl
721	CH_3	$MeOCH_2$(Et)CH	O	2-Br-4-iPr-phenyl
722	CH_3	$MeOCH_2$(Et)CH	O	2,4,6-Me_3-phenyl
723	CH_3	$MeOCH_2$(Et)CH	O	2-Cl-4,6-Me_2-phenyl
724	CH_3	$(MeOCH_2)_2CH$	O	2,4,6-Me_3-phenyl
725	CH_3	$(MeOCH_2)_2CH$	O	2,4-Cl_2-6-Me-phenyl
726	Cl	$(MeOCH_2)_2CH$	O	2,4-Cl_2-6-Me-phenyl
727	Cl	$(MeOCH_2)_2CH$	O	2,4-Br_2-6-Me-phenyl
728	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,4,6-Me_3-phenyl
729	Cl	$MeOC_2H_4(MeOCH_2)CH$	O	2,4,6-Me_3-phenyl
730	Cl	$MeOC_2H_4(MeOCH_2)CH$	O	4-Br-2-OMe-6-Me-phenyl
731	Cl	$(MeOC_2H_4)_2CH$	O	2,4,6-Me_3-phenyl
732	Cl	$MeOCH_2$(Et)CH	O	2,4-Me_2-6-MeO-phenyl
733	Cl	$MeOC_2H_4(MeOCH_2)CH$	O	2,4-Me_2-6-MeO-phenyl
734	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,4-Me_2-6-MeO-phenyl
735	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	4-Br-2,6-Me_2-phenyl
736	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2-Cl-4,6-Me_2-phenyl
737	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,4-Me_2-6-$MeOCH_2$-phenyl
738	CH_3	$(MeOCH_2)_2CH$	O	2,4-Me_2-6-MeO-phenyl
739	CH_3	$(MeOCH_2)_2CH$	O	4-Br-2,6-Me_2-phenyl
740	CH_3	$(MeOCH_2)_2CH$	O	2-Br-6-F-4-Me-phenyl
741	CH_3	$(MeOCH_2)_2CH$	O	2-Cl-4,6-Me_2-phenyl
742	CH_3	$(MeOCH_2)_2CH$	O	2-Cl-4-OMe-6-Me-phenyl
743	CH_3	$(MeOCH_2)_2CH$	O	2,4-Me_2-6-$MeOCH_2$-phenyl
744	Cl	$MeOC_2H_4(MeOCH_2)CH$	O	2,4-Me_2-6-MeO-phenyl
745	Cl	$MeOC_2H_4(MeOCH_2)CH$	O	4-Br-2,6-Me_2-phenyl
746	Cl	$MeOC_2H_4(MeOCH_2)CH$	O	2-Cl-4,6-Me_2-phenyl
747	Cl	$MeOC_2H_4(MeOCH_2)CH$	O	2,4-Me_2-6-$MeOCH_2$-phenyl
748	Cl	$(MeOCH_2)_2CH$	O	2,4-Me_2-6-MeO-phenyl
749	Cl	$(MeOCH_2)_2CH$	O	4-Br-2,6-Me_2-phenyl
750	Cl	$(MeOCH_2)_2CH$	O	2-Cl-4,6-Me_2-phenyl

751	Cl	$(MeOCH_2)_2CH$	O	2,4-Me_2-6-$MeOCH_2$-phenyl
752	Cl	$MeOCH_2(Me)CH$	O	2,4-Me_2-6-MeO-phenyl
753	Cl	$MeOCH_2(Me)CH$	O	4-Br-2,6-Me_2-phenyl
754	Cl	$EtOCH_2(Et)CH$	O	4-Br-2,6-Me_2-phenyl
755	Cl	$EtOCH_2(Me)CH$	O	4-Br-2,6-Me_2-phenyl
756	Cl	$MeOCH_2(Et)CH$	O	4-Br-2,6-F_2-phenyl
757	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2-Br-4,6-Me_2-phenyl
758	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,4-Me_2-6-SMe-phenyl
759	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,4-Me_2-6-SO_2Me-phenyl
760	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	4-NMe_2-2,6-Me_2-phenyl
761	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,4-Cl_2-6-Me-phenyl
762	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	4-Cl-2,6-Me_2-phenyl
763	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,6-Me_2-4-SMe-phenyl
764	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,6-Me_2-4-OMe-phenyl
765	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	2,6-Me_2-4-SO_2Me-phenyl
766	CH_3	$MeOC_2H_4(MeOCH_2)CH$	O	4-MeC(O)-2,6-Me_2-phenyl
767	CH_3	$(MeOCH_2)_2CH$	O	4-Br-2,6-Me_2-phenyl
768	CH_3	$(MeOCH_2)_2CH$	O	4-MeC(O)-2,6-Me_2-phenyl
769	CH_3	$(MeOCH_2)_2CH$	O	2,6-Me_2-4-SMe-phenyl
770	CH_3	$(MeOCH_2)_2CH$	O	2,6-Me_2-4-SO_2Me-phenyl
771	CH_3	$(MeOCH_2)_2CH$	O	4-NMe_2-2,6-Me_2-phenyl
772	CH_3	$(MeOCH_2)_2CH$	O	2-NMe_2-4,6-Me_2-phenyl
773	Cl	$MeOCH_2(Et)CH$	O	2,6-Me_2-4-SMe-phenyl
774	Cl	$MeOCH_2(Et)CH$	O	2,6-Me_2-4-SO_2Me-phenyl
775	Cl	$MeOCH_2(Et)CH$	O	2-Cl-4,6-Me_2-phenyl
776	Cl	$MeOCH_2(Et)CH$	O	4-Br-6-OMe-2-Me-phenyl
777	Cl	$(MeOCH_2)_2CH$	O	2,6-Me_2-4-SMe-phenyl
778	Cl	$(MeOCH_2)_2CH$	O	2,6-Me_2-4-SO_2Me-phenyl
779	Cl	$(MeOCH_2)_2CH$	O	4-Br-6-OMe-2-Me-phenyl
780	CH_3	Et_2CH	O	2,4,6-Me_3-phenyl
781	CH_3	Et_2CH	O	2-Cl-4,6-Me_2-phenyl

