TITLE

AZOLO TRIAZINES AND PYRIMIDINES

FIELD OF THE INVENTION

This invention relates a treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress, by administration of certain [1,5-a]-pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-1,3,5-triazines, [1,5-a]-pyrazolo-pyrimidines and [1,5-a]-1,2,3-triazolo-pyrimidines.

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 feeding 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)].

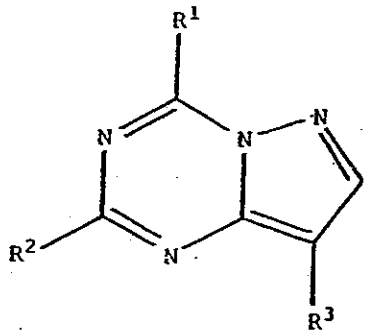
The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α-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)].

Several publications describe corticotropin releasing factor antagonist compounds

and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application US94/11050 , Pfizer WO 95/33750, Pfizer WO 95/34563, Pfizer WO 95/33727 and Pfizer EP 0778 277 A1.

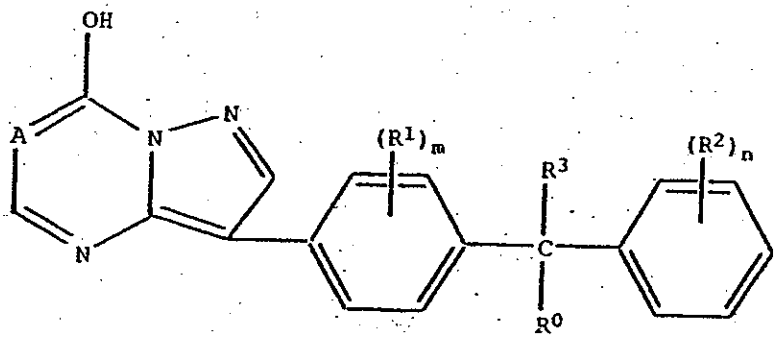
Insofar as is known, [1,5-a]-pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-1,3,5-triazines, [1,5-a]-pyrazolo-pyrimidines and [1,5-a]-1,2,3-triazolo-pyrimidines, have not been previously reported as corticotropin releasing factor antagonist compounds useful in the treatment of psychiatric disorders and neurological diseases. However, there have been publications which teach some of these compounds for other uses.

For instance, EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula



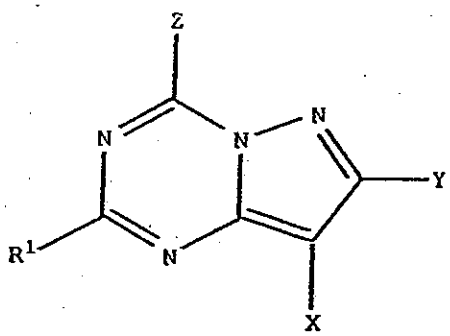
where R^1 is OH or alkanoyl, R^2 is H, OH, or SH, and R^3 is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula



where A is CH or N, R^0 and R^3 are H or alkyl, and R^1 and R^2 are H, alkyl, alkoxyl, alkylthio, nitro, etc., and states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and prostatic carcinoma.

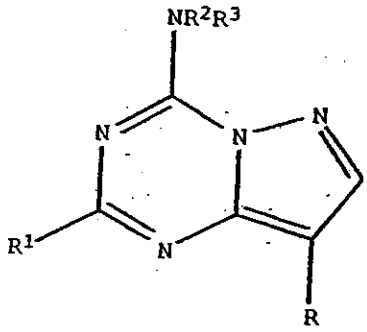
US 3,910,907 (ICI, 1975) discloses pyrazolotriazines of the formula:



where R1 is CH_3, C_2H_5 or C_6H_5, X is H, C_6H_5, m-$CH_3C_6H_4$, CN, COOEt, Cl, I or Br, Y is H, C_6H_5, o-$CH_3C_6H_4$, or p-$CH_3C_6H_4$, and Z is OH, H, CH_3, C_2H_5, C_6H_5, n-C_3H_7, i-C_3H_7, SH, SCH_3, NHC_4H_9, or $N(C_2H_5)_2$, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

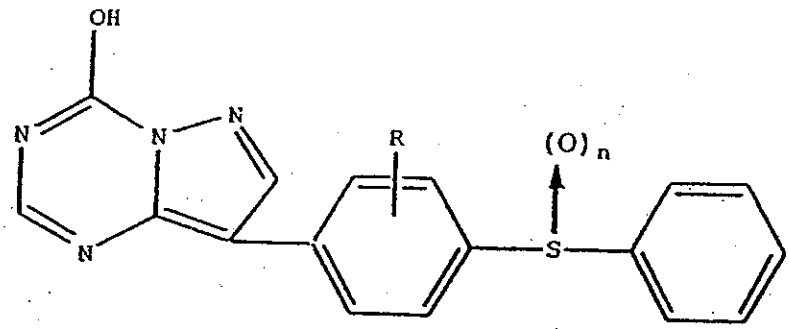
US 3,995,039 discloses pyrazolotriazines of

the formula:



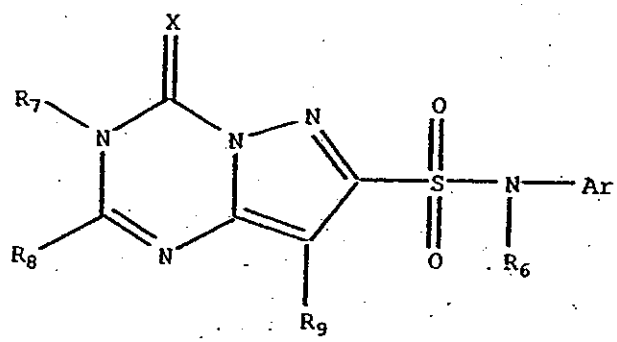
where R^1 is H or alkyl, R^2 is H or alkyl, R^3 is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



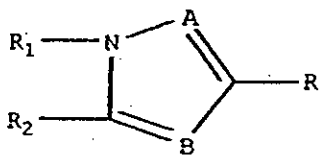
where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

US 4,892,576 discloses pyrazolotriazines of the formula

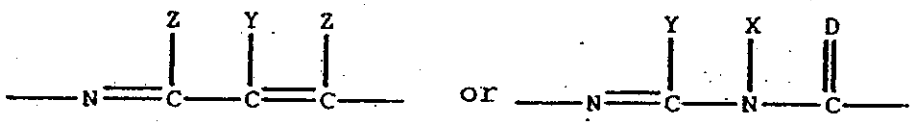


where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, R_6-R_8 are H, alkyl, etc., and R_9 is H, alkyl, phenyl, etc. The patent states that the compounds are useful as herbicides and plant growth regulants.

US 5,484,760 and WO 92/10098 discloses herbicidal compositions containing, among other things, a herbicidal compound of the formula



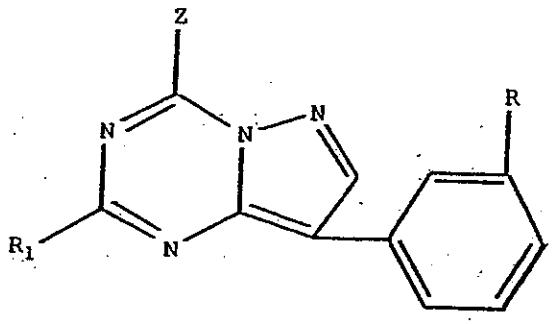
where A can be N, B can be CR_3, R_3 can be phenyl or substituted phenyl, etc., R is $-N(R_4)SO_2R_5$ or $-SO_2N(R_6)R_7$ and R_1 and R_2 can be taken together to form



where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

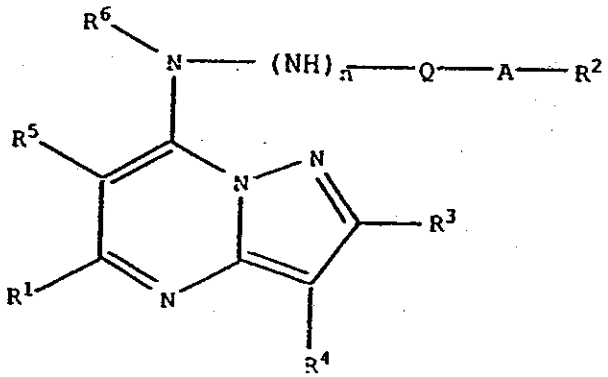
US 3,910,907 and Senga et al., J. Med. Chem.,

1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula



where Z is H, OH, CH_3, C_2H_5, C_6H_5, n-C_3H_7, iso-C_3H_7, SH, SCH_3, NH(n-C_4H_9), or N(C_2H_5)$_2$, R is H or CH_3, and R_1 is CH_3 or C_2H_5. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

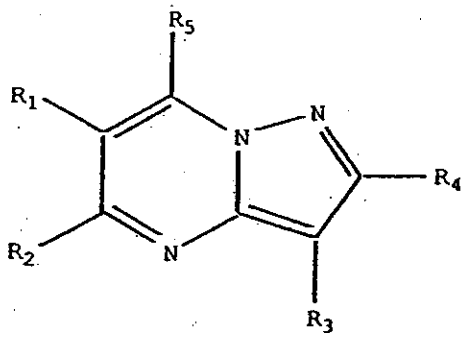
WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula



where Q is carbonyl or sulfonyl, n is 0 or 1, A is a

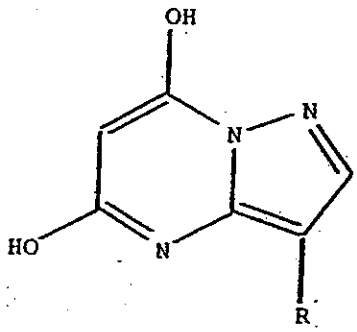
single bond, alkylene or alkenylene, R^1 is H, alkyl, etc., R^2 is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R^3 is H, alkyl or phenyl, R^4 is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R^5 and R^6 are H or alkyl.

EP 0 591 528 (Otsuka, 1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula



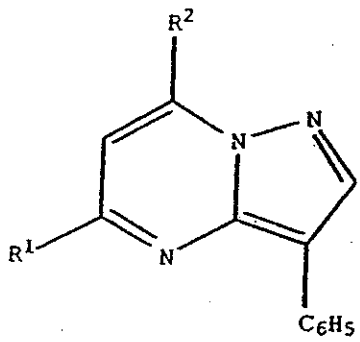
where R_1, R_2, R_3 and R_4 are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R_5 is SR_6 or NR_7R_8, R_6 is pyridyl or optionally substituted phenyl, and R_7 and R_8 are H or optionally substituted phenyl.

Springer et al, J. Med. Chem., 1976, vol. 19, no. 2, 291-296 and Springer U.S. patents 4021,556 and 3,920,652 disclose pyrazolopyrimidines of the formula



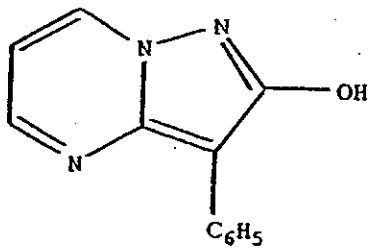
where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula

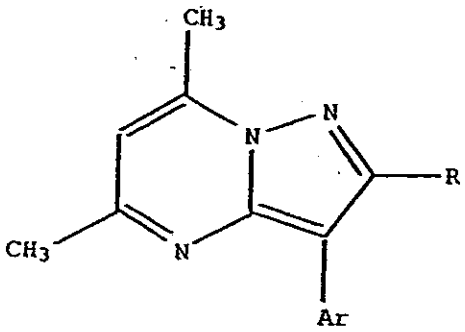


where R^1 is CF_3, C_2F_5, or C_6H_4F, and R^2 is CH_3, C_2H_5, CF_3, or C_6H_4F.

Maquestiau et al., Bull. Soc. Belg., vol.101, no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-a]pyrimidine of the formula



Ibrahim et al., Arch. Pharm. (weinheim) 320, 487-491 (1987) discloses pyrazolo[1,5-a]pyrimidines of the formula

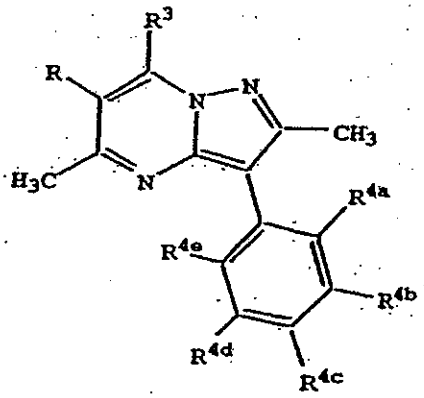


where R is NH2 or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl.

Other references which disclose azolopyrimidines inclued EP 0 511 528 (Otsuka, 1992), US 4,997,940 (Dow, 1991), EP 0 374 448 (Nissan, 1990), US 4,621,556 (ICN,1997), EP 0 531 901 (Fujisawa, 1993), US 4,567,263 (BASF, 1986), EP 0 662 477 (Isagro, 1995), DE 4 243 279 (Bayer, 1994), US 5,397,774 (Upjohn, 1995), EP 0 521 622 (Upjohn, 1993), WO 94/109017 (Upjohn, 1994), J. Med. Chem., 24, 610-613 (1981), and J. Het. Chem., 22, 601 (1985).

SUMMARY OF THE INVENTION

According to a first aspect of the present invention, there is provided a compound of Formula (70)



FORMULA (70)

and geometric isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof selected from the group:

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is

H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -

$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is

H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -

$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H

and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -

NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is Me, R^3 is -$N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}

is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*) -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(n-Pr)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*) - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*) - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH-

(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,

R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Bu)(Et), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)CH_2OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is ME and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH-2-

butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -

N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -

N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H; and

a compound of Formula (70) wherein R is Me, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H.

A second aspect provides a compound and geometric isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof, wherein said compound is selected from: 7-(diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine and 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

A third aspect provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as defined above.

A fourth aspect provides the use of a therapeutically effective amount of a compound as defined above for the manufacture of a medicament for treating effective disorder, anxiety, depression, headache, irritable bowel syndrome, post traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals.

Disclosed are compounds, pharamceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of

inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia

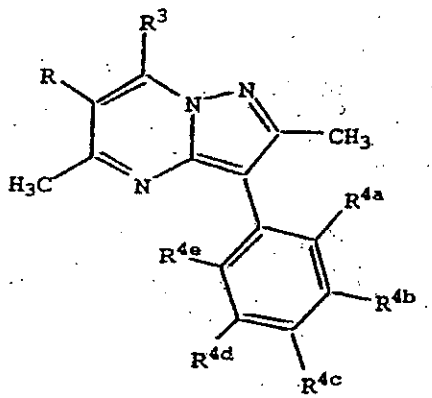
Disclosed further are compounds which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds disclosed can be useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a mammal.

Disclosed yet further are compounds described below which can be useful as antagonists of the corticotropin releasing factor. The compounds disclosed exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. Disclosed are also pharmaceutical compositions containing such compounds of Formulae (1) and (2), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

Disclosed further are the compounds described herein (and especially labelled compounds disclosed) which can also be useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

DETAILED DESCRIPTION OF INVENTION

[1]The present invention provides compounds of Formula (70)



FORMULA (70)

and geometric isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof selected from the group:

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) -

$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is

Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -

$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is

H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(CH_2OMe)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Et)2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Et)2, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(c-

Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}

is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is Me, R^3 is -$N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -

$NHCH(n\text{-}Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*) - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NH(Et)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*) - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is

Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)CH_2OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me

and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is ME and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,

R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is cyclobutylamino, R^{4a} is Me; R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H; and

a compound of Formula (70) wherein R is Me, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H.

[2] Specifically preferred compounds of the present invention include compounds and geometric isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof, wherein said compound is selected from: 7-(diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine and 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

[3]The present invention also provides pharmaceutical compositions comprising a therapeutically effective amount of the above-described compounds and a pharmaceutically acceptable carrier.

[4] The present invention further provides the use of a therapeutically effective amount of the above described compounds for the manufacture of a medicament for treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals.

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. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" means a straight chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(*S*)" means the S enantiomer and the prefix "(*R*)" means the R enantiomer. 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, such as ethenyl, propenyl, and the like. "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, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "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 substitent 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 "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). 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, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) 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 formulas (I) and (II); and the like.