782	CH_3	Et_2CH	O	2-Cl-4-OMe-6-Me-phenyl
783	CH_3	Et_2CH	O	2,4,6-Me_3-pyrid-3-yl
784	CH_3	Et_2CH	O	4,6-Me_2-pyrid-3-yl
785	CH_3	Et_2CH	O	2-Br-6-Me-pyrid-3-yl
786	CH_3	Et_2CH	O	2-Br-6-OMe-pyrid-3-yl
787	CH_3	Et_2CH	O	2,6-Me_2-pyrid-3-yl
788	CH_3	Et_2CH	O	2-Cl-6-Me-pyrid-3-yl
789	CH_3	Et_2CH	O	2-Cl-6-OMe-pyrid-3-yl
790	CH_3	$MeOCH_2(Et)CH$	O	2,4,6-Me_3-pyrid-3-yl
791	CH_3	$MeOCH_2(Et)CH$	O	4,6-Me_2-pyrid-3-yl
792	CH_3	$MeOCH_2(Et)CH$	O	2-Br-6-Me-pyrid-3-yl
793	CH_3	$(MeOCH_2)_2CH$	O	2-Br-6-OMe-pyrid-3-yl
794	CH_3	$(MeOCH_2)_2CH$	O	2,6-Me_2-pyrid-3-yl
795	CH_3	$(MeOCH_2)_2CH$	O	2-Cl-6-Me-pyrid-3-yl
796	CH_3	$(MeOCH_2)_2CH$	O	2-Cl-6-OMe-pyrid-3-yl
797	CH_3	$MeOCH_2(Et)CH$	O	2-Br-6-OMe-pyrid-3-yl
798	CH_3	$MeOCH_2(Et)CH$	O	2,6-Me_2-pyrid-3-yl
799	CH_3	$MeOCH_2(Et)CH$	O	2-Cl-6-Me-pyrid-3-yl
800	CH_3	$MeOCH_2(Et)CH$	O	2-Cl-6-OMe-pyrid-3-yl
801	CH_3	$(MeOCH_2)_2CH$	O	2,4,6-Me_3-pyrid-3-yl
802	CH_3	$(MeOCH_2)_2CH$	O	4,6-Me_2-pyrid-3-yl
803	CH_3	$(MeOCH_2)_2CH$	O	2-Br-6-Me-pyrid-3-yl
804	Cl	Et_2CH	O	2-Br-6-OMe-pyrid-3-yl
805	Cl	Et_2CH	O	2,6-Me_2-pyrid-3-yl
806	Cl	Et_2CH	O	2-Cl-6-Me-pyrid-3-yl
807	Cl	Et_2CH	O	2-Cl-6-OMe-pyrid-3-yl
808	Cl	$MeOCH_2(Et)CH$	O	2,4,6-Me_3-pyrid-3-yl
809	Cl	$MeOCH_2(Et)CH$	O	4,6-Me_2-pyrid-3-yl
810	Cl	$MeOCH_2(Et)CH$	O	2-Br-6-Me-pyrid-3-yl
811	Cl	Et_2CH	O	2,4,6-Me_3-pyrid-3-yl
812	Cl	Et_2CH	O	4,6-Me_2-pyrid-3-yl
813	Cl	Et_2CH	O	2-Br-6-Me-pyrid-3-yl
814	Cl	$MeOCH_2(Et)CH$	O	2-Br-6-OMe-pyrid-3-yl
815	Cl	$MeOCH_2(Et)CH$	O	2,6-Me_2-pyrid-3-yl
816	Cl	$MeOCH_2(Et)CH$	O	2-Cl-6-Me-pyrid-3-yl
817	Cl	$MeOCH_2(Et)CH$	O	2-Cl-6-OMe-pyrid-3-yl

818	Cl	$(MeOCH_2)_2CH$	O	2-Br-6-OMe-pyrid-3-yl
819	Cl	$(MeOCH_2)_2CH$	O	2,6-Me_2-pyrid-3-yl
820	Cl	$(MeOCH_2)_2CH$	O	2-Cl-6-Me-pyrid-3-yl
821	Cl	$(MeOCH_2)_2CH$	O	2-Cl-6-OMe-pyrid-3-yl
822	Cl	$(MeOCH_2)_2CH$	O	2,4,6-Me_3-pyrid-3-yl
823	Cl	$(MeOCH_2)_2CH$	O	4,6-Me_2-pyrid-3-yl
824	Cl	$(MeOCH_2)_2CH$	O	2-Br-6-Me-pyrid-3-yl
825	CH_3	Me(Et)CH	O	2,4,6-Me_3-phenyl
826	CH_3	Me(Et)CH	O	2-Cl-4,6-Me_2-phenyl
827	CH_3	Me(Et)CH	O	2,4-Cl_2-6-Me-phenyl
828	CH_3	Me(Et)CH	O	2,4,6-Cl_3-phenyl
829	CH_3	Me(Et)CH	O	2-Me-4-MeO-phenyl
830	CH_3	Me(Et)CH	O	2-Cl-4-MeO-phenyl
831	CH_3	Me(Et)CH	O	2,4,6-Me_3-5-F-phenyl
832	CH_3	Me(Et)CH	O	2,5-Me_2-4-MeO-phenyl
833	CH_3	Me(Et)CH	O	2,4-Me_2-6-MeO-phenyl
834	CH_3	Me(Et)CH	O	2,6-Cl_2-4-Me-phenyl
835	CH_3	Me(Et)CH	O	2,4-Cl_2-phenyl
836	CH_3	Me(Et)CH	O	2-Cl-4-Me-phenyl
837	CH_3	Me(Et)CH	O	2-Me-4-Cl-phenyl
838	CH_3	Me(Et)CH	O	2-NMe_2-6-Me-pyrid-5-yl
839	CH_3	Me(Et)CH	O	2-NMe_2-4-Me-pyrid-5-yl
840	CH_3	Me(Et)CH	O	2-Cl-4-MeO-6-Me-phenyl
841	CH_3	Me(Et)CH	O	2-Cl-4,6-Me_2-5-F-phenyl
842	CH_3	Me(Et)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
843	CH_3	Me(Et)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
844	CH_3	Me(n-Pr)CH	O	2,4,6-Me_3-phenyl
845	CH_3	Me(n-Pr)CH	O	2-Cl-4,6-Me_2-phenyl
846	CH_3	Me(n-Pr)CH	O	2,4-Cl_2-6-Me-phenyl
847	CH_3	Me(n-Pr)CH	O	2,4,6-Cl_3-phenyl
848	CH_3	Me(n-Pr)CH	O	2-Me-4-MeO-phenyl
849	CH_3	Me(n-Pr)CH	O	2-Cl-4-MeO-phenyl
850	CH_3	Me(n-Pr)CH	O	2,4,6-Me_3-5-F-phenyl
851	CH_3	Me(n-Pr)CH	O	2,5-Me_2-4-MeO-phenyl