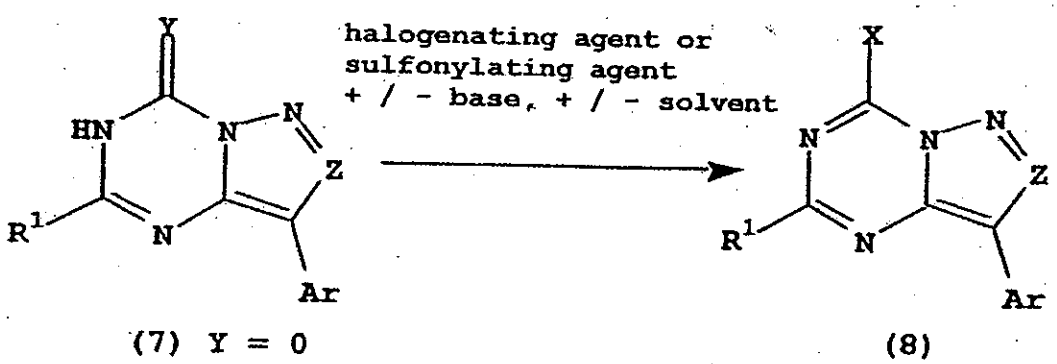
The term "therapeutically effective amount" of a compound of this invention means an amount

effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

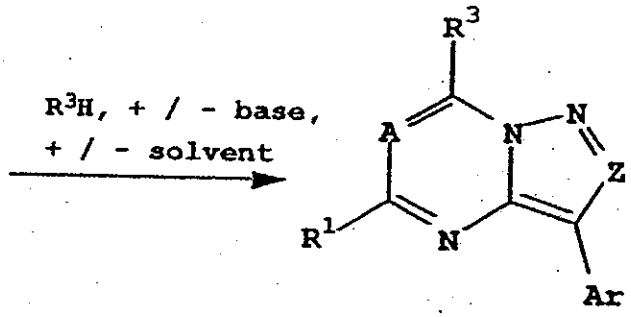
Syntheses

Some compounds of Formula (1) may be prepared from intermediate compounds of Formula (7), using the procedures outlined in Scheme 1:

SCHEME 1



(7) Y = O (8)



(1) A = N

Compounds of Formula (7) (where Y is O) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (8) (where X is halogen, alkanesulfonyloxy,

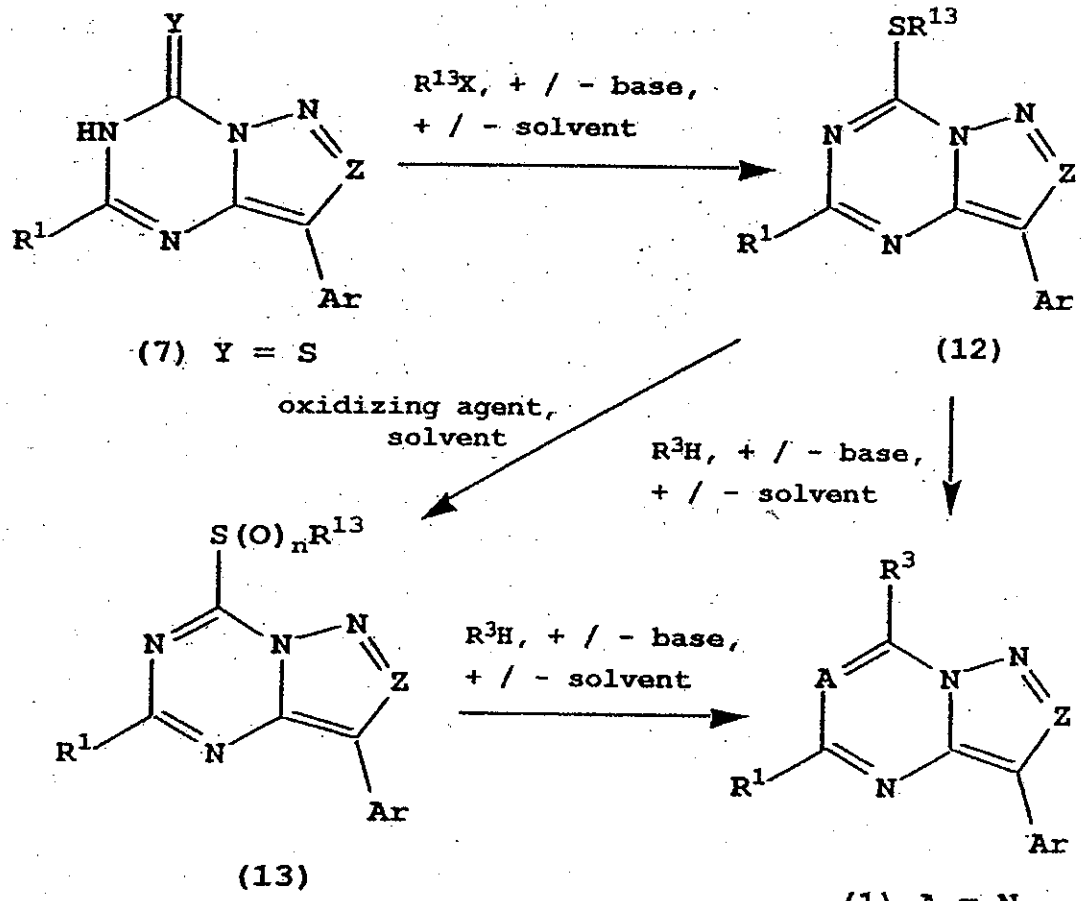
arylsulfonyloxy or haloalkane-sulfonyloxy). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3 or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

Compounds of Formula (8) may be reacted with compounds of Formula R^3H (where R^3 is defined as above except R^3 is not SH, COR^7, CO_2R^7, aryl or heteroaryl)

in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80 to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

Scheme 2 delineates the procedures for converting intermediate compounds of Formula (7) (where Y is S) to some compounds of Formula (1).

SCHEME 2



Compounds of Formula (7) (where Y is S) may be treated with an alkylating agent $R^{13}X$ (where R^{13} is defined as above, except R^{13} is not aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably

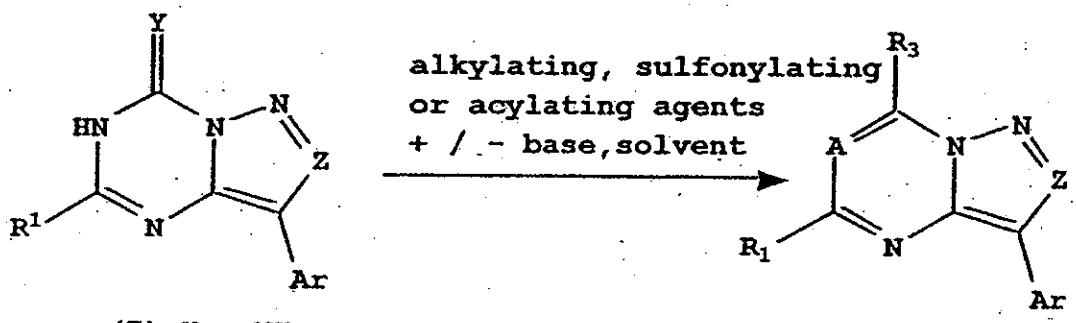
sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably N,N-di-isopropyl-N-ethyl amine or triethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme 1 above. Alternatively, compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may be oxidized to compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) by treatment with an oxidizing agent in the presence of an inert solvent at temperatures ranging from -80°C to 250°C. Oxidizing agents include, but are not limited to, hydrogen peroxide, alkane or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid), dioxirane, oxone, or sodium periodate. Inert solvents may include, but are not limited to, alkanones (3 to 10 carbons, preferably acetone), water, alkyl

alcohols (1 to 6 carbons), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane) or combinations thereof. The choices of oxidant and solvent are known to those skilled in the art (cf. Uemura, S., Oxidation of Sulfur, Selenium and Tellurium, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 7, 762-769). Preferred reaction temperatures range from -20°C to 100°C. Compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme (1) above.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be prepared from compounds of Formula (7), where Y is NH, by the procedures depicted in Scheme 3.

SCHEME 3



(7) Y = NH

(1)

A = N;

R_3 = NR^6R^7, NR^8COR^7, $N(COR^7)_2$, $NR_8CONR^6R^7$ $NR_8CO_2R_{13}$

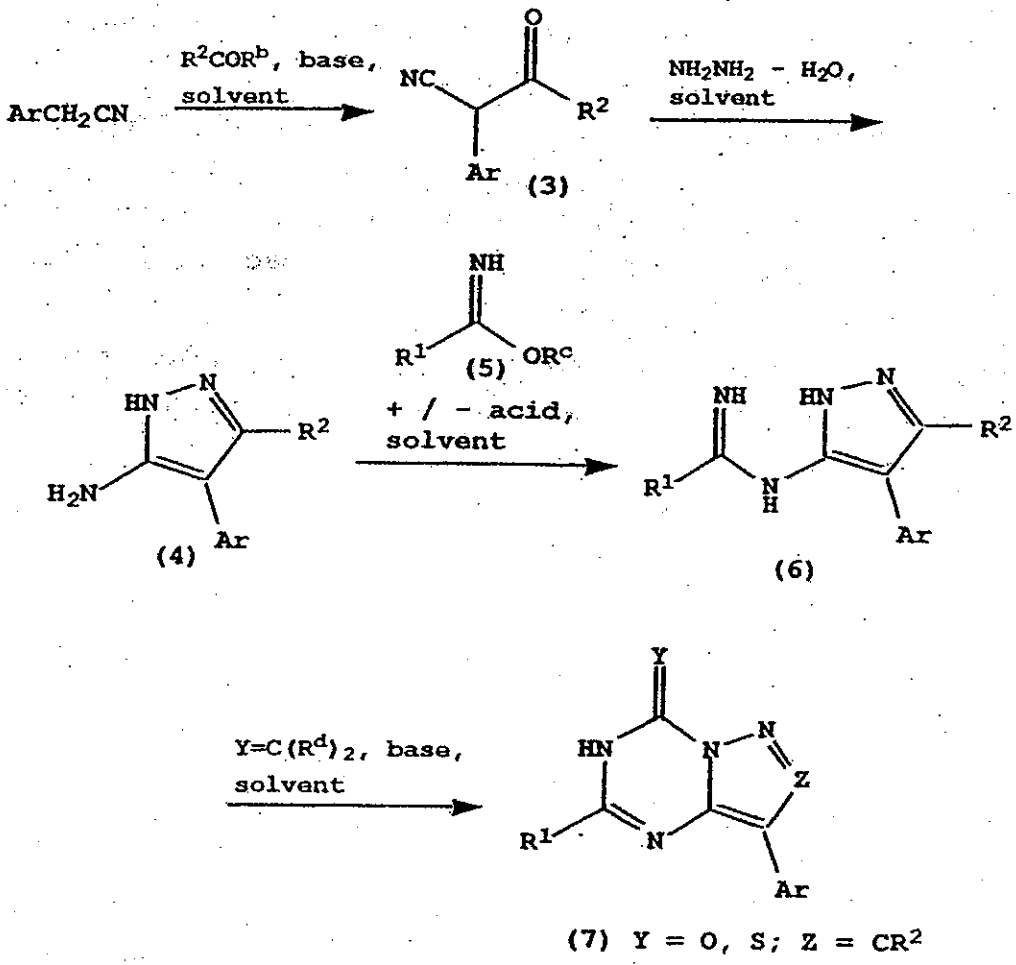
Reaction of compounds of Formula (7), where Y is NH, with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C_1-C_{10} alkyl -halides, -tosylates, -mesylates or -triflates; C_1-C_{10} haloalkyl(1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates; C_2-C_8 alkoxyalkyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C_1-C_4 alkyl)-halides, -tosylates, -

mesylates or -triflates. Acylating agents may include, but are not limited to, C_1-C_{10} alkanoyl halides or anhydrides, C_1-C_{10} haloalkanoyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkanoyl halides or anhydrides, C_3-C_6 cycloalkanoyl halides or anhydrides, C_4-C_{12} cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C_1-C_4) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C_1-C_4) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C_1-C_4) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C_1-C_{10} alkylsulfonyl halides or anhydrides, C_1-C_{10} haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkylsulfonyl halides or anhydrides, C_3-C_6 cycloalkylsulfonyl halides or anhydrides, C_4-C_{12} cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C_1-C_4 alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C_1-C_4 alkyl)sulfonyl halides or anhydrides, heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C_1-C_4 alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower

alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Scheme 4 delineates procedures, which may be employed to prepare intermediate compounds of Formula (7), where Y is O, S and Z is CR^2.

SCHEME 4



Compounds of the formula $ArCH_2CN$ are reacted with compounds of the formula R^2COR^b, where R^2 is defined above and R^b is halogen, cyano, lower alkoxy (1 to 6 carbons) or lower alkanoyloxy (1 to 6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from -78°C to 200°C to afford compounds of Formula (3). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal

dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (3) may be treated with hydrazine-hydrate in the presence of an inert solvent at temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to produce compounds of Formula (4). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Compounds of Formula (4) may be reacted with compounds of Formula (5) (where R^c is alkyl (1-6 carbons)) in the

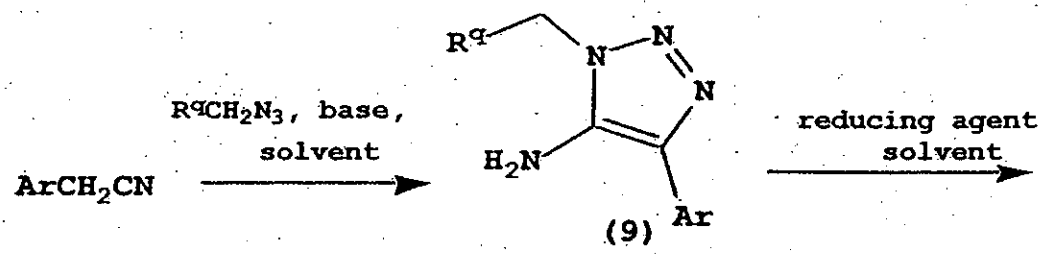
presence or absence of an acid in the presence of an inert solvent at temperatures ranging from 0°C to 200°C to produce compounds of Formula (6). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, water, alkanenitriles (1 to 6 carbons, preferably acetonitrile), halocarbons of 1 to 6 carbons and 1 to 6 halogens (preferably dichloromethane or chloroform), alkyl alcohols of 1 to 10 carbons (preferably ethanol), dialkyl ethers (4 to 12 carbons, preferably diethyl ether or di-isopropylether) or cyclic ethers such as dioxan or tetrahydrofuran. Preferred temperatures range from ambient temprature to 100°C.

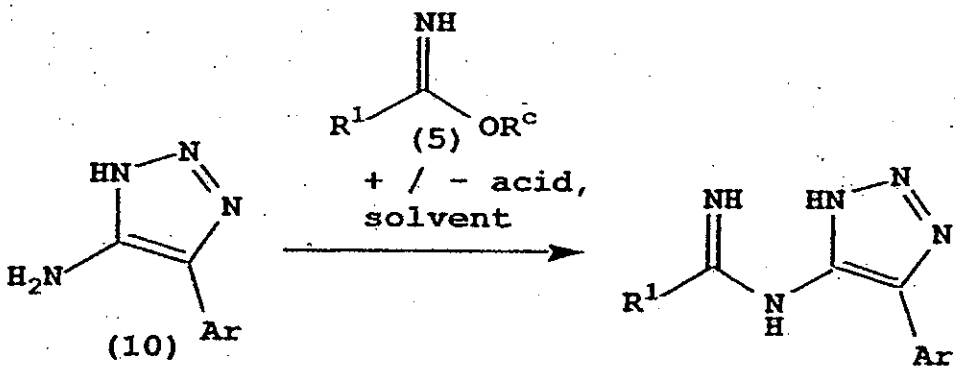
Compounds of Formula (6) may be converted to intermediate compounds of Formula (7) by treatment with compounds $C{=}Y(R^d)_2$ (where Y is O or S and R^d is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent at reaction temperatures from -50°C to 200°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkali metal carbonates, alkali metal hydroxides, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may

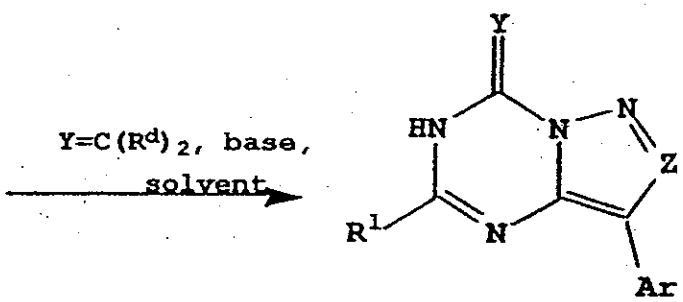
include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred temperatures are 0°C to 150°C.

Intermediate compounds of Formula (7), where Z is N, may be synthesized according the methods outlined in Scheme 5.

SCHEME 5







(7) Y = O, S; Z =N

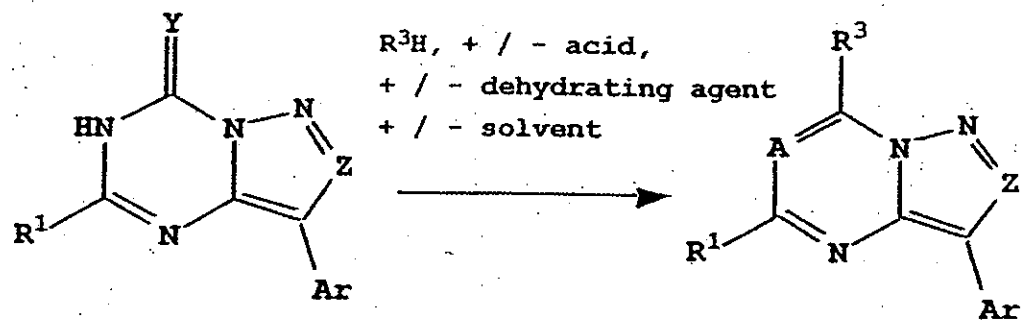
Compounds of $ArCH_2CN$ are reacted with compounds of Formula $R^qCH_2N_3$ (where R^q is a phenyl group optionally substituted by H, alkyl (1 to 6 carbons) or alkoxy (1 to 6 carbons) in the presence or absence of a base in an inert solvent at temperatures ranging from 0°C to 200°C to generate compounds of Formula (9). Bases may

include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide, sodium ethoxide or potassium t-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from ambient temperature to 100°C. Compounds of Formula (9) may be treated with a reducing agent in an inert solvent at -100°C to 100°C to afford products of Formula (10). Reducing agents include, but are not limited to, (a) hydrogen gas in combination with noble metal catalysts such as Pd-on-carbon, PtO_2, Pt-on-carbon, Rh-on-alumina or Raney nickel, (b) alkali metals (preferably sodium) in combination with liquid ammonia or (c) ceric ammonium nitrate. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably

diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). The preferred reaction temperatures are -50°C to 60°C. Compounds of Formula (9) are then converted to compounds of Formula (7) (where Z is N) via intermediates of Formula (11) using the reagents and reaction conditions outlined in Scheme 4 for the conversion of compounds of Formula (4) to compounds of Formula (7) (where Z is CR^2).

Compounds of Formula (1) may also be prepared from compounds of Formula (7) (where Y is O, S and Z is defined above) as outlined in Scheme 6:

SCHEME 6



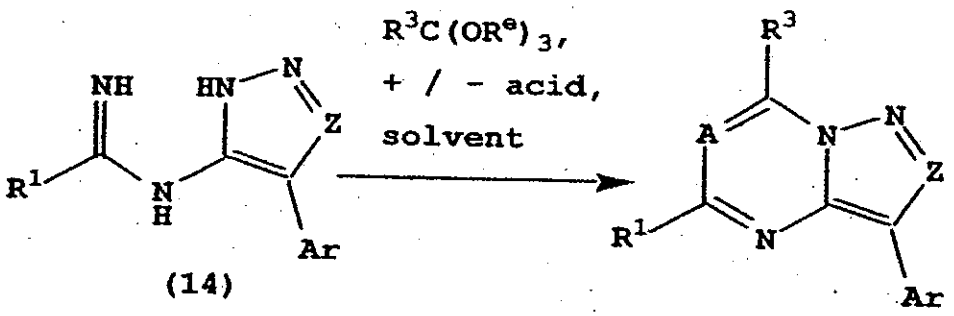
(7) Y = O, S; Z = N, CR^2 (1) A = N

Compounds of Formula (7) may be reacted with compounds of Formula R^3H in the presence of a dehydrating agent in an inert solvent at reaction temperatures ranging from 0°C to 250°C. Dehydrating agents include, but are not limited to, P_2O_5, molecular sieves or inorganic or organic acids. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic

acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably glyme or diglyme), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or halocarbons of 1 to 10 carbons and 1 to 10 halogens (preferably chloroform). Preferred reaction temperatures range from ambient temperature to 150°C.

Some compounds of Formula (1) (where A is N) may also be prepared by the methods shown in Scheme 7:

SCHEME 7



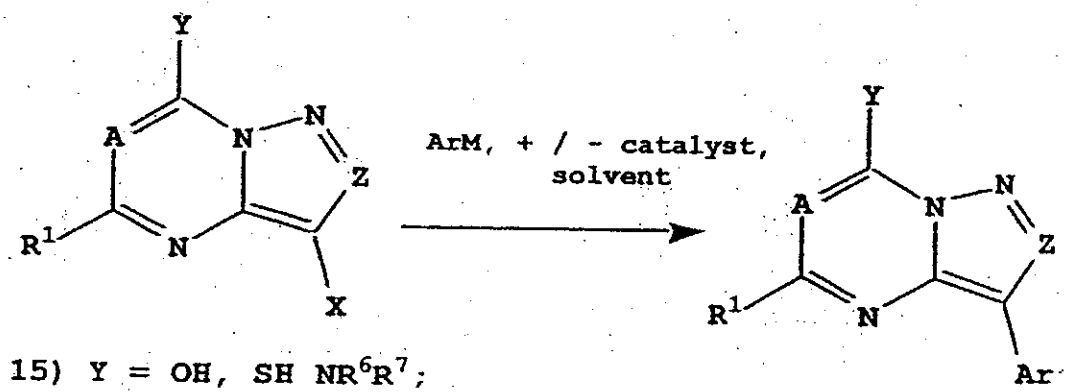
(14) (1) A = N

Intermediate compounds of Formula (14), where Z is defined above, may be reacted with compounds of Formula $R^3C(OR^e)3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may

include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 50°C to 150°C.

Intermediate compounds of Formula (7) may also be synthesized by the reactions displayed in Scheme 8.

SCHEME 8



15) Y = OH, SH NR^6R^7;
Z = N, CR^2,
X = Br, Cl, I, B(OR"")2

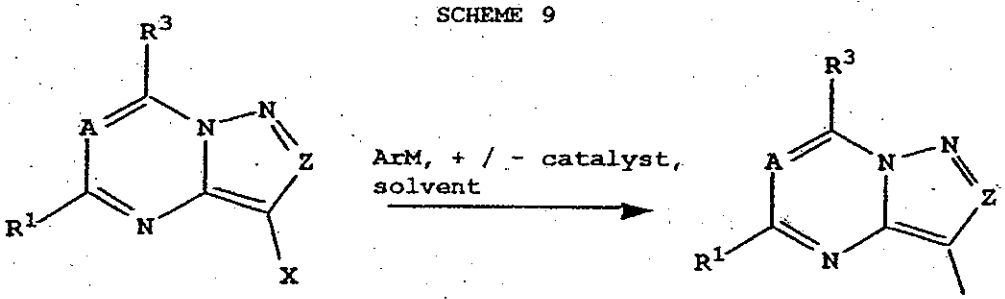
(7) A = N

Compounds of Formula (15), (where Y is OH, SH, NR^6R^7; Z is defined above, X is Br, Cl, I, O_3SCF_3 or $B(OR"")_2$ and R"" is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ. Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as $Pd(PPh_3)_4$), palladium halides or alkanoates (such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$) or nickel complexes (such as $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C.
The choices of M and X are known to those skilled in the art (cf. Imamoto, T., Organocerium Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 231-250; Knochel, P., Organozinc, Organocadmium and Organomercury Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon

Press, 1991), 1, 211-230; Knight, D.W., Coupling Reactions between sp^2 Carbon Centers, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 3, 481-520).

Compounds of Formula (1) may also be prepared using the methods shown in Scheme 9.

SCHEME 9



(16) X = Br, Cl, I, $B(OR"")_2$, O_3SCF_3

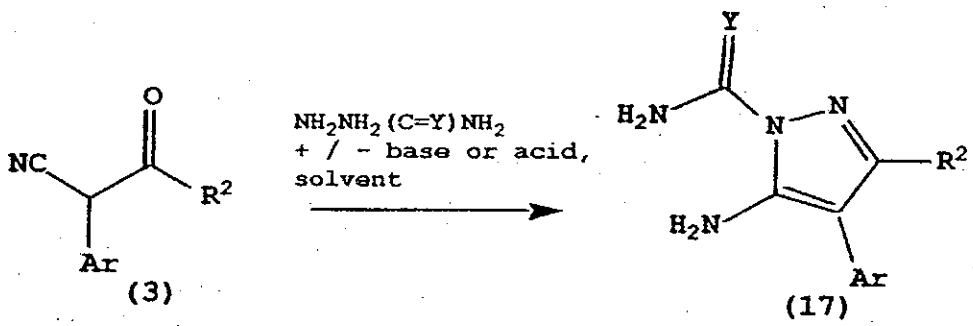
(1)

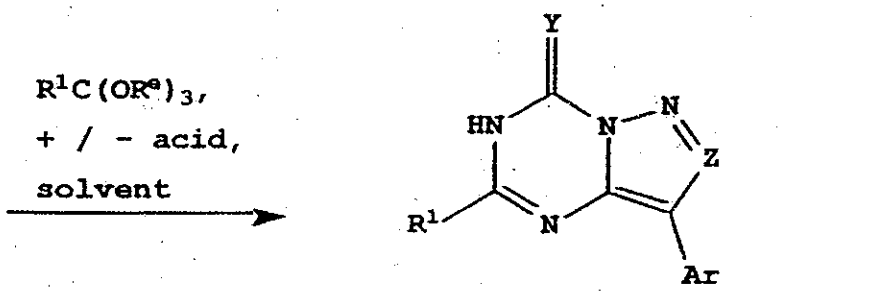
Compounds of Formula (16), where A, Z, R^1 and R^3 are defined above and X is Br, Cl, I, O_3SCF_3 or $B(OR"")_2$ and R"" is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ (see the above references in Comprehensive Organic Synthesis). Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as $Pd(PPh_3)_4$), palladium halides or alkanoates (such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$) or nickel complexes (such as $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines

(preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C.

Intermediate compounds of Formula (7) (where Y is O, S, NH, Z is CR^2 and R^1, R^2 and Ar are defined as above) may be prepared as illustrated in Scheme 10.

SCHEME 10





(7) Y = O, S, NH; Z = CR^2

Compounds of Formula (3) may be reacted with compounds

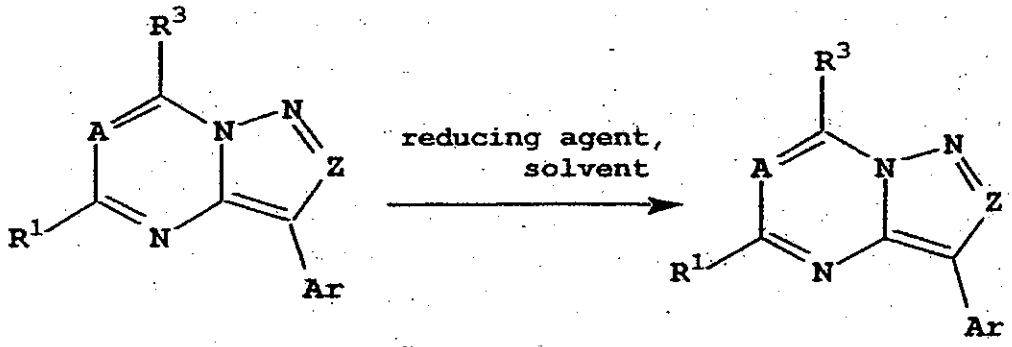
of Formula $H_2NNH(C=Y)NH_2$, where Y is O, S or NH, in the presence or absence of a base or acid in an inert solvent at temperatures from 0°C to 250°C to produce compounds of Formula (17). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane).

Preferred reaction temperatures range from 0°C to 150°C. Compounds of Formula (17) may then be reacted with compounds of Formula $R^3C(OR^e)3$, where R^e may be

alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 50°C to 150°C.

In Scheme 11, the procedures which may be used to convert compounds of Formula (1), where R^3 is COR^7, CO_2R^7, NR^8COR^7 and $CONR^6R^7$, to other compounds of Formula (1), where R^3 is $CH(OH)R^7$, CH_2OH, $NR^8CH_2R^7$ and $CH_2NR^6R^7$ by treatment with a reducing agent in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 11



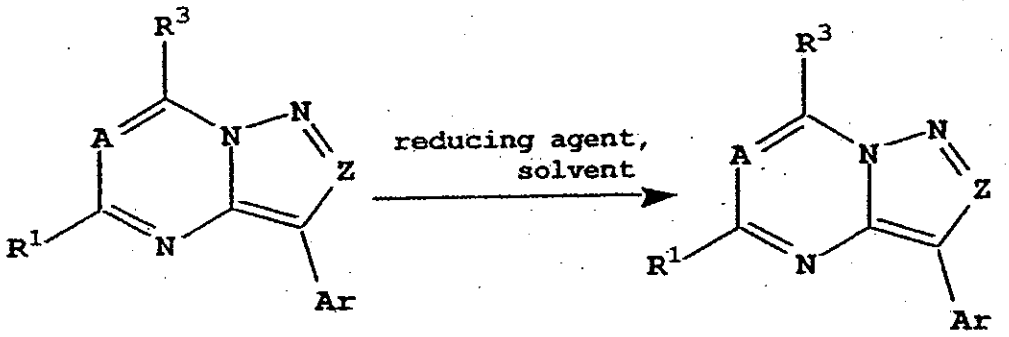
(1) R^3 = COR^7, CO_2R^7, $CONR^6R^7$

(1) R^3 = $C(OH)R^7$, CH_2OH, $CH_2NR^6R^7$

Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides, or dialkyl aluminum hydrides (such as di-isobutylaluminum hydride). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

In Scheme 12, the procedures are shown which may be used to convert compounds of Formula (1), where R^3 is COR^7 or CO_2R^7, to other compounds of Formula (1), where R^3 is $C(OH)(R^7)_2$ by treatment with a reagent of Formula R^7M in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 12

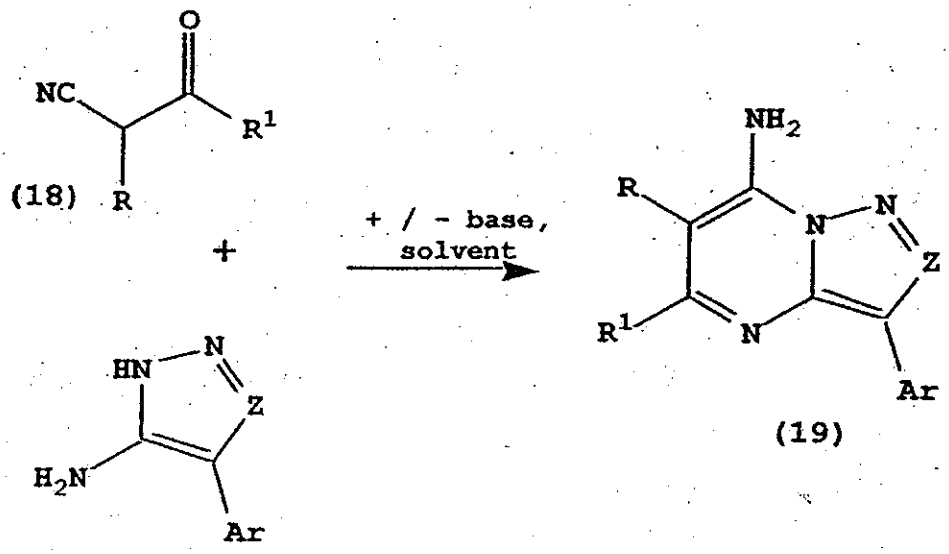


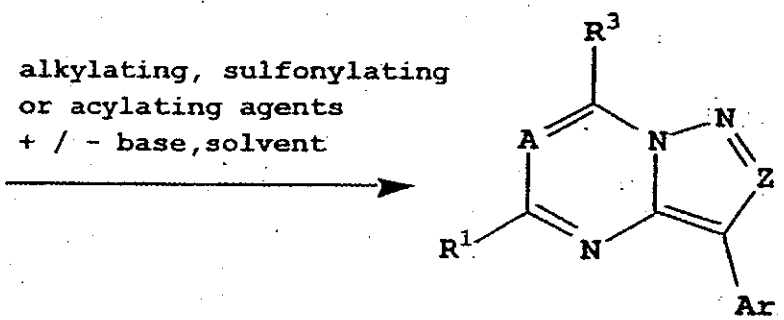
(1) $R^3 = COR^7$, CO_2R^7, (1) $R^3 = C(OH)(R^7)$

M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (1), where R^3 may be - NR^8COR^7, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, - $NR^8SO_2R^7$, may be synthesized as depicted in Scheme 13.