852	CH_3	Me(n-Pr)CH	O	2,4-Me_2-6-MeO-phenyl
853	CH_3	Me(n-Pr)CH	O	2,6-Cl_2-4-Me-phenyl
854	CH_3	Me(n-Pr)CH	O	2,4-Cl_2-phenyl
855	CH_3	Me(n-Pr)CH	O	2-Cl-4-Me-phenyl
856	CH_3	Me(n-Pr)CH	O	2-Me-4-Cl-phenyl
857	CH_3	Me(n-Pr)CH	O	2-NMe_2-6-Me-pyrid-5-yl
858	CH_3	Me(n-Pr)CH	O	2-NMe_2-4-Me-pyrid-5-yl
859	CH_3	Me(n-Pr)CH	O	2-Cl-4-MeO-6-Me-phenyl
860	CH_3	Me(n-Pr)CH	O	2-Cl-4,6-Me_2-5-F-phenyl
861	CH_3	Me(n-Pr)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
862	CH_3	Me(n-Pr)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
863	CH_3	c-Pr_2CH	O	2,4,6-Me_3-phenyl
864	CH_3	c-Pr_2CH	O	2-Cl-4,6-Me_2-phenyl
865	CH_3	c-Pr_2CH	O	2,4-Cl_2-6-Me-phenyl
866	CH_3	c-Pr_2CH	O	2,4,6-Cl_3-phenyl
867	CH_3	c-Pr_2CH	O	2-Me-4-MeO-phenyl
868	CH_3	c-Pr_2CH	O	2-Cl-4-MeO-phenyl
869	CH_3	c-Pr_2CH	O	2,4,6-Me_3-5-F-phenyl
870	CH_3	c-Pr_2CH	O	2,5-Me_2-4-MeO-phenyl
871	CH_3	c-Pr_2CH	O	2,4-Me_2-6-MeO-phenyl
872	CH_3	c-Pr_2CH	O	2,6-Cl_2-4-Me-phenyl
873	CH_3	c-Pr_2CH	O	2,4-Cl_2-phenyl
874	CH_3	c-Pr_2CH	O	2-Cl-4-Me-phenyl
875	CH_3	c-Pr_2CH	O	2-Me-4-Cl-phenyl
876	CH_3	c-Pr_2CH	O	2-NMe_2-6-Me-pyrid-5-yl
877	CH_3	c-Pr_2CH	O	2-NMe_2-4-Me-pyrid-5-yl
878	CH_3	c-Pr_2CH	O	2-Cl-4-MeO-6-Me-phenyl
879	CH_3	c-Pr_2CH	O	2-Cl-4,6-Me_2-5-F-phenyl
880	CH_3	c-Pr_2CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
881	CH_3	c-Pr_2CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
882	CH_3	c-Pr(Me)CH	O	2,4,6-Me_3-phenyl

883	CH_3	c-Pr(Me)CH	O	2-Cl-4,6-Me_2-phenyl
884	CH_3	c-Pr(Me)CH	O	2,4-Cl_2-6-Me-phenyl
885	CH_3	c-Pr(Me)CH	O	2,4,6-Cl_3-phenyl
886	CH_3	c-Pr(Me)CH	O	2-Me-4-MeO-phenyl
887	CH_3	c-Pr(Me)CH	O	2-Cl-4-MeO-phenyl
888	CH_3	c-Pr(Me)CH	O	2,4,6-Me_3-5-F-phenyl
889	CH_3	c-Pr(Me)CH	O	2,5-Me_2-4-MeO-phenyl
890	CH_3	c-Pr(Me)CH	O	2,4-Me_2-6-MeO-phenyl
891	CH_3	c-Pr(Me)CH	O	2,6-Cl_2-4-Me-phenyl
892	CH_3	c-Pr(Me)CH	O	2,4-Cl_2-phenyl
893	CH_3	c-Pr(Me)CH	O	2-Cl-4-Me-phenyl
894	CH_3	c-Pr(Me)CH	O	2-Me-4-Cl-phenyl
895	CH_3	c-Pr(Me)CH	O	2-NMe_2-6-Me-pyrid-5-yl
896	CH_3	c-Pr(Me)CH	O	2-NMe_2-4-Me-pyrid-5-yl
897	CH_3	c-Pr(Me)CH	O	2-Cl-4-MeO-6-Me-phenyl
898	CH_3	c-Pr(Me)CH	O	2-Cl-4,6-Me_2-5-F-phenyl
899	CH_3	c-Pr(Me)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
900	CH_3	c-Pr(Me)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
901	CH_3	c-Pr(Et)CH	O	2,4,6-Me_3-phenyl
902	CH_3	c-Pr(Et)CH	O	2-Cl-4,6-Me_2-phenyl
903	CH_3	c-Pr(Et)CH	O	2,4-Cl_2-6-Me-phenyl
904	CH_3	c-Pr(Et)CH	O	2,4,6-Cl_3-phenyl
905	CH_3	c-Pr(Et)CH	O	2-Me-4-MeO-phenyl
906	CH_3	c-Pr(Et)CH	O	2-Cl-4-MeO-phenyl
907	CH_3	c-Pr(Et)CH	O	2,4,6-Me_3-5-F-phenyl
908	CH_3	c-Pr(Et)CH	O	2,5-Me_2-4-MeO-phenyl
909	CH_3	c-Pr(Et)CH	O	2,4-Me_2-6-MeO-phenyl
910	CH_3	c-Pr(Et)CH	O	2,6-Cl_2-4-Me-phenyl
911	CH_3	c-Pr(Et)CH	O	2,4-Cl_2-phenyl
912	CH_3	c-Pr(Et)CH	O	2-Cl-4-Me-phenyl
913	CH_3	c-Pr(Et)CH	O	2-Me-4-Cl-phenyl
914	CH_3	c-Pr(Et)CH	O	2-NMe_2-6-Me-pyrid-5-yl
915	CH_3	c-Pr(Et)CH	O	2-NMe_2-4-Me-pyrid-5-yl
916	CH_3	c-Pr(Et)CH	O	2-Cl-4-MeO-6-Me-phenyl

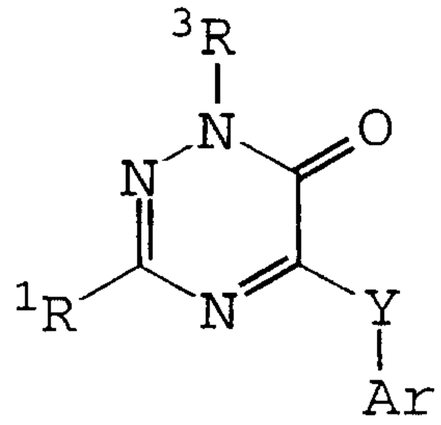
917	CH_3	c-Pr(Et)CH	O	2-Cl-4,6-Me_2-5-F-phenyl
918	CH_3	c-Pr(Et)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
919	CH_3	c-Pr(Et)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
920	CH_3	c-Pr(n-Pr)CH	O	2,4,6-Me_3-phenyl
921	CH_3	c-Pr(n-Pr)CH	O	2-Cl-4,6-Me_2-phenyl
922	CH_3	c-Pr(n-Pr)CH	O	2,4-Cl_2-6-Me-phenyl
923	CH_3	c-Pr(n-Pr)CH	O	2,4,6-Cl_3-phenyl
924	CH_3	c-Pr(n-Pr)CH	O	2-Me-4-MeO-phenyl
925	CH_3	c-Pr(n-Pr)CH	O	2-Cl-4-MeO-phenyl
926	CH_3	c-Pr(n-Pr)CH	O	2,4,6-Me_3-5-F-phenyl
927	CH_3	c-Pr(n-Pr)CH	O	2,5-Me_2-4-MeO-phenyl
928	CH_3	c-Pr(n-Pr)CH	O	2,4-Me_2-6-MeO-phenyl
929	CH_3	c-Pr(n-Pr)CH	O	2,6-Cl_2-4-Me-phenyl
930	CH_3	c-Pr(n-Pr)CH	O	2,4-Cl_2-phenyl
931	CH_3	c-Pr(n-Pr)CH	O	2-Cl-4-Me-phenyl
932	CH_3	c-Pr(n-Pr)CH	O	2-Me-4-Cl-phenyl
933	CH_3	c-Pr(n-Pr)CH	O	2-NMe_2-6-Me-pyrid-5-yl
934	CH_3	c-Pr(n-Pr)CH	O	2-NMe_2-4-Me-pyrid-5-yl
935	CH_3	c-Pr(n-Pr)CH	O	2-Cl-4-MeO-6-Me-phenyl
936	CH_3	c-Pr(n-Pr)CH	O	2-Cl-4,6-Me_2-5-F-phenyl
937	CH_3	c-Pr(n-Pr)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
938	CH_3	c-Pr(n-Pr)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
939	CH_3	c-Pr(n-Bu)CH	O	2,4,6-Me_3-phenyl
940	CH_3	c-Pr(n-Bu)CH	O	2-Cl-4,6-Me_2-phenyl
941	CH_3	c-Pr(n-Bu)CH	O	2,4-Cl_2-6-Me-phenyl
942	CH_3	c-Pr(n-Bu)CH	O	2,4,6-Cl_3-phenyl
943	CH_3	c-Pr(n-Bu)CH	O	2-Me-4-MeO-phenyl
944	CH_3	c-Pr(n-Bu)CH	O	2-Cl-4-MeO-phenyl
945	CH_3	c-Pr(n-Bu)CH	O	2,4,6-Me_3-5-F-phenyl
946	CH_3	c-Pr(n-Bu)CH	O	2,5-Me_2-4-MeO-phenyl
947	CH_3	c-Pr(n-Bu)CH	O	2,4-Me_2-6-MeO-phenyl

948	CH_3	c-Pr(n-Bu)CH	O	2,6-Cl_2-4-Me-phenyl
949	CH_3	c-Pr(n-Bu)CH	O	2,4-Cl_2-phenyl
950	CH_3	c-Pr(n-Bu)CH	O	2-Cl-4-Me-phenyl
951	CH_3	c-Pr(n-Bu)CH	O	2-Me-4-Cl-phenyl
952	CH_3	c-Pr(n-Bu)CH	O	2-NMe_2-6-Me-pyrid-5-yl
953	CH_3	c-Pr(n-Bu)CH	O	2-NMe_2-4-Me-pyrid-5-yl
954	CH_3	c-Pr(n-Bu)CH	O	2-Cl-4-MeO-6-Me-phenyl
955	CH_3	c-Pr(n-Bu)CH	O	2-Cl-4,6-Me_2-5-F-phenyl
956	CH_3	c-Pr(n-Bu)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
957	CH_3	c-Pr(n-Bu)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
958	CH_3	c-PrCH_2(Et)CH	O	2,4,6-Me_3-phenyl
959	CH_3	c-PrCH_2(Et)CH	O	2-Cl-4,6-Me_2-phenyl
960	CH_3	c-PrCH_2(Et)CH	O	2,4-Cl_2-6-Me-phenyl
961	CH_3	c-PrCH_2(Et)CH	O	2,4,6-Cl_3-phenyl
962	CH_3	c-PrCH_2(Et)CH	O	2-Me-4-MeO-phenyl
963	CH_3	c-PrCH_2(Et)CH	O	2-Cl-4-MeO-phenyl
964	CH_3	c-PrCH_2(Et)CH	O	2,4,6-Me_3-5-F-phenyl
965	CH_3	c-PrCH_2(Et)CH	O	2,5-Me_2-4-MeO-phenyl
966	CH_3	c-PrCH_2(Et)CH	O	2,4-Me_2-6-MeO-phenyl
967	CH_3	c-PrCH_2(Et)CH	O	2,6-Cl_2-4-Me-phenyl
968	CH_3	c-PrCH_2(Et)CH	O	2,4-Cl_2-phenyl
969	CH_3	c-PrCH_2(Et)CH	O	2-Cl-4-Me-phenyl
970	CH_3	c-PrCH_2(Et)CH	O	2-Me-4-Cl-phenyl
971	CH_3	c-PrCH_2(Et)CH	O	2-NMe_2-6-Me-pyrid-5-yl
972	CH_3	c-PrCH_2(Et)CH	O	2-NMe_2-4-Me-pyrid-5-yl
973	CH_3	c-PrCH_2(Et)CH	O	2-Cl-4-MeO-6-Me-phenyl
974	CH_3	c-PrCH_2(Et)CH	O	2-Cl-4,6-Me_2-5-F-phenyl
975	CH_3	c-PrCH_2(Et)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
976	CH_3	c-PrCH_2(Et)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
977	CH_3	Et_2CH	O	2,4-Cl_2-6-Me-phenyl
978	CH_3	Et_2CH	O	2,4,6-Cl_3-phenyl

979	CH_3	Et_2CH	O	2-Me-4-MeO-phenyl
980	CH_3	Et_2CH	O	2-Cl-4-MeO-phenyl
981	CH_3	Et_2CH	O	2,4,6-Me_3-5-F-phenyl
982	CH_3	Et_2CH	O	2,5-Me_2-4-MeO-phenyl
983	CH_3	Et_2CH	O	2,4-Me_2-6-MeO-phenyl
984	CH_3	Et_2CH	O	2,6-Cl_2-4-Me-phenyl
985	CH_3	Et_2CH	O	2,4-Cl_2-phenyl
986	CH_3	Et_2CH	O	2-Cl-4-Me-phenyl
987	CH_3	Et_2CH	O	2-Me-4-Cl-phenyl
988	CH_3	Et_2CH	O	2-NMe_2-6-Me-pyrid-5-yl
989	CH_3	Et_2CH	O	2-NMe_2-4-Me-pyrid-5-yl
990	CH_3	Et_2CH	O	2-Cl-4,6-Me_2-5-F-phenyl
991	CH_3	Et_2CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
992	CH_3	Et_2CH	O	6-Me-2,3-dihydro-benzofuran-5-yl

Additional compounds, wherein Y = oxygen that can be synthesized using synthetic Scheme 6 or Scheme 7 are listed in Table 4