SCHEME 13





(1)

A = CR

R_3 = NR^6R^7, NR^8COR^7, $N(COR^7)_2$, $NR_8CONR^6R^7$, $NR_8CO_2R_{13}$

Reaction of compounds of Formula (18), where R and R^1 are defined above, with compounds of Formula (4) or (10) in the presence or absence of base in an inert solvent may produce compounds of Formula (19) at

temperatures ranging from -50°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

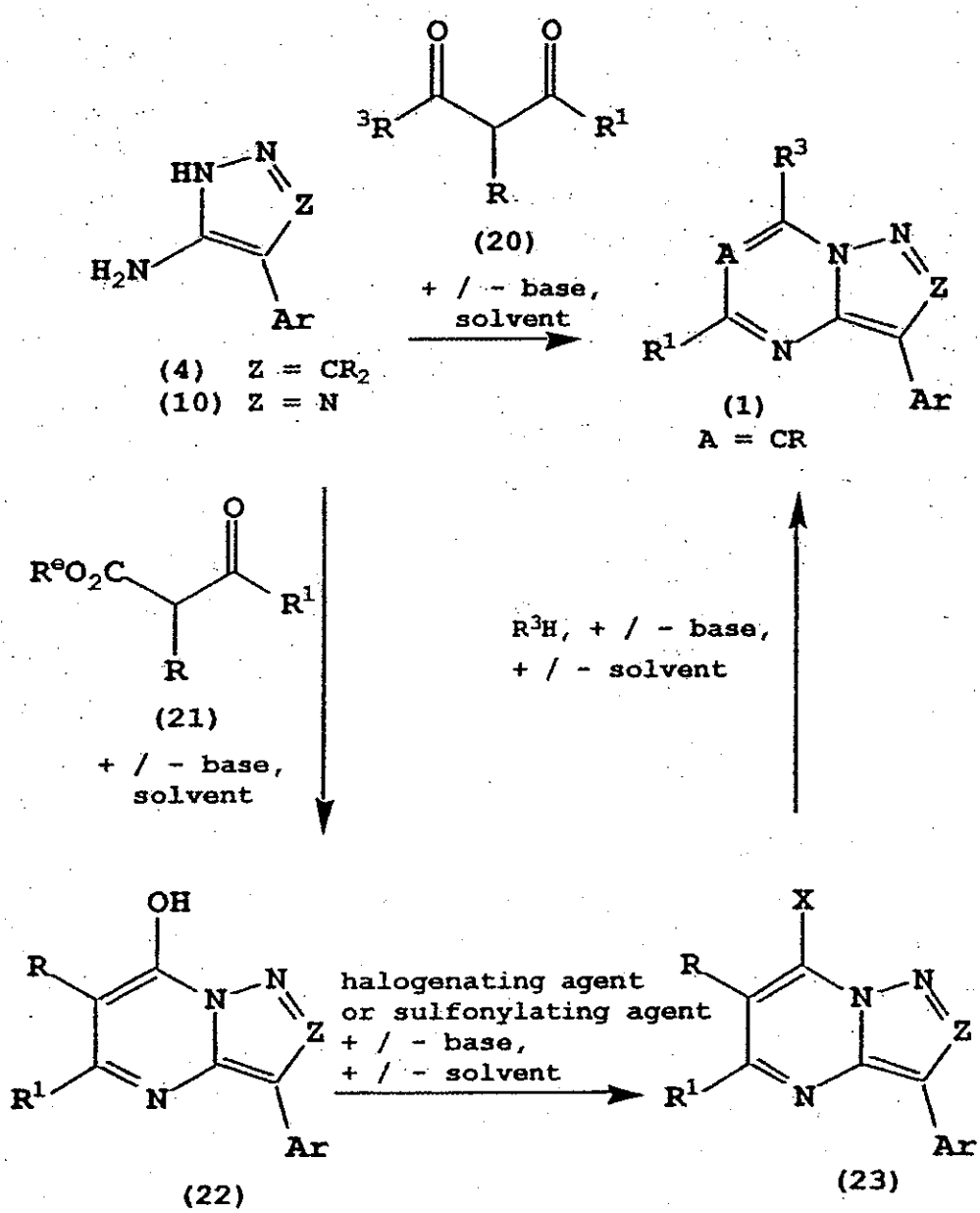
Compounds of Formula (19) may then be reacted with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C_1-C_{10} alkyl -halides, -tosylates, -mesylates or -triflates; C_1-C_{10} haloalkyl(1 - 10 halogens)-halides, -tosylates, -

mesylates or -triflates; C_2-C_8 alkoxyalkyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C_1-C_{10} alkanoyl halides or anhydrides, C_1-C_{10} haloalkanoyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkanoyl halides or anhydrides, C_3-C_6 cycloalkanoyl halides or anhydrides, C_4-C_{12} cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C_1-C_4) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C_1-C_4) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C_1-C_4) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C_1-C_{10} alkylsulfonyl halides or anhydrides, C_1-C_{10} haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkylsulfonyl halides or anhydrides, C_3-C_6 cycloalkylsulfonyl halides or anhydrides, C_4-C_{12} cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C_1-C_4 alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C_1-C_4 alkyl)sulfonyl halides or anhydrides, heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C_1-C_4 alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably

sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (1), where A is CR and R is defined above, may be synthesized by the methods depicted in Scheme 14.

SCHEME 14



Compounds of Formula (4) or (10) may be treated with compounds of Formula (20), where R^1 and R^3 are defined above in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is

defined above. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Alternatively, compounds of Formula (1) where A is CR and R is defined above, may be synthesized through intermediates (22) and (23).

Compounds of Formula (4) or (10) may be treated with compounds of Formula (21), where R^1 is defined above and R^e is alkyl (1 - 6 carbons), in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is defined above. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide),

alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene) Preferred reaction temperatures range from 0°C to 100°C. Compounds of Formula (22) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (23) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkane-sulfonyloxy). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3 or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium

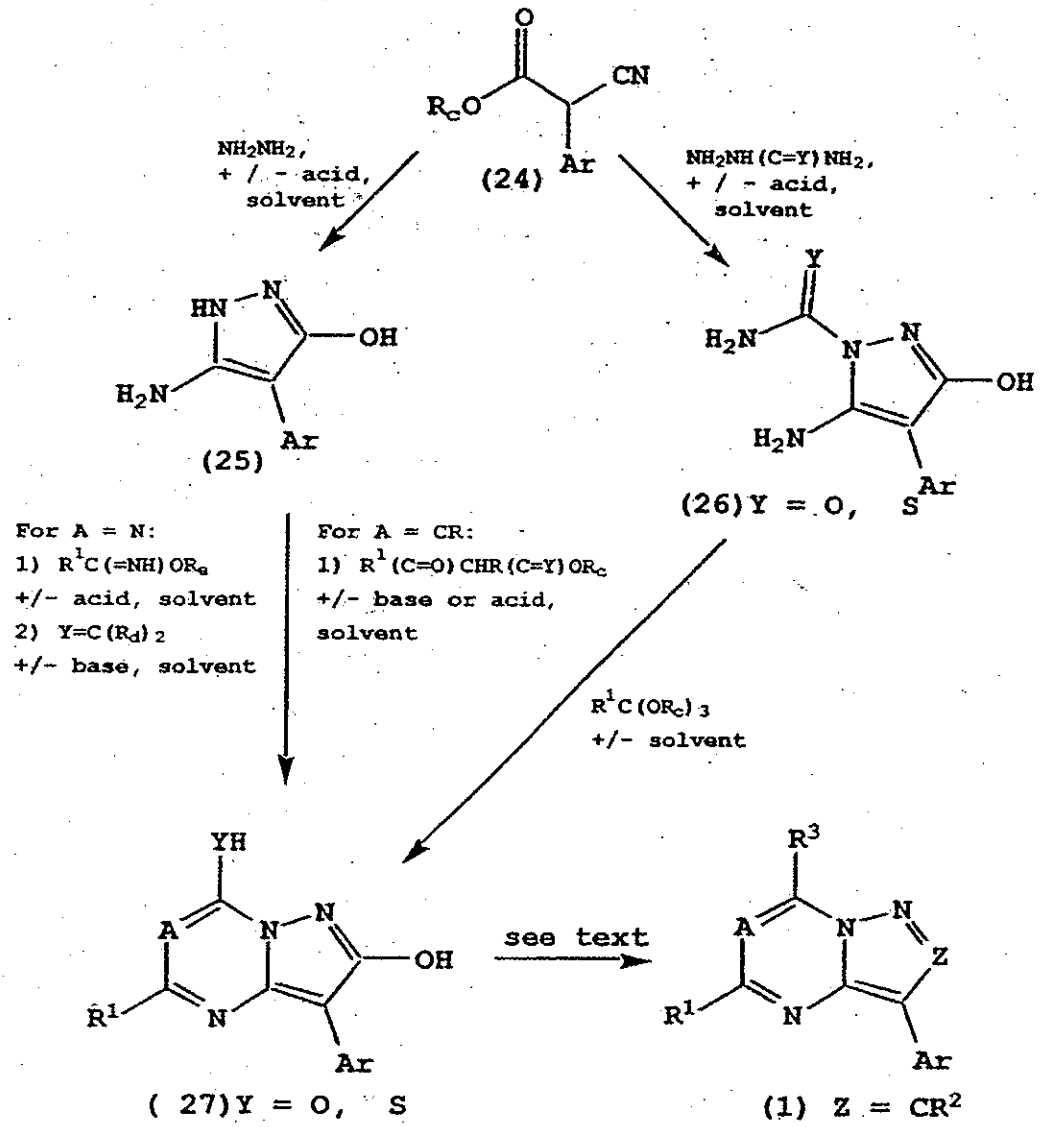
ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

Compounds of Formula (23) may be reacted with compounds of Formula R^3H (where R3 is defined as above except R^3 is not SH, COR^7, CO_2R^7, aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines

(preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

Some compounds of Formula (1) may also be prepared using the methods shown in Scheme 15.

SCHEME 15



A compound of Formula (24) (R_C is a lower alkyl group and Ar is defined as above) may be reacted with hydrazine in the presence or absence of an inert solvent to afford an intermediate of Formula (25), where Ar is defined as above. The conditions employed are similar to those used for the preparation of intermediate of Formula (4) from compound of Formula (3) in Scheme 4. Compounds of Formula (25), where A is N, may be reacted with reagents of the formula

$R^1C(=NH)OR_e$, where R^1 is defined above and R_e is a lower alkyl group) in the presence or absence of an acid in an inert solvent, followed by reaction with a compound of formula YisC(R_d)2 (where Y is O or S and R^d is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent to give compounds of Formula (27) (where A is N and Y is O, S). The conditions for these transformations are the same as those employed for the conversions of compound of Formula (4) to compound of Formula (7) in Scheme 4.

Alternatively, compounds of Formula (25), where A is CR, may be reacted with compounds of the formula $R^1(C=O)CHR(C=Y)OR_c$ (where R^1 and R are defined as above and R_c is a lower alkyl group) to give a compound of Formula (27) (where A is CR) using conditions similar to those employed for the conversion of compounds of Formula (21) to compounds of Formula (22) in Scheme 14. Intermediates of Formula (27) (where Y is O) may be treated with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H or R^2H in the presence or absence of a base in an inert solvent to give compounds of Formula (1) (where Z is CR^2).

It will be recognized by those skilled in the art that various combinations of halogenating agents, sulfonylating agents, R^3H or R^2H may be used in different orders of reaction sequences in Scheme 15 to afford compounds of Formula (1). For example, in some cases, it may be desirable to react compounds with stoichiometric amounts of halogenating agents or sulfonylating agents, react with R^2H (or R^3H), then repeat the reaction with halogenating agents or sulfonylating agents and react with R^3H (or R^2H) to

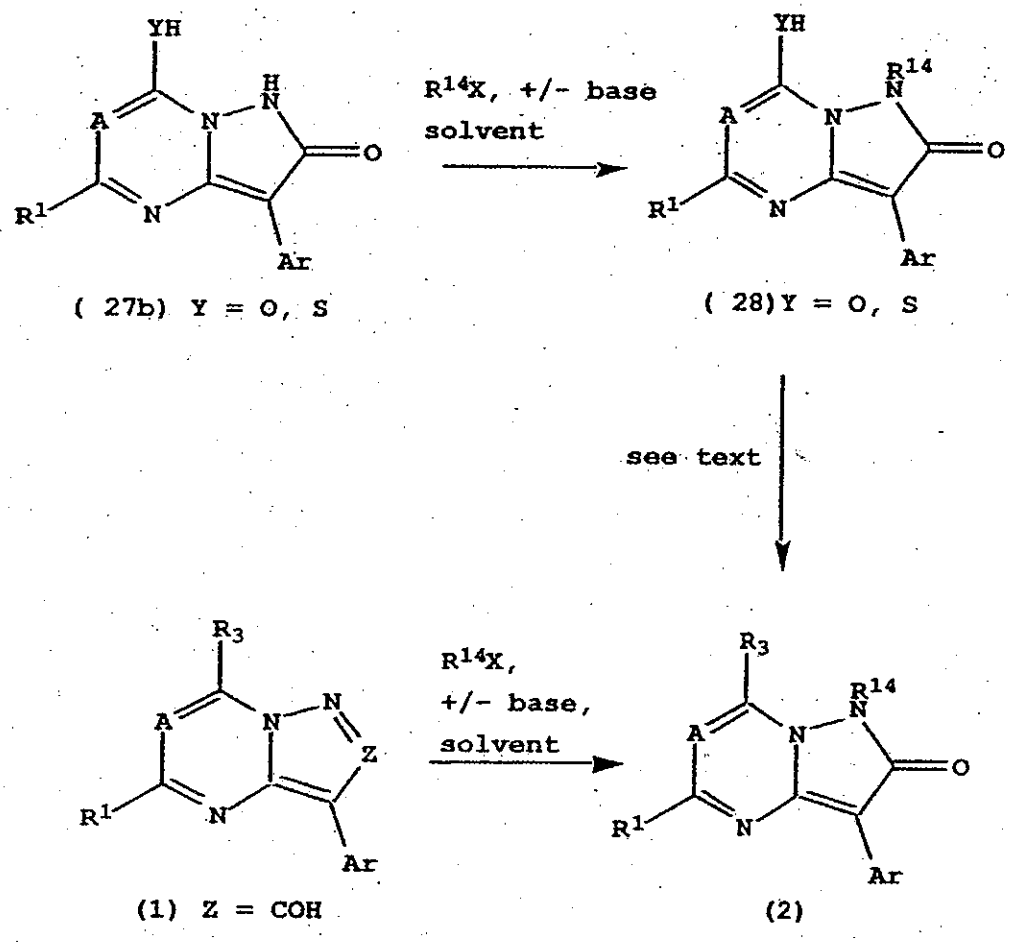
give compounds of Formula (1). The reaction conditions and reagents used for these conversions are similar to the ones employed for the conversion of intermediate compounds of Formulae (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N).

Alternatively, compounds of Formula (27) (where Y is S) may be converted to compounds of Formula (1) in Scheme 15. Intermediate compounds of Formula (27) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or absence of a base in an inert solvent to give a compound of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1) may be prepared from compounds of Formula (24), using an alternate route as depicted in Scheme 15. Compounds of Formula (24) may be converted to compounds of Formula (27) via reaction with compounds of formula $NH_2NH(C{=}NH)NH_2$ in the presence or absence of an acid in an inert solvent, followed by reaction with compounds $R^1C(OR_c)_3$ (where R_c is lower alkyl and R^1 is defined as above), using the conditions employed for the conversion of compounds of Formulae (3) to (17) to (7) in Scheme 10.

Some compounds of Formula (2) may be prepared by the methods illustrated in Scheme 16.