Table 4



Ex. No.	R^1	R^3	Y	Ar	mp
1000	CH_3	Et_2CH	O	2,4,6-Me_3-phenyl	
1001	CH_3	Et_2CH	O	2-Cl-4,6-Me_2-phenyl	
1002	CH_3	Et_2CH	O	2,4-Cl_2-6-Me-phenyl	
1003	CH_3	Et_2CH	O	2,4,6-Cl_3-phenyl	
1004	CH_3	Et_2CH	O	2-Me-4-MeO-phenyl	
1005	CH_3	Et_2CH	O	2-Cl-4-MeO-phenyl	
1006	CH_3	Et_2CH	O	2,4,6-Me_3-5-F-phenyl	
1007	CH_3	Et_2CH	O	2,5-Me_2-4-MeO-phenyl	
1008	CH_3	Et_2CH	O	2,4-Me_2-6-MeO-phenyl	
1009	CH_3	Et_2CH	O	2,6-Cl_2-4-Me-phenyl	
1010	CH_3	Et_2CH	O	2,4-Cl_2-phenyl	
1011	CH_3	Et_2CH	O	2-Cl-4-Me-phenyl	
1012	CH_3	Et_2CH	O	2-Me-4-Cl-phenyl	
1013	CH_3	Et_2CH	O	2-NMe_2-6-Me-pyrid-5-yl	
1014	CH_3	Et_2CH	O	2-NMe_2-4-Me-pyrid-5-yl	
1015	CH_3	Et_2CH	O	2-Cl-4-MeO-6-Me-phenyl	
1016	CH_3	Et_2CH	O	2-Cl-4,6-Me_2-5-F-phenyl	
1017	CH_3	Et_2CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl	
1018	CH_3	Et_2CH	O	6-Me-2,3-dihydro-benzofuran-5-yl	

Utility

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

The following is a description of the isolation of cell membranes containing cloned human CRF-R1 receptors for use in the standard binding assay as well as a description of the assay itself.

Messenger RNA was isolated from human hippocampus. The mRNA was reverse transcribed using oligo (dt) 12-18 and the coding region was amplified by PCR from start to stop codons The resulting PCR fragment was cloned into the EcoRV site of pGEMV, from whence the insert was reclaimed using XhoI + XbaI and cloned into the XhoI + XbaI sites of vector pm3ar (which contains a CMV promoter, the SV40 't' splice and early poly A signals, an Epstein-Barr viral origin of replication, and a hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400 mM hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately 1 x 10^8 of the suspended cells were then centrifuged to form a pellet and frozen.

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 mg/l aprotinin, 1 mg/ml leupeptin and 1 mg/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12

min, the pellet is resuspended to a protein concentration of 360 mg/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 ml capacity. To each well is added 50 ml of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 ml of ^{125}I-ovine-CRF (^{125}I-o-CRF) (final concentration 150 pM) and 150 ml of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I-o-CRF binding to cell membranes at various dilutions of test drug are analyzed by the iterative curve fitting program LIGAND [P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (**1980**)], which provides Ki values for inhibition which are then used to assess biological activity.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF. Compounds with a K_i less than 100 nM for the inhibition of CRF are desirable. A number of compounds of the invention have been made and tested in the above assay and shown to have K_i values less than 100 nM thus confirming the utility of the invention.

<u>Inhibition of CRF-Stimulated Adenylate Cyclase Activity</u>

Inhibition of CRF-stimulated adenylate cyclase activity was performed as described by G. Battaglia et al. *Synapse* **1**:572 (**1987**). Briefly, assays were carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides

(concentration range 10^{-9} to 10^{-6m}) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions were initiated by the addition of 1 mM ATP/^{32}P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [^{3}H]cAMP (approximately 40,000 dpm) was added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP was performed by sequential elution over Dowex and alumina columns. Recovery was consistently greater than 80%.

A compound of this invention was tested in this assay and found to be active; IC_{50} < 10000 nM.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (**1990**)

Compounds may be tested in any species of rodent or small mammal. Disclosure of the assays herein is not intended to limit the enablement of the invention.

Compounds of this invention have utility in the treatment of inbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be

administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to

mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped

into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

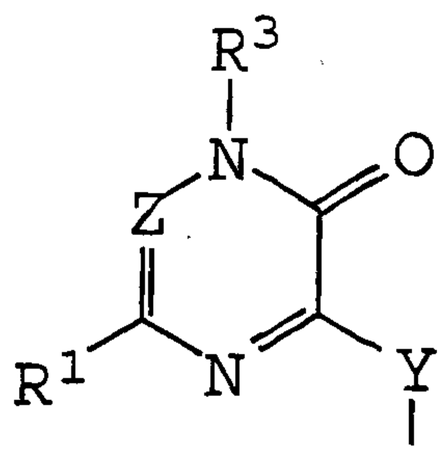
Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Claims:

1. A compound of Formula I



(I)

or a pharmaceutically acceptable salt form thereof, wherein Z is CR^2 or N;

when Z is CR^2:

Y is NR^4, O or $S(O)_n$;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, indolinyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, benzothiazolyl, indazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 4 R^5 groups; wherein Ar is attached to Y through an unsaturated carbon;

R^1 is H, halo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CONR^6R^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, -

COR^7, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl;

R^2 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, halo, -CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-OR^{11}$, -SH or $-S(O)_nR^{12}$;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, $-S(O)_2R^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl,
with the proviso that when R^3 is aryl, Ar is not imidazolyl;

R^4 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_2-C_6 alkenyl or C_2-C_6 alkynyl is optionally substituted with C_1-C_4 alkyl or C_3-C_6 cycloalkyl and wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, heterocyclyl, $-NO_2$, halo, -CN, C_1-C_4 haloalkyl, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, -SH, and $-S(O)_nR^{13}$,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$ and $-S(O)_nR^{13}$;

R^6 and R^7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or $-NR^6R^7$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;
wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl,

C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl, biphenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, $-CN$, $-OR^{15}$, $-SH$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-OC(O)R^{14}$, $-NO_2$, $-NR^8COR^{15}$, $-N(COR^{15})_2$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, $-NR^{15}R^{16}$ and $-CONR^{15}R^{16}$;

heterocyclyl is 5- to 10- membered heterocyclic ring which may be saturated, partially unsaturated or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, wherein the heterocyclic ring is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, $-CN$, $-OR^{15}$, $-SH$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-OC(O)R^{14}$, $-NR^8COR^{15}$, $-N(COR^{15})_2$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, $-NR^{15}R^{16}$, and $-CONR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2;

and wherein, when Z is N:

Y is NR^4, O or $S(O)_n$;

Ar, R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, aryl, heterocyclyl and n are as defined above, but

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, $-CN$, $-S(O)_2R^{13}$, $-CO_2R^7$, $-COR^7$ or $-CONR^6R^7$,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents

independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7, -$CONR^6R^7$, aryl and heterocyclyl,

with the proviso that when R^3 is aryl, Ar is not imidazolyl.