SCHEME 16



(27b) Y = O, S

(28)Y = O, S

(1) Z = COH

(2)

Compounds of Formula (27b) may be treated with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures of Formula (28). Compounds of Formula (28) (Y is O) may then be converted to compounds of Formula (2) by treatment with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H in the presence or absence of a base in an inert solvent to give

compounds of Formula (2). The reaction conditions used for these conversions are similar to the ones employed for the conversion of intermediate compounds (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N). Alternatively, compounds of Formula (28) (Y is S) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or absence of a base in an inert solvent to give a compound of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1), where Z is COH, may be converted to compounds of Formula (2) as illustrated in Scheme 16. Treatment with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures (2). It will be recognized by one skilled in the art that the methods used in Scheme 16 may also be used to prepare compounds of Formula (1) where Z is COR^7.

For Scheme 16, the terms "base" and " inert solvent" may have the meanings given below. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably

sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on an IBM-Bruker FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources

and, where necessary, purified prior to use according to the general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

EXAMPLE 1

Preparation of
2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]
-pyrazolo-[1,3,5]-triazin-4(3H)-one
(Formula 7, where Y is O, R_1 is CH_3, Z is C-CH_3,
Ar is 2,4-dimethylphenyl)

A. 1-Cyano-1-(2,4-dimethylphenyl)propan-2-one

Sodium pellets (9.8g, 0.43 mol) were added portionwise to a solution of 2,4-dimethylphenylacetonitrile (48 g, 0.33 mol) in ethyl acetate (150 mL) at ambient temperature. The reaction mixture was heated to reflux temperature and stirred for 16 hours. The resulting suspension was cooled to room temperature and filtered. The collected precipitate was washed with copious amounts of ether and then air-dried. The solid was dissolved in water and a 1N HCl solution was added until the pH = 5-6. The mixture was extracted with ethyl acetate (3 X 200 mL);

the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to afford a white solid (45.7g, 74% yield): NMR ($CDCl_3$,300 MHz):; CI-MS: 188 (M + H).

B. 5-Amino-4-(2,4-dimethylphenyl)-3-methylpyrazole

A mixture of 1-cyano-1-(2,4-dimethylphenyl)propan-2-one (43.8g, 0.23 mol), hydrazine-hydrate (22 mL, 0.46 mol), glacial acetic acid (45 mL, 0.78 mol) and toluene (500 mL) were stirred at reflux temperature for 18 hours in an apparatus fitted with a Dean-Stark trap. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. The residue was dissolved in 6N HCl and the resulting solution was extracted with ether three times. A concentrated ammonium hydroxide solution was added to the aqueous layer until pH = 11. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a pale brown viscous oil (34.6g, 75% yield): NMR ($CDCl_3$,300 MHz): 7.10 (s, 1H), 7.05 (d, 2H, J=1), 2.37 (s, 3H), 2.10 (s, 3H); CI-MS: 202 (M + H).

C. 5-Acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt

Ethyl acetamidate hydrochloride (60g, 0.48 mol) was added quickly to a rapidly stirred mixture of potassium carbonate (69.5g, 0.50 mol), dichloromethane (120 mL) and water (350 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 120 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed by simple distillation and the pot residue, a

clear pale yellow liquid, (35.0 g) was used without further purification.

Glacial aetic acid (9.7 mL, 0.17 mol) was added to a stirred mixture of 5-amino-4-(2,4-dimethylphenyl)-3-methylpyrazole (34g, 0.17 mol), ethyl acetamidate (22g, 0.25 mol) and acetonitrile (500 mL). The resulting reaction mixture was stirred at room temperature for 3 days; at the end of which time, it was concentrated in vacuo to about one-third of its original volume. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. The white solid was dried *in vacuo* (31.4g, 61% yield): NMR (DMSO-d_6,300 MHz): 7.00 (s, 1H), 6.90 (dd, 2H, J=7, 1), 2.28 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H); CI-MS: 243 (M + H).

D. 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one

Sodium pellets (23g, 1 mol) were added portionwise to ethanol (500 mL) with vigorous stirring. After all the sodium reacted, 5-acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt (31.2g, 0.1 mol) and diethyl carbonate (97 mL, 0.8 mol) were added. The resulting reaction mixture was heated to reflux temperature and stirred for 18 hours. The mix was cooled to room temperature and solvent was removed in vacuo. The residue was dissolved in water and a 1N HCl solution was added slowly until pH = 5-6. The aqueous layer was extracted with ethyl acetate three times; the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a pale tan solid (26g, 98% yield): NMR ($CDCl_3$,300 MHz): 7.15(s, 1H), 7.09 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H); CI-MS: 269 (M + H).

EXAMPLE 2

Preparation of
5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(6H)-one
(Formula 7, where Y is O, R_1 is CH_3, Z is N, Ar is 2,4,6-trimethylphenyl)

A. 1-Phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole

A mixture of 2,4,6-trimethylbenzyl cyanide (1.0g, 6.3 mmol), benzyl azide (0.92g, 6.9 mmol) and potassium t-butoxide (0.78g, 6.9 mmol) in tetrahydrofuran (10mL) was stirred at ambient temperature for 2.5 days. The resulting suspension was diluted with water and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a brown oil. Trituration with ether and filtration afforded a yellow solid (1.12g, 61% yield): NMR ($CDCl_3$,300 MHz):7.60-7.30 (m, 5H), 7.30-7.20 (m, 2H), 5.50 (s, 2H), 3.18 (br s, 2H), 2.30 (s, 3H), 2.10 (s, 6H); CI-MS: 293 (M + H).

B. 4-(2,4,6-Trimethylphenyl)-5-aminotriazole

Sodium (500 mg, 22 mmol) was added with stirring to a mixture of liquid ammonia (30 mL) and 1-phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole (1.1g, 3.8 mmol). The reaction mixture was stirred until a dark green color persisted. An ammonium chloride solution (mL) was added and the mixture was stirred while warming to ambient temperature over 16 hours. The residue was treated with a 1M HCl solution and filtered. The aqueous layer was basified with a concentrated ammonium hydroxide solution (pH = 9) and then extracted with ethyl acetate three times. The

combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a yellow solid (520 mg), which was homogeneous by thin layer chromatography (ethyl acetate): NMR ($CDCl_3$,300 MHz): 6.97 (s, 2H), 3.68-3.50 (br.s, 2H), 2.32 (s, 3H), 2.10 (s, 6H); CI-MS: 203 (M + H).

C. 4-(2,4,6-Trimethylphenyl)-5-acetamidinotriazole, acetic acid salt

A mixture of 4-(2,4,6-trimethylphenyl)-5-aminotriazole (400 mg, 1.98 mmol), ethyl acetamidate (261 mg, 3 mmol) and glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (6 mL) was stirred at ambient temperature for 4 hours. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. Drying *in vacuo* afforded a white solid (490 mg, 82% yield): NMR (DMSO-d_6,300 MHz):7.90-7.70 (br s, 0.5H), 7.50-7.20 (br. s, 0.5H), 6.90 (s, 2H), 6.90 (s, 2H), 3.50-3.10 (br s, 3H), 2.30-2.20 (br s, 3H), 2.05 (d, 1H, J = 7), 1.96 (s, 6H), 1.87 (s, 6H); CI-MS: 244 (M + H).

D. 5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(4H)-one

Sodium (368 mg, 16.2 mmol) was added with stirring to ethanol (10 mL) at room temperature. After the sodium had reacted, 4-(2,4,6-trimethylphenyl)-5-acetamidino-triazole, acetic acid salt (490 mg, 1.6 mmol) and diethyl carbonate (1.6 mL, 13 mmol) were added. The reaction mixture was stirred at reflux temperature for 5 hours, then cooled to room temperature. The reaction mixture was diluted with water; a 1N HCl solution was added until pH = 5-6 and three extractions with ethyl acetate were performed.

The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a yellow residue. Trituration with ether and filtration afforded a yellow solid (300 mg, 69% yield): NMR ($CDCl_3$,300 MHz): 6.98 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H), 2.10 (s, 6H); CI-MS: 270 (M + H).

EXAMPLE 3

Preparation of 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

(Formula 1, where R^3 is $CH(CHCO_2CH_3)_2$, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dimethylphenyl)

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]- pyrazolotriazine

A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a] -pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed *in vacuo*. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (Rf = 0.5) Solvent was removed in vacuo to afford a yellow oil (1.0g, 68% yield): NMR ($CDCl_3$,300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7,1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

B. 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

Sodium hydride (60% in oil, 80 mg, 2 mmol) was washed with hexanes twice, decanted after each washing and taken up in anhydrous tetrahydrofuran (THF, 1 mL). A solution of diethyl malonate (0.32g, 2 mmol) in THF (2 mL) was added dropwise over 5 min, during which time vigorous gas evolution ensued. A solution of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolotriazine (0.5g, 1.75 mmol) in THF (2 mL) was added and the reaction mixture was then stirred under a nitrogen atmosphere for 48 hours. The resulting suspension was poured onto water and extracted three times with ethyl acetate. The combined organic layers were washed once with brine, dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown oil. Column chromatography (ethyl acetate:hexanes::1:9) afforded, after removal of solvent *in vacuo*, a pale yellow solid (Rf = 0.2, 250 mg, 35% yield): mp 50-52°C; NMR ($CDCl_3$, 300 MHz): 12.35 (br.s, 1H, 7.15-7.00 (m, 3H), 4.40 (q, 2H, J = 7), 4.30 (q, 2H, J = 7), 2.4, 2.35, 2.3, 2.2, 2.1 (5 s, 12H), 1.4 (t, 3H, J = 7), 1.35-1.25 (m, 3H); CI-HRMS: Calcd: 411.2032, Found: 411.2023.

EXAMPLE 6

Preparation of 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

(Formula 1, where R^3 is $NHCH(CH_2OCH_3)_2$, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dichlorophenyl)

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]- pyrazolotriazine

A mixture of 2,7-dimethyl-8-(2,4 dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed in vacuo. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (Rf = 0.5) Solvent was removed *in vacuo* to afford a yellow oil (1.0g, 68% yield): NMR ($CDCl_3$,300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7,1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

B. 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4- dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

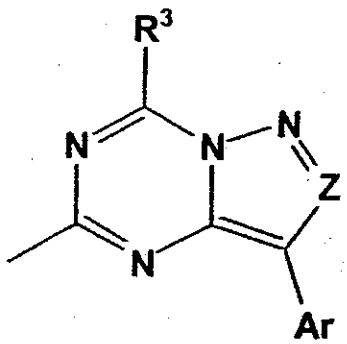
A mixture of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Part A, 570 mg, 1.74 mmol), 1,3-dimethoxypropyl-2-aminopropane (25mg, 2.08 mmol) and ethanol (10 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was poured onto water (25 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo*. Column chromatography (CH_2Cl_2:CH_3OH::50:1) afforded one fraction. Removal of solvent *in vacuo* gave a solid (250 mg, 35% yield): mp 118-120°C; NMR ($CDCl_3$,300 MHz): 7.50 (s, 1H), 7.28 (dd, 2H, J = 8,1),

6.75 (d, 1H, J = 8), 4.70-4.58 (m, 1H), 3.70-3.55 (m, 4H), 3.43 (s, 6H), 2.50 (s, 3H), 2.35 (s, 3H); CI-HRMS: Calcd: 409.1072, Found: 409.1085; Analysis Calcd. for $C_{18}H_{21}Cl_2N_5O_2$: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following additional examples of Tables 1-4 may be prepared.

The examples delineated in TABLE 1 may be prepared by the methods outlined in Examples 1, 2, 3 or 6. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

TABLE 1



Ex.	Z	R_3	Ar	mp(°C)
6[a]	C-Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	118-120
391[bz]	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph	oil

395[bu]	C-Me	NEt_2	2-Me-4,6-$(MeO)_2$Ph	114
396[bv]	C-Me	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph	145-146

NOTES FOR TABLE 1:

a) Analysis Calcd: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

bu) Analysis Calcd: C: 65.90, H: 7.72, N, 18.27; Found: C: 65.77, H: 7.62, N: 18.26.

bv) Analysis Calcd: C: 65.02, H: 7.38, N, 18.96; Found: C: 65.01, H: 7.43, N: 18.68.

bz) CI-HRMS: Calcd: 430.2454; Found: 430.2468(M + H);

EXAMPLE 431

Preparation of 2,4,7-dimethyl-8-(4-methoxy-2-methylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Formula 1, where R^3 is CH_3, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dimethylphenyl)

5-Acetamidino-4-(4-methoxy-2-methylphenyl)-3-methylpyrazole, acetic acid salt (602 mg, 2 mmol) was mixed with a saturated $NaHCO_3$ solution (10 mL). The aqueous mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was taken up in toluene (10 mL) and trimethyl orthoacetate (0.36 g, 3 mmol) was added to the suspension. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and stirred for 16 hours. After being cooled to ambient temperature, the reaction

mixture was concentrated in vacuo to give an oily solid. Column chromatography ($CHCl_3$:MeOH::9:1) afforded, after removal of solvent in vacuo, a yellow viscous oil (Rf = 0.6, 210 mg, 37% yield): NMR ($CDCl_3$, 300 MHz): 7.15 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.85 (dd, 1H, J = 8,1), 3.85 (s, 3H), 2.95 (s, 3H), 2.65 (s, 3H), 2.4 (s, 3H), 2.15 (s, 3H); CI-HRMS: Calcd: 283.1559, Found: 283.1554 (M + H).

EXAMPLE 432

7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine
(Formula 1 where A is CH, R1 is Me, R3 is OH, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

5-Amino-4-(2-chloro-4-methylphenyl)-3-methylpyrazole (1.86 g, 8.4 mmol) was dissolved in glacial acetic acid (30 mL) with stirring. Ethyl acetoacetate (1.18 mL, 9.2 mmol) was then added dropwise to the resulting solution. The reaction mixture was then heated to reflux temperature and stirred for 16 hours, then cooled to room temperature. Ether (100 mL) was added and the resulting precipitate was collected by filtration. Drying in vacuo afforded a white solid (1.0 g, 42% yield): NMR ($CDCl_3$, 300Hz): 8.70 (br.s 1H), 7.29 (s, 1H), 7.21-7.09 (m, 2H), 5.62 (s, 1H), 2.35 (s, 6H), 2.29 (s, 3H); CI-MS: 288 (M+H).

EXAMPLE 433

7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine

(Formula 1 where A is CH, R1 is Me, R3 is Cl, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

A mixture of 7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (1.0 g, 3.5 mmol), phosphorus oxychloride (2.7 g, 1.64 mL, 17.4 mmol), N,N-diethylaniline (0.63 g, 0.7 mL, 4.2 mmol) and toluene (20 mL) was stirred at reflux temperature for 3 hours, then it was cooled to ambient temperature. The volatiles were removed in vacuo. Flash chromatography (EtOAc:hexane::1:2) on the residue gave 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (900 mg, 84% yield) as a yellow oil: NMR ($CDCl_3$, 300Hz): 7.35 (s, 1H), 7.28-7.26 (m, 1H), 71.6 (d, 1H, J = 7), 6.80 (s, 1H), 2.55 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H); CI- MS: 306 (M+H).