2. The compound of Claim 1 wherein:

Z is CR^2;

Y is NR^4, O, $S(O)_n$;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, indolinyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, benzothiazolyl, indazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 4 R^5 groups; wherein Ar is attached to Y through an unsaturated carbon;

R^1 is H, halo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, -OR^7, -SH, -$S(O)_nR^{13}$, -COR^7, -$CONR^6R^7$, -CO_2R^7, -$OC(O)R^{13}$, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, or -NR^6R^7, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^7, -SH, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -$OC(O)R^{13}$, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7, -$CONR^6R^7$, aryl and heterocyclyl;

R^2 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, halo, -CN, C_1-C_4 haloalkyl, -NR^9R^{10}, -NR^9COR^{10}, -$NR^9CO_2R^{10}$, -OR^{11}, -SH or -$S(O)_nR^{12}$;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, -OR^7, -$S(O)_2R^{13}$, -COR^7, -CO_2R^7, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$CONR^6R^7$, -$NR^8CO_2R^7$, or -NR^6R^7,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7, -$CONR^6R^7$, aryl and heterocyclyl,

with the proviso that when R^3 is aryl, Ar is not imidazolyl;

R^4 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_2-C_6 alkenyl or C_2-C_6 alkynyl is optionally substituted with C_1-C_4 alkyl or C_3-C_6 cycloalkyl and wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, -OR^7, -$S(O)_nR^{12}$, -CO_2R^7, -NR^6R^7 or -NR^9COR^{10};

R^5 is independently selected at each occurrence from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, heterocyclyl, -NO_2, halo, -CN, C_1-C_4 haloalkyl, -NR^6R^7, -NR^8COR^7, -$NR^8CO_2R^7$, -OR^7, -COR^7, -CO_2R^7, -$CONR^6R^7$, -$CON(OR^9)R^7$, -SH, and -$S(O)_nR^{13}$,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each

occurrence from C_1-C_4 alkyl, -NO_2, halo, -CN, -OR^7, -COR^7, -CO_2R^7, -$CONR^6R^7$, -NR^6R^7, -NR^8COR^7, -$NR^8CO_2R^7$ and -$S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or NR^6R^7 taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or -NR^6R^7;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, -NR^6R^7, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, -$NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or -$NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl, biphenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^{15}, -SH, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -$OC(O)R^{14}$, -NO_2, -NR^8COR^{15}, -$N(COR^{15})_2$, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$, -$NR^{15}R^{16}$ and -$CONR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^{15}, -SH, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -$OC(O)R^{14}$, -NR^8COR^{15}, -$N(COR^{15})_2$, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$, -$NR^{15}R^{16}$ and -$CONR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

3. The compound of Claim 2 wherein:

Z is CR^2;

Y is NR^4 or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_4 alkyl, cyclopropyl, C_1-C_4 haloalkyl, -CN, -NR^6R^7, -$CONR^6R^7$, -OR^7, -COR^7, -CO_2R^7 or -$S(O)_nR^{13}$, wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -NR^8COR^7, -$NR^8CO_2R^7$, -NR^6R^7 and aryl;

R^2 is H, C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, $-S(O)_2R^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, aryl and heterocyclyl;

R^4 is H, C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_8 cycloalkylalkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, CO_2R^7 and $-S(O)_nR^{13}$, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_4-C_8 cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7 and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or $-NR^6R^7$ taken together as a

whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$ and $-NR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from

C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -CO_2R^{15}, -NR^8COR^{15}, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$, and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

4. The compound of Claim 3 wherein:

Z is CR^2;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_4 alkyl, cyclopropyl, C_1-C_3 haloalkyl, -CN, -NR^6R^7, -$CONR^6R^7$, -COR^7, -CO_2R^7, -OR^7 or -$S(O)_nR^{13}$ wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_3-C_4 cycloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -NR^6R^7;

R^2 is H;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl or aryl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -CO_2R^7, -NR^8COR^7, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7 and aryl;

R^4 is H, allyl, or C_1-C_4 alkyl, wherein C_1-C_4 alkyl is optionally substituted with C_1-C_4 alkyl, -OR^7, -$S(O)_2R^{12}$, -CO_2R^7, -NR^6R^7 or -NR^9COR^{10};

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, -NO_2, -NR^6R^7, -COR^7, -OR^7, -$CONR^6R^7$, -$CON(OR^9)R^7$, -CO_2R^7 and -$S(O)_nR^{13}$, wherein C_1-C_6 alkyl is substituted with 0 to 3 substituents

independently selected at each occurrence from C_1-C_4 alkyl, -NO_2, halo, -CN, -NR^6R^7, COR^7, -OR^7, -$CONR^6R^7$, CO_2R^7 and -$S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_2-C_8 alkoxyalkyl;

wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8, R^9 and R^{10} are independently at each occurrence H or C_1-C_4 alkyl;

R^{12} and R^{13} are independently at each occurrence C_1-C_4 alkyl or -NR^6R^7;

R^{14} is C_1-C_4 alkyl or -$NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

5. The compound of Claim 4 wherein:

Z is CR^2;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 2 to 4 R^5 groups;

R^1 is H, Cl, Br, methyl, ethyl, cyclopropyl, or -CN,

R^2 is H;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl or aryl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -CF_3, halo, -CN, -OR^7, and aryl;

R^4 is H, methyl, ethyl, i-propyl, n-propyl, n-butyl, i-butyl, s-butyl, n-butyl, or allyl;

R^5 is independently selected at each occurrence from methyl, ethyl, i-propyl, n-propyl, aryl, $-CF_3$, halo, -CN, $-N(CH_3)_2$, $-C(=O)CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, and $-S(O)_2CH_3$;

R^{14} is C_1-C_4 alkyl or $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$ and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

6. The compound of claim 4 selected from the group consisting of:

3-[(2,4-Dibromophenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2,4-Dibromophenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Chloro-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4,6-Dimethyl-2-iodophenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Bromo-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Acetyl-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4,6-Dimethyl-2-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4,6-Dimethyl-2-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Chloro-2-iodo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-phenyl-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dibromophenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4-Dichloro-6-methylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4-Dichloro-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4-Dibromo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(2-methoxyethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-(2-methoxy-1-methylethyl)-2(1H)-pyrazinone;

(+/-)3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-(2-methoxy-1-methylethyl)-2(1H)-pyrazinone;

(+/-)3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(ethoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-(2-ethoxy-1-methylethyl)-2(1H)-pyrazinone;

and

(+/-)3-[(4-Bromo-2,6-difluorophenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Bromo-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-(N,N-dimethylamino)phenyl)-amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dichloro-6-methylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Chloro-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4,6-Dimethyl-2-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone; and

3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-(1-ethylpropyl)-2(1H)-pyrazinone.

7. The compound of Claim 2 wherein:

Z is CR^2;

Y is NR^4 or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, -

COR^7, $-CONR^6R^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, $-CN$, $-OR^7$, $-SH$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl;

R^2 is H, C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl;

R^3 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl and $-NR^6R^7$,
wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, $-CN$, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and $-CONR^6R^7$;

R^4 is H, C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, heterocyclyl, $-NO_2$, halo, $-CN$, C_1-C_4 haloalkyl, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, $-CN$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$ and $-S(O)_nR^{13}$;

R^6 and R^7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl (C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or -NR^6R^7 taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;
wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or -NR^6R^7;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, -NR^6R^7, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, -$NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or -$NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 , -NR^8COR^{15}, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$ and -$NR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -CO_2R^{15}, -NR^8COR^{15}, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$, and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

8. The compound of Claim 7 wherein:

Z is CR^2;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -$CONR^6R^7$, -CO_2R^7 or -NR^6R^7, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^7, -SH, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -$OC(O)R^{13}$, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7, -$CONR^6R^7$, aryl and heterocyclyl;

R^2 is H;

R^3 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl and -NR^6R^7,

wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and $-CONR^6R^7$;

R^4 is H, allyl, or C_1-C_4 alkyl, wherein C_1-C_4 alkyl is optionally substituted with C_1-C_4 alkyl, $-OR^7$, $-S(O)_2R^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, $-CO_2R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_6 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7 and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_2-C_8 alkoxyalkyl;

wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8, R^9 and R^{10} are independently at each occurrence H or C_1-C_4 alkyl;

R^{12} and R^{13} are independently at each occurrence C_1-C_4 alkyl or $-NR^6R^7$;

R^{14} is C_1-C_4 alkyl or $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$ and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

9. The compound of Claim 1 wherein:

Z is N;

Y is NR^4, O or $S(O)_n$;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, indolinyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, benzothiazolyl, indazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 4 R^5 groups; wherein Ar is attached to Y through an unsaturated carbon;

R^1 is H, halo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CONR^6R^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-S(O)_2R^{13}$, $-CO_2R^7$, $-COR^7$ or $-CONR^6R^7$,

wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-$

$NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl,

with the proviso that when R^3 is aryl, Ar is not imidazolyl;

R^4 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_2-C_6 alkenyl or C_2-C_6 alkynyl is optionally substituted with C_1-C_4 alkyl or C_3-C_6 cycloalkyl and wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, heterocyclyl, halo, C_1-C_4 haloalkyl, $-CN$, $-NO_2$, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, $-CN$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$ and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or NR^6R^7 taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl, biphenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^{15}$, -SH, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-OC(O)R^{14}$, $-NO_2$, $-NR^8COR^{15}$, $-N(COR^{15})_2$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, $-NR^{15}R^{16}$ and $-CONR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from

C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^{15}, -SH, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -$OC(O)R^{14}$, -NR^8COR^{15}, -$N(COR^{15})_2$, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$, -$NR^{15}R^{16}$ and -$CONR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

10. The compound of Claim 9 wherein:

Z is N;

Y is NR^4 or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, aryl, -CN, C_1-C_4 haloalkyl, -NR^6R^7, -$CONR^6R^7$, -OR^7, -COR^7, -CO_2R^7 or -$S(O)_nR^{13}$,
wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_3 alkyl, C_3-C_6 cycloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -NR^8COR^7, -$NR^8CO_2R^7$, -NR^6R^7 and aryl;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, -$S(O)_2R^{13}$, -COR^7, -CO_2R^7 or -$CONR^6R^7$,
wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -CO_2R^7, -NR^8COR^7, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7, aryl and heterocyclyl;

R^4 is H, C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, -OR^7, -$S(O)_nR^{12}$, -CO_2R^7, -NR^6R^7 or -NR^9COR^{10};

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_8 cycloalkylalkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, -NO_2, -NR^6R^7, -COR^7, -OR^7, -$CONR^6R^7$, -$CON(OR^9)R^7$, CO_2R^7 and -$S(O)_nR^{13}$,
wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_4-C_8 cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, -NO_2, halo, -CN, -NR^6R^7, COR^7, -OR^7, -$CONR^6R^7$, CO_2R^7 and -$S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or -NR^6R^7 taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or -NR^6R^7;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, -NR^6R^7, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$, $-CO_2R^{15}$, $-NO_2$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$ and $-NR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, $-OR^{15}$, $-S(O)_nR^{14}$, $-CO_2R^{15}$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$, $-NR^8CO_2R^{15}$, and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

11. The compound of Claim 10 wherein:

Z is N;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_4 alkyl, C_1-C_3 haloalkyl, cyclopropyl, -CN, $-NR^6R^7$, $-CONR^6R^7$, $-COR^7$, $-CO_2R^7$, $-OR^7$ or $-S(O)_nR^{13}$

wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each

occurrence from C_3-C_4 cycloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -NR^6R^7;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl or aryl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -CO_2R^7, -NR^8COR^7, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7 and aryl;

R^4 is H, allyl, or C_1-C_4 alkyl, wherein C_1-C_4 alkyl is optionally substituted with C_1-C_4 alkyl, -OR^7, -$S(O)_2R^{12}$, -CO_2R^7, -NR^6R^7 or -NR^9COR^{10};

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, -NO_2, -NR^6R^7, -COR^7, -OR^7, -$CONR^6R^7$, -$CON(OR^9)R^7$, -CO_2R^7 and -$S(O)_nR^{13}$, wherein C_1-C_6 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, -NO_2, halo, -CN, -NR^6R^7, COR^7, -OR^7, -$CONR^6R^7$, CO_2R^7 and -$S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_2-C_8 alkoxyalkyl;
wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8, R^9 and R^{10} are independently at each occurrence H or C_1-C_4 alkyl;

R^{12} and R^{13} are independently at each occurrence C_1-C_4 alkyl or -NR^6R^7;

R^{14} is C_1-C_4 alkyl or -$NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from

C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

12. The compound of Claim 11, wherein:

Z is N;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 2 to 4 R^5 groups;

R^1 is H, methyl, ethyl, cyclopropyl, -CF_3, or -$N(CH_3)_2$;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl or aryl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -CF_3, halo, -CN, -OR^7, and aryl;

R^4 is H, methyl, ethyl, i-propyl, n-propyl, n-butyl, i-butyl, s-butyl, n-butyl, or allyl;

R^5 is independently selected at each occurrence from methyl, ethyl, i-propyl, n-propyl, aryl, -CF_3, halo, -CN, -$N(CH_3)_2$, -$C(=O)CH_3$, -OCH_3, -OCH_2CH_3, -OCF_3, and -$S(O)_2CH_3$;

R^{14} is C_1-C_4 alkyl or -$NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

13. The compound of Claim 1 wherein:

Z is N;

Y is NR^4 or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CONR^6R^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, or $-NR^6R^7$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or C_3-C_8 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, $-OR^7$, -SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$, $-CONR^6R^7$, aryl and heterocyclyl;

R^3 is C_1-C_4 alkyl, -CN, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-COR^7$, $-CO_2R^7$ or $-CONR^6R^7$, wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and $-CONR^6R^7$;

R^4 is H, C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein C_1-C_6 alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

R^5 is independently selected at each occurrence from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, heterocyclyl, $-NO_2$, halo, -CN, C_1-C_4 haloalkyl, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$ and $-S(O)_nR^{13}$, wherein C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-

C_{12} cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-CONR^6R^7$, $-NR^6R^7$, $-NR^8COR^7$, $-NR^8CO_2R^7$ and $-S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl, heterocyclyl(C_1-C_4 alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or NR^6R^7 taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8 is independently at each occurrence H or C_1-C_4 alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-NR^6R^7$;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-;