EXAMPLE 434

7-(pentyl-3-amino)-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine

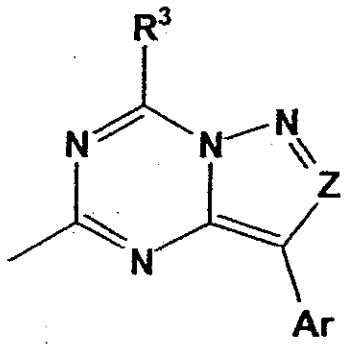
(Formula 1 where A is CH, R1 is Me, R3 is pentyl-3-amino, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

A solution of 3-pentylamine (394mg, 6.5 mmol) and 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (200 mg, 0.65 mmol) in dimethylsulfoxide (DMSO, 10 mL) was stirred at 150°C for 2 hours; then it was cooled to ambient temperature. The reaction mixture was then poured onto water (100 mL) and mixed. Three extractions with dichloromethane, washing the combined organic layers with brine, drying over $MgSO_4$, filtration and removal of solvent in vacuo produced a yellow solid. Flash chromatography (EtOAc:hexanes::1:4) afforded a white

solid (140 mg, 60% yield): mp 139-141°C; NMR ($CDCl_3$, 300Hz):7.32 (s, 1H), 7.27 (d, 1H, J = 8), 7.12 (d, 1H, J = 7), 6.02 (d, 1H, J = 9), 5.78 (s, 1H), 3.50-3.39 (m, 1H), 2.45 (s, 3H), 2.36 (s, 6H), 1.82-1.60 (m, 4H), 1.01 (t, 6H, J = 8); Analysis Calcd for $C_{20}H_{25}ClN_4$: C, 67.31, H, 7.06, N, 15.70, Cl: 9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

The examples delineated in Table 7 may be prepared by the methods outlined in Examples 1, 2, 3 or 6. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

Table 7



Ex.	Z	R_3	Ar	mp(°C)
1200[a]	C-Me	2-ethylpiperidyl	2-Me-4-OMePh	58-59.5
1201[b]	C-Me	cyclobutylamino	2-Me-4-OMePh	94.5-96
1202[c]	C-Me	$N(Me)CH_2CH=CH_2$	2-Me-4-OMePh	oil
1203[d]	C-Me	$N(CH_2CH=CH_2)_2$	2-Me-4-OMePh	oil

1204	C-Me	N(Et)CH_2c-Pr	2-Me-4-OMePh	
1205[e]	C-Me	$NHCH_2$-2-tetrahydrofuryl	2-Me-4-OMePh	
amorphous				
1206[ay]	C-Me	N(Pr)CH_2c-Pr	2-Me-4-OMePh	oil
1207[az]	C-Me	N(Me)Pr	2-Me-4-OMePh	oil
1208[f]	C-Me	N(Me)Et	2-Me-4-OMePh	oil
1209[g]	C-Me	N(Me)Bu	2-Me-4-OMePh	oil
1210[h]	C-Me	N(Me)propargyl	2-Me-4-OMePh	oil
1211[i]	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	2-Me-4-OMePh	oil
1212[j]	C-Me	N(CH_2CH_2OMe)$CH_2CH=CH_2$	2-Me-4-OMePh	oil
1213[k]	C-Me	N(CH_2CH_2OMe)Me	2-Me-4-OMePh	oil
1214	C-Me	N(CH_2CH_2OMe)Et	2-Me-4-OMePh	
1215	C-Me	N(CH_2CH_2OMe)Pr	2-Me-4-OMePh	
1216	C-Me	N(CH_2CH_2OMe)CH_2c-Pr	2-Me-4-OMePh	
1217[m]	C-Me	NH(CH(CH_3)CH_2CH_3)	2-Me-4-OMePh	oil
1218	C-Me	NHCH(c-Pr)$_2$	2-Me-4-OMePh	
1219[n]	C-Me	NH-2-hexyl	2-Me-4-OMePh	oil
1220[o]	C-Me	NH-2-propyl	2-Me-4-OMePh	oil
1221[p]	C-Me	$NHCH_2$-2-tetrahydrofuryl	2-Me-4-OMePh	
amorphous				
1222[q]	C-Me	NEt(cyclohexyl)	2-Me-4-OMePh	oil
1223	C-Me	2-ethylpiperidyl	2,5-Me_2-4-OMePh	
1224	C-Me	cyclobutylamino	2,5-Me_2-4-OMePh	
1225	C-Me	N(Me)$CH_2CH=CH_2$	2,5-Me_2-4-OMePh	
1226	C-Me	N(Et)CH_2c-Pr	2,5-Me_2-4-OMePh	
1227	C-Me	N(Pr)CH_2c-Pr	2,5-Me_2-4-OMePh	
1228	C-Me	N(Me)Pr	2,5-Me_2-4-OMePh	
1229	C-Me	N(Me)Et	2,5-Me_2-4-OMePh	

1230	C-Me	N(Me)Bu	2,5-Me_2-4-OMePh
1231	C-Me	N(Me)propargyl	2,5-Me_2-4-OMePh
1232	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	2,5-Me_2-4-OMePh
1233	C-Me	N(CH_2CH_2OMe)$CH_2CH=CH_2$	2,5-Me_2-4-OMePh
1234	C-Me	N(CH_2CH_2OMe)Me	2,5-Me_2-4-OMePh
1235	C-Me	N(CH_2CH_2OMe)Et	2,5-Me_2-4-OMePh
1236	C-Me	N(CH_2CH_2OMe)Pr	2,5-Me_2-4-OMePh
1237	C-Me	N(CH_2CH_2OMe)CH_2c-Pr	2,5-Me_2-4-OMePh
1238	C-Me	NH(CH(CH_3)CH_2CH_3)	2,5-Me_2-4-OMePh
1239	C-Me	NHCH(c-Pr)$_2$	2,5-Me_2-4-OMePh
1240	C-Me	2-ethylpiperidyl	2,4-$(OMe)_2$Ph
1241	C-Me	cyclobutylamino	2,4-$(OMe)_2$Ph
1245	C-Me	N(Me)$CH_2CH=CH_2$	2,4-$(OMe)_2$Ph
1255[r]	C-Me	N($CH_2CH=CH_2$)$_2$	2,4-$(OMe)_2$Ph64.8-65.6
1256	C-Me	N(Et)CH_2c-Pr	2,4-$(OMe)_2$Ph
1257	C-Me	N(Pr)CH_2c-Pr	2,4-$(OMe)_2$Ph
1258	C-Me	N(Me)Pr	2,4-$(OMe)_2$Ph
1259	C-Me	N(Me)Et	2,4-$(OMe)_2$Ph
1260	C-Me	N(Me)Bu	2,4-$(OMe)_2$Ph
1261	C-Me	N(Me)propargyl	2,4-$(OMe)_2$Ph
1262	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	2,4-$(OMe)_2$Ph
1263	C-Me	N(CH_2CH_2OMe)$CH_2CH=CH_2$	2,4-$(OMe)_2$Ph
1264	C-Me	N(CH_2CH_2OMe)Me	2,4-$(OMe)_2$Ph
1265	C-Me	N(CH_2CH_2OMe)Et	2,4-$(OMe)_2$Ph
1266	C-Me	N(CH_2CH_2OMe)Pr	2,4-$(OMe)_2$Ph
1267	C-Me	N(CH_2CH_2OMe)CH_2c-Pr	2,4-$(OMe)_2$Ph
1268[s]	C-Me	NH(CH(CH_3)CH_2CH_3)	2,4-$(OMe)_2$Ph137.8-138.3
1269	C-Me	NHCH(c-Pr)$_2$	2,4-$(OMe)_2$Ph

1270[t]	C-Me	$N(CH_2CH_2OMe)_2$	$2,4-(OMe)_2Ph$	oil
1271[u]	C-Me	$NHCH(Et)_2$	$2,4-(OMe)_2Ph$	128-129.4
1272	C-Me	$N(Et)_2$	$2,4-(OMe)_2Ph$	
1273[v]	C-Me	$N(Pr)_2$	$2,4-(OMe)_2Ph$	
1274	C-Me	2-ethylpiperidyl	$2,4-(OMe)_2-5-MePh$	
1275	C-Me	cyclobutylamino	$2,4-(OMe)_2-5-MePh$	
1276	C-Me	$N(Me)CH_2CH=CH_2$	$2,4-(OMe)_2-5-MePh$	
1277	C-Me	$N(Et)CH_2c-Pr$	$2,4-(OMe)_2-5-MePh$	
1278	C-Me	$N(Pr)CH_2c-Pr$	$2,4-(OMe)_2-5-MePh$	
1279	C-Me	N(Me)Pr	$2,4-(OMe)_2-5-MePh$	
1280	C-Me	N(Me)Et	$2,4-(OMe)_2-5-MePh$	
1281	C-Me	N(Me)Bu	$2,4-(OMe)_2-5-MePh$	
1282	C-Me	N(Me)propargyl	$2,4-(OMe)_2-5-MePh$	
1283	C-Me	$NH(CH(CH_3)CH(CH_3)CH_3)$	$2,4-(OMe)_2-5-MePh$	
1284	C-Me	$N(CH_2CH_2OMe)CH_2CH=CH_2$	$2,4-(OMe)_2-5-MePh$	
1285	C-Me	$N(CH_2CH_2OMe)Me$	$2,4-(OMe)_2-5-MePh$	
1286	C-Me	$N(CH_2CH_2OMe)Et$	$2,4-(OMe)_2-5-MePh$	
1287	C-Me	$N(CH_2CH_2OMe)Pr$	$2,4-(OMe)_2-5-MePh$	
1288	C-Me	$N(CH_2CH_2OMe)CH_2c-Pr$	$2,4-(OMe)_2-5-MePh$	
1289	C-Me	$NH(CH(CH_3)CH_2CH_3)$	$2,4-(OMe)_2-5-MePh$	
1290	C-Me	$NHCH(c-Pr)_2$	$2,4-(OMe)_2-5-MePh$	
1291	C-Me	$N(CH_2CH_2OMe)_2$	$2,4-(OMe)_2-5-MePh$	
1292	C-Me	$NHCH(Et)_2$	$2,4-(OMe)_2-5-MePh$	
1293	C-Me	$N(Et)_2$	$2,4-(OMe)_2-5-MePh$	
1294	C-Me	2-ethylpiperidyl	$2,4-(OMe)_2-5-ClPh$	
1295	C-Me	cyclobutylamino	$2,4-(OMe)_2-5-ClPh$	
1296	C-Me	$N(Me)CH_2CH=CH_2$	$2,4-(OMe)_2-5-ClPh$	
1297	C-Me	$N(Et)CH_2c-Pr$	$2,4-(OMe)_2-5-ClPh$	
1298	C-Me	$N(Pr)CH_2c-Pr$	$2,4-(OMe)_2-5-ClPh$	

1299	C-Me	N(Me)Pr	2,4-$(OMe)_2$-5-ClPh	
1300	C-Me	N(Me)Et	2,4-$(OMe)_2$-5-ClPh	
1301	C-Me	N(Me)Bu	2,4-$(OMe)_2$-5-ClPh	
1302	C-Me	N(Me)propargyl	2,4-$(OMe)_2$-5-ClPh	
1303	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	2,4-$(OMe)_2$-5-ClPh	
1304	C-Me	N(CH_2CH_2OMe)$CH_2CH=CH_2$	2,4-$(OMe)_2$-5-ClPh	
1305	C-Me	N(CH_2CH_2OMe)Me	2,4-$(OMe)_2$-5-ClPh	
1306	C-Me	N(CH_2CH_2OMe)Et	2,4-$(OMe)_2$-5-ClPh	
1307	C-Me	N(CH_2CH_2OMe)Pr	2,4-$(OMe)_2$-5-ClPh	
1308	C-Me	N(CH_2CH_2OMe)CH_2c-Pr	2,4-$(OMe)_2$-5-ClPh	
1309	C-Me	NH(CH(CH_3)CH_2CH_3)	2,4-$(OMe)_2$-5-ClPh	
1310	C-Me	NHCH(c-Pr)$_2$	2,4-$(OMe)_2$-5-ClPh	
1311	C-Me	N(CH_2CH_2OMe)$_2$	2,4-$(OMe)_2$-5-ClPh	
1312	C-Me	NHCH(Et)$_2$	2,4-$(OMe)_2$-5-ClPh	
1313	C-Me	N(Et)$_2$	2,4-$(OMe)_2$-5-ClPh	
1314[y]	C-Me	2-ethylpiperidyl	2-Me-4,6-$(OMe)_2$Ph	145-149
1315[z]	C-Me	cyclobutylamino	2-Me-4,6-$(OMe)_2$Ph	131-133
1316[aa]	C-Me	N(Me)$CH_2CH=CH_2$	2-Me-4,6-$(OMe)_2$Ph	oil
1317	C-Me	N(Et)CH_2c-Pr	2-Me-4,6-$(OMe)_2$Ph	
1318[ab]	C-Me	N(Pr)CH_2c-Pr	2-Me-4,6-$(OMe)_2$Ph	oil
1319[ac]	C-Me	N(Me)Pr	2-Me-4,6-$(OMe)_2$Ph	oil
1320[ad]	C-Me	N(Me)Et	2-Me-4,6-$(OMe)_2$Ph	oil
1321[ae]	C-Me	N(Me)Bu	2-Me-4,6-$(OMe)_2$Ph	oil

1322	C-Me	N(Me)propargyl	2-Me-4,6-$(OMe)_2$Ph	
1323	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	2-Me-4,6-$(OMe)_2$Ph	
1324	C-Me	N(CH_2CH_2OMe)$CH_2CH=CH_2$	2-Me-4,6-$(OMe)_2$Ph	
1325	C-Me	N(CH_2CH_2OMe)Me	2-Me-4,6-$(OMe)_2$Ph	
1326[af]	C-Me	N(CH_2CH_2OMe)Et	2-Me-4,6-$(OMe)_2$Ph	oil
1327	C-Me	N(CH_2CH_2OMe)Pr	2-Me-4,6-$(OMe)_2$Ph	
1328[ag]	C-Me	N(CH_2CH_2OMe)CH_2c-Pr	2-Me-4,6-$(OMe)_2$Ph	oil
1329[ax]	C-Me	NH(CH(CH_3)CH_2CH_3)	2-Me-4,6-$(OMe)_2$Ph	107-110
1330	C-Me	NHCH(c-Pr)$_2$	2-Me-4,6-$(OMe)_2$Ph	
1331[w]	C-Me	N(CH_2CH_2OMe)$_2$	2-Me-4,6-$(OMe)_2$Ph	
1332	C-Me	NHCH(Et)$_2$	2-Me-4,6-$(OMe)_2$Ph	
1333	C-Me	N(Et)$_2$	2-Me-4,6-$(OMe)_2$Ph	
1334[x]	C-Me	NEt(Bu)	2-Me-4,6-$(OMe)_2$Ph	oil
1335	C-Me	2-ethylpiperidyl	2-Cl-4,6-$(OMe)_2$Ph	
1336	C-Me	cyclobutylamino	2-Cl-4,6-$(OMe)_2$Ph	
1337	C-Me	N(Me)$CH_2CH=CH_2$	2-Cl-4,6-$(OMe)_2$Ph	
1338	C-Me	N(Et)CH_2c-Pr	2-Cl-4,6-$(OMe)_2$Ph	
1339	C-Me	N(Pr)CH_2c-Pr	2-Cl-4,6-$(OMe)_2$Ph	
1340	C-Me	N(Me)Pr	2-Cl-4,6-$(OMe)_2$Ph	
1341	C-Me	N(Me)Et	2-Cl-4,6-$(OMe)_2$Ph	
1342	C-Me	N(Me)Bu	2-Cl-4,6-$(OMe)_2$Ph	
1343	C-Me	N(Me)propargyl	2-Cl-4,6-$(OMe)_2$Ph	
1344	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	2-Cl-4,6-$(OMe)_2$Ph	
1345	C-Me	N(CH_2CH_2OMe)$CH_2CH=CH_2$	2-Cl-4,6-$(OMe)_2$Ph	
1346	C-Me	N(CH_2CH_2OMe)Me	2-Cl-4,6-$(OMe)_2$Ph	
1347	C-Me	N(CH_2CH_2OMe)Et	2-Cl-4,6-$(OMe)_2$Ph	
1348	C-Me	N(CH_2CH_2OMe)Pr	2-Cl-4,6-$(OMe)_2$Ph	

1349	C-Me	$N(CH_2CH_2OMe)CH_2c\text{-}Pr$	$2\text{-}Cl\text{-}4,6\text{-}(OMe)_2Ph$
1350	C-Me	$NH(CH(CH_3)CH_2CH_3)$	$2\text{-}Cl\text{-}4,6\text{-}(OMe)_2Ph$
1351	C-Me	$NHCH(c\text{-}Pr)_2$	$2\text{-}Cl\text{-}4,6\text{-}(OMe)_2Ph$
1352	C-Me	$NHCH(Et)_2$	$2\text{-}Cl\text{-}4,6\text{-}(OMe)_2Ph$
1353	C-Me	$N(Et)_2$	$2\text{-}Cl\text{-}4,6\text{-}(OMe)_2Ph$
1354	C-Me	2-ethylpiperidyl	2-Cl-4-OMe-Ph
1355	C-Me	cyclobutylamino	2-Cl-4-OMe-Ph
1356	C-Me	$N(Me)CH_2CH{=}CH_2$	2-Cl-4-OMe-Ph
1357	C-Me	$N(Et)CH_2c\text{-}Pr$	2-Cl-4-OMe-Ph
1358	C-Me	$N(Pr)CH_2c\text{-}Pr$	2-Cl-4-OMe-Ph
1359	C-Me	N(Me)Pr	2-Cl-4-OMe-Ph
1360	C-Me	N(Me)Et	2-Cl-4-OMe-Ph
1361	C-Me	N(Me)Bu	2-Cl-4-OMe-Ph
1362	C-Me	N(Me)propargyl	2-Cl-4-OMe-Ph
1363	C-Me	$NH(CH(CH_3)CH(CH_3)CH_3)$	2-Cl-4-OMe-Ph
1364	C-Me	$N(CH_2CH_2OMe)CH_2CH{=}CH_2$	2-Cl-4-OMe-Ph
1365	C-Me	$N(CH_2CH_2OMe)Me$	2-Cl-4-OMe-Ph
1366	C-Me	$N(CH_2CH_2OMe)Et$	2-Cl-4-OMe-Ph
1367	C-Me	$N(CH_2CH_2OMe)Pr$	2-Cl-4-OMe-Ph
1368	C-Me	$N(CH_2CH_2OMe)CH_2c\text{-}Pr$	2-Cl-4-OMe-Ph
1369	C-Me	$NH(CH(CH_3)CH_2CH_3)$	2-Cl-4-OMe-Ph
1370	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-OMe-Ph
1371	C-Me	2-ethylpiperidyl	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$
1372	C-Me	cyclobutylamino	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$
1373	C-Me	$N(Me)CH_2CH{=}CH_2$	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$
1374	C-Me	$N(Et)CH_2c\text{-}Pr$	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$
1375	C-Me	$N(Pr)CH_2c\text{-}Pr$	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$
1376	C-Me	N(Me)Pr	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$
1377	C-Me	N(Me)Et	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$
1378	C-Me	N(Me)Bu	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$
1379	C-Me	N(Me)propargyl	$2\text{-}Me\text{-}4,5\text{-}(OMe)_2Ph$