R^{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{15}R^{16}$;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine,

piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 , -NR^8COR^{15}, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$ and -$NR^{15}R^{16}$;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -CO_2R^{15}, -NR^8COR^{15}, -$NR^8CONR^{15}R^{16}$, -$NR^8CO_2R^{15}$, and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

14. The compound of Claim 13 wherein:

Z is N;

Y is NR^4;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

R^1 is H, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, aryl, heterocyclyl, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -$CONR^6R^7$, -CO_2R^7 or -NR^6R^7, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, -CN, -OR^7, -SH, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -$OC(O)R^{13}$, -NR^8COR^7, -$N(COR^7)_2$, -$NR^8CONR^6R^7$, -$NR^8CO_2R^7$, -NR^6R^7, -$CONR^6R^7$, aryl and heterocyclyl;

R^3 is C_1-C_4 alkyl, -CN, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, -COR^7 or -CO_2R^7,

wherein C_1-C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, halo, -CN, -OR^7, -$S(O)_nR^{13}$, -COR^7, -CO_2R^7, -NR^8COR^7, -NR^6R^7 and -$CONR^6R^7$;

R^4 is H, allyl, or C_1-C_4 alkyl, wherein C_1-C_4 alkyl is optionally substituted with C_1-C_4 alkyl, -OR^7, -$S(O)_2R^{12}$, -CO_2R^7, -NR^6R^7 or -NR^9COR^{10};

R^5 is independently selected at each occurrence from C_1-C_6 alkyl, aryl, heterocyclyl, C_1-C_4 haloalkyl, halo, -CN, -NO_2, -NR^6R^7, -COR^7, -OR^7, -$CONR^6R^7$, -$CON(OR^9)R^7$, -CO_2R^7 and -$S(O)_nR^{13}$, wherein C_1-C_6 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, -NO_2, halo, -CN, -NR^6R^7, COR^7, -OR^7, -$CONR^6R^7$, CO_2R^7 and -$S(O)_nR^{13}$;

R^6 and R7 are independently selected at each occurrence from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_2-C_8 alkoxyalkyl;

wherein C_1-C_4 alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C_1-C_4 alkoxy groups;

R^8, R^9 and R^{10} are independently at each occurrence H or C_1-C_4 alkyl;

R^{12} and R^{13} are independently at each occurrence C_1-C_4 alkyl or -NR^6R^7;

R^{14} is C_1-C_4 alkyl or -$NR^{15}R^{16}$;

R^{15} and R^{16} are independently at each occurrence H, C_1-C_4 alkyl or C_2-C_8 alkoxyalkyl;

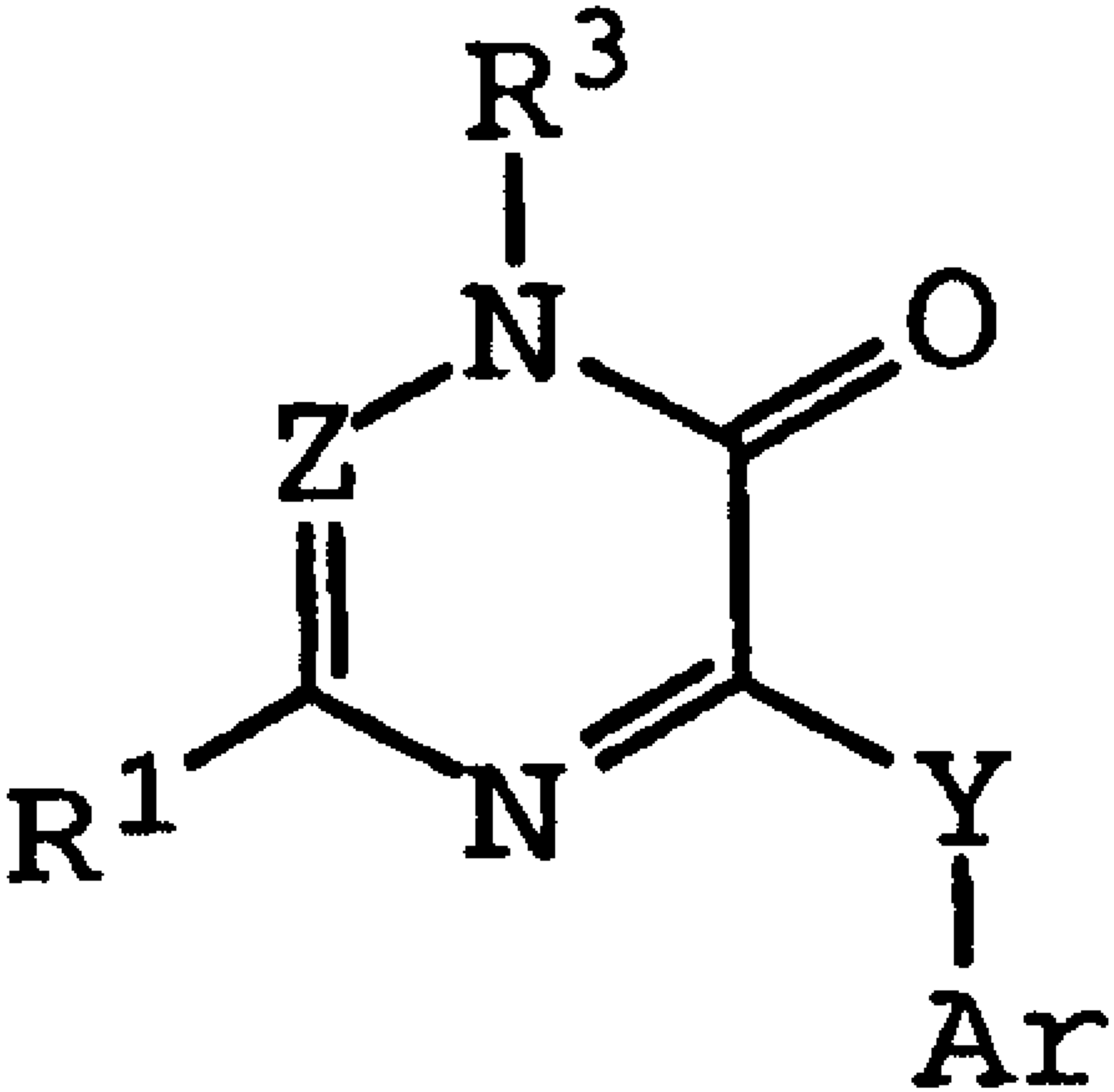
aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, -CN, -OR^{15}, -$S(O)_nR^{14}$, -COR^{15}, -CO_2R^{15}, -NO_2 and -$NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

15. Use of a compound as defined in any one of claims 1 to 14 for treating affective disorders, anxiety, depression, post-traumatic stress disorders,

supranuclear palsy, seizure disorders, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, or fertility problems in a mammal in need of such treatment.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula (I) as defined in any one of Claims 1-14.



(I)