1380	C-Me	NH(CH(CH$_3$)CH(CH$_3$)CH$_3$)	2-Me-4,5-(OMe)$_2$Ph	
1381	C-Me	N(CH$_2$CH$_2$OMe)CH$_2$CH=CH$_2$	2-Me-4,5-(OMe)$_2$Ph	
1382	C-Me	N(CH$_2$CH$_2$OMe)Me	2-Me-4,5-(OMe)$_2$Ph	
1383	C-Me	N(CH$_2$CH$_2$OMe)Et	2-Me-4,5-(OMe)$_2$Ph	
1384	C-Me	N(CH$_2$CH$_2$OMe)Pr	2-Me-4,5-(OMe)$_2$Ph	
1385	C-Me	N(CH$_2$CH$_2$OMe)CH$_2$c-Pr	2-Me-4,5-(OMe)$_2$Ph	
1386	C-Me	NH(CH(CH$_3$)CH$_2$CH$_3$)	2-Me-4,5-(OMe)$_2$Ph	
1387	C-Me	NHCH(c-Pr)$_2$	2-Me-4,5-(OMe)$_2$Ph	
1388	C-Me	N(CH$_2$CH$_2$OMe)$_2$	2-Me-4,5-(OMe)$_2$Ph	
1389	C-Me	NHCH(Et)$_2$	2-Me-4,5-(OMe)$_2$Ph	
1390	C-Me	N(Et)$_2$	2-Me-4,5-(OMe)$_2$Ph	
1391	C-Me	NEt(Bu)	2-Me-4,5-(OMe)$_2$Ph	
1392	C-Me	2-ethylpiperidyl	2-Cl-4,5-(OMe)$_2$Ph	
1393[ab]	C-Me	cyclobutylamino	2-Cl-4,5-(OMe)$_2$Ph	121-122
1394[ai]	C-Me	N(Me)CH$_2$CH=CH$_2$	2-Cl-4,5-(OMe)$_2$Ph	122-126
1395	C-Me	N(Et)CH$_2$c-Pr	2-Cl-4,5-(OMe)$_2$Ph	
1396[aj]	C-Me	N(Pr)CH$_2$c-Pr	2-Cl-4,5-(OMe)$_2$Ph	oil
1397[ak]	C-Me	N(Me)Pr	2-Cl-4,5-(OMe)$_2$Ph	115-117
1398[al]	C-Me	N(Me)Et	2-Cl-4,5-(OMe)$_2$Ph	115-119
1399[am]	C-Me	N(Me)Bu	2-Cl-4,5-(OMe)$_2$Ph	oil
1400	C-Me	N(Me)propargyl	2-Cl-4,5-(OMe)$_2$Ph	
1401	C-Me	NH(CH(CH$_3$)CH(CH$_3$)CH$_3$)	2-Cl-4,5-(OMe)$_2$Ph	
1402	C-Me	N(CH$_2$CH$_2$OMe)CH$_2$CH=CH$_2$	2-Cl-4,5-(OMe)$_2$Ph	
1403	C-Me	N(CH$_2$CH$_2$OMe)Me	2-Cl-4,5-(OMe)$_2$Ph	

1404[an]	C-Me	$N(CH_2CH_2OMe)Et$	2-Cl-4,5-$(OMe)_2$Ph	oil
1405	C-Me	$N(CH_2CH_2OMe)Pr$	2-Cl-4,5-$(OMe)_2$Ph	
1406[ao]	C-Me	$N(CH_2CH_2OMe)CH_2c$-Pr	2-Cl-4,5-$(OMe)_2$Ph	oil
1407	C-Me	$NH(CH(CH_3)CH_2CH_3)$	2-Cl-4,5-$(OMe)_2$Ph	
1408	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4,5-$(OMe)_2$Ph	
1409[ap]	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,5-$(OMe)_2$Ph	oil
1410[aq]	C-Me	$NHCH(Et)_2$	2-Cl-4,5-$(OMe)_2$Ph	104-106
1411[ar]	C-Me	$N(Et)_2$	2-Cl-4,5-$(OMe)_2$Ph	oil
1412[as]	C-Me	NEt(Bu)	2-Cl-4,5-$(OMe)_2$Ph	oil
1413	C-Me	2-ethylpiperidyl	2-Cl-4-OMe-5-MePh	
1414	C-Me	cyclobutylamino	2-Cl-4-OMe-5-MePh	
1415	C-Me	$N(Me)CH_2CH{=}CH_2$	2-Cl-4-OMe-5-MePh	
1416	C-Me	$N(Et)CH_2c$-Pr	2-Cl-4-OMe-5-MePh	
1417	C-Me	$N(Pr)CH_2c$-Pr	2-Cl-4-OMe-5-MePh	
1418	C-Me	N(Me)Pr	2-Cl-4-OMe-5-MePh	
1419	C-Me	N(Me)Et	2-Cl-4-OMe-5-MePh	
1420	C-Me	N(Me)Bu	2-Cl-4-OMe-5-MePh	
1421	C-Me	N(Me)propargyl	2-Cl-4-OMe-5-MePh	
1422	C-Me	$NH(CH(CH_3)CH(CH_3)CH_3)$	2-Cl-4-OMe-5-MePh	
1423	C-Me	$N(CH_2CH_2OMe)CH_2CH{=}CH_2$	2-Cl-4-OMe-5-MePh	
1424	C-Me	$N(CH_2CH_2OMe)Me$	2-Cl-4-OMe-5-MePh	
1425	C-Me	$N(CH_2CH_2OMe)Et$	2-Cl-4-OMe-5-MePh	
1426	C-Me	$N(CH_2CH_2OMe)Pr$	2-Cl-4-OMe-5-MePh	
1427	C-Me	$N(CH_2CH_2OMe)CH_2c$-Pr	2-Cl-4-OMe-5-MePh	
1428	C-Me	$NH(CH(CH_3)CH_2CH_3)$	2-Cl-4-OMe-5-MePh	
1429	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-OMe-5-MePh	
1430	C-Me	$NHCH(Et)_2$	2-Cl-4-OMe-5-MePh	

1431	C-Me	$N(Et)_2$	2-Cl-4-OMe-5-MePh
1432	C-Me	NEt(Bu)	2-Cl-4-OMe-5-MePh
1433	C-Me	2-ethylpiperidyl	2-Cl-6-OMe-4-MePh
1434	C-Me	cyclobutylamino	2-Cl-6-OMe-4-MePh
1435	C-Me	$N(Me)CH_2CH=CH_2$	2-Cl-6-OMe-4-MePh
1436	C-Me	$N(Et)CH_2c$-Pr	2-Cl-6-OMe-4-MePh
1437	C-Me	$N(Pr)CH_2c$-Pr	2-Cl-6-OMe-4-MePh
1438	C-Me	N(Me)Pr	2-Cl-6-OMe-4-MePh
1439	C-Me	N(Me)Et	2-Cl-6-OMe-4-MePh
1440	C-Me	N(Me)Bu	2-Cl-6-OMe-4-MePh
1441	C-Me	N(Me)propargyl	2-Cl-6-OMe-4-MePh
1442	C-Me	$NH(CH(CH_3)CH(CH_3)CH_3)$	2-Cl-6-OMe-4-MePh
1443	C-Me	$N(CH_2CH_2OMe)CH_2CH=CH_2$	2-Cl-6-OMe-4-MePh
1444	C-Me	$N(CH_2CH_2OMe)Me$	2-Cl-6-OMe-4-MePh
1445	C-Me	$N(CH_2CH_2OMe)Et$	2-Cl-6-OMe-4-MePh
1446	C-Me	$N(CH_2CH_2OMe)Pr$	2-Cl-6-OMe-4-MePh
1447	C-Me	$N(CH_2CH_2OMe)CH_2c$-Pr	2-Cl-6-OMe-4-MePh
1448	C-Me	$NH(CH(CH_3)CH_2CH_3)$	2-Cl-6-OMe-4-MePh
1449	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-6-OMe-4-MePh
1450	C-Me	$NHCH(Et)_2$	2-Cl-6-OMe-4-MePh
1451	C-Me	$N(Et)_2$	2-Cl-6-OMe-4-MePh
1452	C-Me	NEt(Bu)	2-Cl-6-OMe-4-MePh
1453	C-Me	2-ethylpiperidyl	2,6-Me_2-4-OMePh
1454	C-Me	cyclobutylamino	2,6-Me_2-4-OMePh
1455	C-Me	$N(Me)CH_2CH=CH_2$	2,6-Me_2-4-OMePh
1456	C-Me	$N(Et)CH_2c$-Pr	2,6-Me_2-4-OMePh
1457	C-Me	$N(Pr)CH_2c$-Pr	2,6-Me_2-4-OMePh
1458	C-Me	N(Me)Pr	2,6-Me_2-4-OMePh
1459	C-Me	N(Me)Et	2,6-Me_2-4-OMePh
1460	C-Me	N(Me)Bu	2,6-Me_2-4-OMePh
1461	C-Me	N(Me)propargyl	2,6-Me_2-4-OMePh

1462	C-Me	NH(CH(CH$_3$)CH(CH$_3$)CH$_3$)	2,6-Me$_2$-4-OMePh	
1463	C-Me	N(CH$_2$CH$_2$OMe)CH$_2$CH=CH$_2$	2,6-Me$_2$-4-OMePh	
1464	C-Me	N(CH$_2$CH$_2$OMe)Me	2,6-Me$_2$-4-OMePh	
1465	C-Me	N(CH$_2$CH$_2$OMe)Et	2,6-Me$_2$-4-OMePh	
1466	C-Me	N(CH$_2$CH$_2$OMe)Pr	2,6-Me$_2$-4-OMePh	
1467	C-Me	N(CH$_2$CH$_2$OMe)CH$_2$c-Pr	2,6-Me$_2$-4-OMePh	
1468	C-Me	NH(CH(CH$_3$)CH$_2$CH$_3$)	2,6-Me$_2$-4-OMePh	
1469	C-Me	NHCH(c-Pr)$_2$	2,6-Me$_2$-4-OMePh	
1470	C-Me	NHCH(Et)$_2$	2,6-Me$_2$-4-OMePh	
1471	C-Me	N(Et)$_2$	2,6-Me$_2$-4-OMePh	
1472	C-Me	NEt(Bu)	2,6-Me$_2$-4-OMePh	
1473	C-Me	2-ethylpiperidyl	2-Cl-4-OMe-5-FPh	
1474	C-Me	cyclobutylamino	2-Cl-4-OMe-5-FPh	
1475[be]	C-Me	N(Me)CH$_2$CH=CH$_2$	2-Cl-4-OMe-5-FPh	oil
1476	C-Me	N(Et)CH$_2$c-Pr	2-Cl-4-OMe-5-FPh	
1478	C-Me	N(Pr)CH$_2$c-Pr	2-Cl-4-OMe-5-FPh	
1479[bb]	C-Me	N(Me)Pr	2-Cl-4-OMe-5-FPh	oil
1480[bc]	C-Me	N(Me)Et	2-Cl-4-OMe-5-FPh	oil
1481	C-Me	N(Me)Bu	2-Cl-4-OMe-5-FPh	
1482	C-Me	N(Me)propargyl	2-Cl-4-OMe-5-FPh	
1483	C-Me	NH(CH(CH$_3$)CH(CH$_3$)CH$_3$)	2-Cl-4-OMe-5-FPh	
1484	C-Me	N(CH$_2$CH$_2$OMe)CH$_2$CH=CH$_2$	2-Cl-4-OMe-5-FPh	
1485	C-Me	N(CH$_2$CH$_2$OMe)Me	2-Cl-4-OMe-5-FPh	
1486	C-Me	N(CH$_2$CH$_2$OMe)Et	2-Cl-4-OMe-5-FPh	
1487	C-Me	N(CH$_2$CH$_2$OMe)Pr	2-Cl-4-OMe-5-FPh	
1488	C-Me	N(CH$_2$CH$_2$OMe)CH$_2$c-Pr	2-Cl-4-OMe-5-FPh	
1489[bd]	C-Me	NH(CH(CH$_3$)CH$_2$CH$_3$)	2-Cl-4-OMe-5-FPh	solid

1490	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-OMe-5-FPh	
1491[be]	C-Me	$NHCH(Et)_2$	2-Cl-4-OMe-5-FPh	oil
1492[bf]	C-Me	$N(Et)_2$	2-Cl-4-OMe-5-FPh	96-98
1493[bg]	C-Me	NEt(Bu)	2-Cl-4-OMe-5-FPh	oil
1494	C-Me	2-ethylpiperidyl	2-Cl-4-OMe-6-MePh	
1495	C-Me	cyclobutylamino	2-Cl-4-OMe-6-MePh	
1496	C-Me	$N(Me)CH_2CH{=}CH_2$	2-Cl-4-OMe-6-MePh	
1497	C-Me	$N(Et)CH_2c\text{-}Pr$	2-Cl-4-OMe-6-MePh	
1498	C-Me	$N(Pr)CH_2c\text{-}Pr$	2-Cl-4-OMe-6-MePh	
1499	C-Me	N(Me)Pr	2-Cl-4-OMe-6-MePh	
1500	C-Me	N(Me)Et	2-Cl-4-OMe-6-MePh	
1501	C-Me	N(Me)Bu	2-Cl-4-OMe-6-MePh	
1502	C-Me	N(Me)propargyl	2-Cl-4-OMe-6-MePh	
1503	C-Me	$NH(CH(CH_3)CH(CH_3)CH_3)$	2-Cl-4-OMe-6-MePh	
1504	C-Me	$N(CH_2CH_2OMe)CH_2CH{=}CH_2$	2-Cl-4-OMe-6-MePh	
1505	C-Me	$N(CH_2CH_2OMe)Me$	2-Cl-4-OMe-6-MePh	
1506	C-Me	$N(CH_2CH_2OMe)Et$	2-Cl-4-OMe-6-MePh	
1507	C-Me	$N(CH_2CH_2OMe)Pr$	2-Cl-4-OMe-6-MePh	
1508	C-Me	$N(CH_2CH_2OMe)CH_2c\text{-}Pr$	2-Cl-4-OMe-6-MePh	
1509	C-Me	$NH(CH(CH_3)CH_2CH_3)$	2-Cl-4-OMe-6-MePh	
1510	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-OMe-6-MePh	
1511	C-Me	$NHCH(Et)_2$	2-Cl-4-OMe-6-MePh	
1512	C-Me	$N(Et)_2$	2-Cl-4-OMe-6-MePh	
1513	C-Me	NEt(Bu)	2-Cl-4-OMe-6-MePh	
1514	C-Me	2-ethylpiperidyl	$6\text{-}Me_2N\text{-}4\text{-}Me$-pyrid-3-yl	
1515	C-Me	cyclobutylamino	$6\text{-}Me_2N\text{-}4\text{-}Me$-pyrid-3-yl	
1516	C-Me	$N(Me)CH_2CH{=}CH_2$	$6\text{-}Me_2N\text{-}4\text{-}Me$-pyrid-3-yl	

1517	C-Me	N(Et)CH_2c-Pr	6-Me_2N-4-Me-pyrid-3-yl	
1518	C-Me	N(Pr)CH_2c-Pr	6-Me_2N-4-Me-pyrid-3-yl	
1519	C-Me	N(Me)Pr	6-Me_2N-4-Me-pyrid-3-yl	
1520	C-Me	N(Me)Et	6-Me_2N-4-Me-pyrid-3-yl	
1521	C-Me	N(Me)Bu	6-Me_2N-4-Me-pyrid-3-yl	
1522	C-Me	N(Me)propargyl	6-Me_2N-4-Me-pyrid-3-yl	
1523	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	6-Me_2N-4-Me-pyrid-3-yl	
1524	C-Me	N(CH_2CH_2OMe)CH_2CH=CH_2	6-Me_2N-4-Me-pyrid-3-yl	
1525	C-Me	N(CH_2CH_2OMe)Me	6-Me_2N-4-Me-pyrid-3-yl	
1526[at]	C-Me	N(CH_2CH_2OMe)Et	6-Me_2N-4-Me-pyrid-3-yl	oil
1527	C-Me	N(CH_2CH_2OMe)Pr	6-Me_2N-4-Me-pyrid-3-yl	
1528	C-Me	N(CH_2CH_2OMe)CH_2c-Pr	6-Me_2N-4-Me-pyrid-3-yl	
1529	C-Me	NH(CH(CH_3)CH_2CH_3)	6-Me_2N-4-Me-pyrid-3-yl	
1530	C-Me	NHCH(c-Pr)$_2$	6-Me_2N-4-Me-pyrid-3-yl	
1531[au]	C-Me	N(CH_2CH_2OMe)$_2$	6-Me_2N-4-Me-pyrid-3-yl	103-104
1532[av]	C-Me	NHCH(Et)$_2$	6-Me_2N-4-Me-	

			pyrid-3-yl	
				153-154
1533[aw]	C-Me	$N(Et)_2$	6-Me_2N-4-Me-pyrid-3-yl	
				117-118
1534	C-Me	2-ethylpiperidyl	6-MeO-4-Me-pyrid-3-yl	
1535	C-Me	cyclobutylamino	6-MeO-4-Me-pyrid-3-yl	
1536	C-Me	$N(Me)CH_2CH=CH_2$	6-MeO-4-Me-pyrid-3-yl	
1537	C-Me	$N(Et)CH_2c$-Pr	6-MeO4-Me-pyrid-3-yl	
1538	C-Me	$N(Pr)CH_2c$-Pr	6-MeO-4-Me-pyrid-3-yl	
1539	C-Me	N(Me)Pr	6-MeO-4-Me-pyrid-3-yl	
1540	C-Me	N(Me)Et	6-MeO-4-Me-pyrid-3-yl	
1541	C-Me	N(Me)Bu	6-MeO-4-Me-pyrid-3-yl	
1542	C-Me	N(Me)propargyl	6-MeO-4-Me-pyrid-3-yl	
1543	C-Me	$NH(CH(CH_3)CH(CH_3)CH_3)$	6-MeO-4-Me-pyrid-3-yl	
1544	C-Me	$N(CH_2CH_2OMe)CH_2CH=CH_2$	6-MeO-4-Me-pyrid-3-yl	
1545	C-Me	$N(CH_2CH_2OMe)Me$	6-MeO-4-Me-pyrid-3-yl	
1546	C-Me	$N(CH_2CH_2OMe)Et$	6-MeO-4-Me-pyrid-3-yl	
1547	C-Me	$N(CH_2CH_2OMe)Pr$	6-MeO-4-Me-pyrid-3-yl	

1548	C-Me	$N(CH_2CH_2OMe)CH_2c$-Pr	6-MeO-4-Me-pyrid-3-yl
1549	C-Me	$NH(CH(CH_3)CH_2CH_3)$	6-MeO-4-Me-pyrid-3-yl
1550	C-Me	$NHCH(c\text{-}Pr)_2$	6-MeO-4-Me-pyrid-3-yl
1551	C-Me	$N(CH_2CH_2OMe)_2$	6-MeO-4-Me-pyrid-3-yl
1552	C-Me	$NHCH(Et)_2$	6-MeO-4-Me-pyrid-3-yl
1553	C-Me	$N(Et)_2$	6-MeO-4-Me-pyrid-3-yl
1554	C-Me	2-ethylpiperidyl	$4,6\text{-}Me_2$-pyrid-3-yl
1555	C-Me	cyclobutylamino	$4,6\text{-}Me_2$-pyrid-3-yl
1556	C-Me	$N(Me)CH_2CH{=}CH_2$	$4,6\text{-}Me_2$-pyrid-3-yl
1557	C-Me	$N(Et)CH_2c$-Pr	$4,6\text{-}Me_2$-pyrid-3-yl
1558	C-Me	$N(Pr)CH_2c$-Pr	$4,6\text{-}Me_2$-pyrid-3-yl
1559	C-Me	N(Me)Pr	$4,6\text{-}Me_2$-pyrid-3-yl
1560	C-Me	N(Me)Et	$4,6\text{-}Me_2$-pyrid-3-yl
1561	C-Me	N(Me)Bu	$4,6\text{-}Me_2$-pyrid-3-yl
1562	C-Me	N(Me)propargyl	$4,6\text{-}Me_2$-pyrid-3-yl
1563	C-Me	$NH(CH(CH_3)CH(CH_3)CH_3)$	$4,6\text{-}Me_2$-pyrid-3-yl

1564	C-Me	$N(CH_2CH_2OMe)CH_2CH=CH_2$	4,6-Me_2-pyrid-3-yl
1565	C-Me	$N(CH_2CH_2OMe)Me$	4,6-Me_2-pyrid-3-yl
1566	C-Me	$N(CH_2CH_2OMe)Et$	4,6-Me_2-pyrid-3-yl
1567	C-Me	$N(CH_2CH_2OMe)Pr$	4,6-Me_2-pyrid-3-yl
1568	C-Me	$N(CH_2CH_2OMe)CH_2c$-Pr	4,6-Me_2-pyrid-3-yl
1569	C-Me	$NH(CH(CH_3)CH_2CH_3)$	4,6-Me_2-pyrid-3-yl
1570	C-Me	$NHCH(c\text{-}Pr)_2$	4,6-Me_2-pyrid-3-yl
1571	C-Me	$N(CH_2CH_2OMe)_2$	4,6-Me_2-pyrid-3-yl
1572	C-Me	$NHCH(Et)_2$	4,6-Me_2-pyrid-3-yl
1573	C-Me	$N(Et)_2$	4,6-Me_2-pyrid-3-yl
1574	C-Me	2-ethylpiperidyl	2,6-Me_2-pyrid-3-yl
1575	C-Me	cyclobutylamino	2,6-Me_2-pyrid-3-yl
1576	C-Me	$N(Me)CH_2CH=CH_2$	2,6-Me_2-pyrid-3-yl
1577	C-Me	$N(Et)CH_2c$-Pr	2,6-Me_2-pyrid-3-yl
1578	C-Me	$N(Pr)CH_2c$-Pr	2,6-Me_2-pyrid-3-yl
1579	C-Me	N(Me)Pr	2,6-Me_2-pyrid-3-yl

1580	C-Me	N(Me)Et	2,6-Me_2-pyrid-3-yl
1581	C-Me	N(Me)Bu	2,6-Me_2-pyrid-3-yl
1582	C-Me	N(Me)propargyl	2,6-Me_2-pyrid-3-yl
1583	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	2,6-Me_2-pyrid-3-yl
1584	C-Me	N(CH_2CH_2OMe)$CH_2CH=CH_2$	2,6-Me_2-pyrid-3-yl
1585	C-Me	N(CH_2CH_2OMe)Me	2,6-Me_2-pyrid-3-yl
1586	C-Me	N(CH_2CH_2OMe)Et	2,6-Me_2-pyrid-3-yl
1587	C-Me	N(CH_2CH_2OMe)Pr	2,6-Me_2-pyrid-3-yl
1588	C-Me	N(CH_2CH_2OMe)CH_2c-Pr	2,6-Me_2-pyrid-3-yl
1589	C-Me	NH(CH(CH_3)CH_2CH_3)	2,6-Me_2-pyrid-3-yl
1590	C-Me	NHCH(c-Pr)$_2$	2,6-Me_2-pyrid-3-yl
1591	C-Me	N(CH_2CH_2OMe)$_2$	2,6-Me_2-pyrid-3-yl
1592	C-Me	NHCH(Et)$_2$	2,6-Me_2-pyrid-3-yl
1593	C-Me	N(Et)$_2$	2,6-Me_2-pyrid-3-yl
1594	C-Me	2-ethylpiperidyl	4-MeO-6-Me-pyrid-3-yl
1595	C-Me	cyclobutylamino	4-MeO-6-Me-pyrid-3-yl
1596	C-Me	N(Me)$CH_2CH=CH_2$	4-MeO-6-Me-

			pyrid-3-yl
1597	C-Me	N(Et)CH_2c-Pr	4-MeO-6-Me-pyrid-3-yl
1598	C-Me	N(Pr)CH_2c-Pr	4-MeO-6-Me-pyrid-3-yl
1599	C-Me	N(Me)Pr	4-MeO-6-Me-pyrid-3-yl
1600	C-Me	N(Me)Et	4-MeO-6-Me-pyrid-3-yl
1601	C-Me	N(Me)Bu	4-MeO-6-Me-pyrid-3-yl
1602	C-Me	N(Me)propargyl	4-MeO-6-Me-pyrid-3-yl
1603	C-Me	NH(CH(CH_3)CH(CH_3)CH_3)	4-MeO-6-Me-pyrid-3-yl
1604	C-Me	N(CH_2CH_2OMe)$CH_2CH=CH_2$	4-MeO-6-Me-pyrid-3-yl
1605	C-Me	N(CH_2CH_2OMe)Me	4-MeO-6-Me-pyrid-3-yl
1606	C-Me	N(CH_2CH_2OMe)Et	4-MeO-6-Me-pyrid-3-yl
1607	C-Me	N(CH_2CH_2OMe)Pr	4-MeO-6-Me-pyrid-3-yl
1608	C-Me	N(CH_2CH_2OMe)CH_2c-Pr	4-MeO-6-Me-pyrid-3-yl
1609	C-Me	NH(CH(CH_3)CH_2CH_3)	4-MeO-6-Me-pyrid-3-yl
1610	C-Me	NHCH(c-Pr)$_2$	4-MeO-6-Me-pyrid-3-yl
1611	C-Me	N(CH_2CH_2OMe)$_2$	4-MeO-6-Me-pyrid-3-yl
1612	C-Me	NHCH(Et)$_2$	4-MeO-6-Me-pyrid-3-yl

1613	C-Me	$N(Et)_2$	4-MeO-6-Me-pyrid-3-yl
1614	C-Me	2-ethylpiperidyl	2-Br-4,5-$(OMe)_2$Ph
1615	C-Me	cyclobutylamino	2-Br-4,5-$(OMe)_2$Ph
1616	C-Me	$N(Me)CH_2CH=CH_2$	2-Br-4,5-$(OMe)_2$Ph
1617	C-Me	$N(Et)CH_2$c-Pr	2-Br-4,5-$(OMe)_2$Ph
1618	C-Me	$N(Pr)CH_2$c-Pr	2-Br-4,5-$(OMe)_2$Ph
1619	C-Me	N(Me)Pr	2-Br-4,5-$(OMe)_2$Ph
1620	C-Me	N(Me)Et	2-Br-4,5-$(OMe)_2$Ph
1621	C-Me	N(Me)Bu	2-Br-4,5-$(OMe)_2$Ph
1622	C-Me	N(Me)propargyl	2-Br-4,5-$(OMe)_2$Ph
1623	C-Me	$NH(CH(CH_3)CH(CH_3)CH_3)$	2-Br-4,5-$(OMe)_2$Ph
1624	C-Me	$N(CH_2CH_2OMe)CH_2CH=CH_2$	2-Br-4,5-$(OMe)_2$Ph
1625	C-Me	$N(CH_2CH_2OMe)Me$	2-Br-4,5-$(OMe)_2$Ph
1626	C-Me	$N(CH_2CH_2OMe)Et$	2-Br-4,5-$(OMe)_2$Ph
1627	C-Me	$N(CH_2CH_2OMe)Pr$	2-Br-4,5-$(OMe)_2$Ph
1628	C-Me	$N(CH_2CH_2OMe)CH_2$c-Pr	2-Br-4,5-$(OMe)_2$Ph
1629	C-Me	$NH(CH(CH_3)CH_2CH_3)$	2-Br-4,5-$(OMe)_2$Ph
1630	C-Me	$NHCH(c\text{-}Pr)_2$	2-Br-4,5-$(OMe)_2$Ph
1631	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4,5-$(OMe)_2$Ph
1632	C-Me	$NHCH(Et)_2$	2-Br-4,5-$(OMe)_2$Ph
1633	C-Me	$N(Et)_2$	2-Br-4,5-$(OMe)_2$Ph
1634	C-Me	NEt(Bu)	2-Br -4,5-$(OMe)_2$Ph

Notes for Table 7:

a) CI-MS: 330 $(M + H)^+$;

b) CI-MS: 338 $(M + H)^+$;

c) CI-MS: 338 $(M + H)^+$;

d) CI-MS: 400 $(M + H)^+$;

f) CI-MS: 326 $(M + H)^+$;

g) CI-MS: 354 $(M + H)^+$;

h) CI-MS: 336 $(M + H)^+$;

i) CI-MS: 354 $(M + H)^+$;

j) CI-MS: 378 $(M + H)^+$;

k) CI-HRMS: Calcd 356.2087 $(M + H)^+$, Found: 356.2071:

m) CI-MS: 340 $(M + H)^+$;

n) CI-MS: 368 $(M + H)^+$;

o) CI-MS: 326 $(M + H)^+$;

p) CI-MS: 368 $(M + H)^+$;

q) CI-MS: 394 $(M + H)^+$;

r) CI-HRMS: Calcd 380.2087 $(M + H)^+$, Found: 380.2078;

s) CI-HRMS: Calcd 356.2008 $(M + H)^+$, Found: 356.1997;

t) CI-HRMS: Calcd 416.2220 $(M + H)^+$, Found: 416.2005;

u) CI-HRMS: Calcd 370.2243 $(M + H)^+$, Found: 370.2246;

v) CI-HRMS: Calcd 380.2400 $(M + H)^+$, Found: 384.2382;

w) CI-HRMS: Calcd 429.2376 $(M + H)^+$, Found: 429.2358;

x) CI-HRMS: Calcd 397.2478 $(M + H)^+$, Found: 397.2484;

y) CI-HRMS: Calcd 410.5438 $(M + H)^+$, Found: 410.2558;

z) CI-HRMS: Calcd 368.4625 $(M + H)^+$, Found: 368.2100;

aa) CI-HRMS: Calcd 368.2090 $(M + H)^+$, Found: 368.4625;

ab) CI-MS 410 $(M + H)^+$;

ac) CI-HRMS: Calcd 370.4785 $(M + H)^+$, Found: 370.2246;

ad) CI-HRMS: Calcd 356.4514 $(M + H)^+$, Found: 356.2086;

ae) CI-MS 384 $(M + H)^+$;

af) CI-MS 400 $(M + H)^+$;

ag) CI-MS 426 $(M + H)^+$;

ah) CI-HRMS: Calcd 388.1553 $(M + H)^+$, Found: 388.1554;

ai) CI-HRMS: Calcd 388.1540 $(M + H)^+$, Found: 358.1546;

aj) CI-HRMS: Calcd 430.2005 $(M + H)^+$, Found: 430.2006;

ak) CI-HRMS: Calcd 390.1683 $(M + H)^+$, Found: 390.1682;

al) CI-HRMS: Calcd 376.1554 $(M + H)^+$, Found: 376.1548;

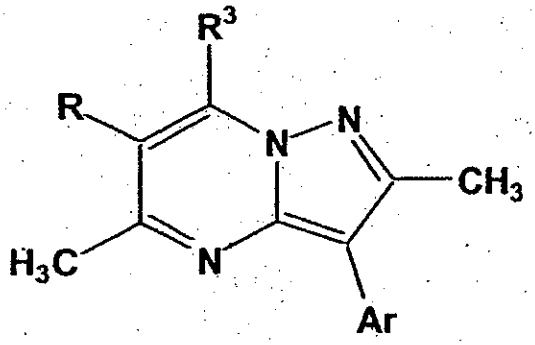
am) CI-HRMS: Calcd 404.1853 $(M + H)^+$, Found: 404.1850;

an) CI-HRMS: Calcd 420.1810 $(M + H)^+$, Found: 420.1809;

ao) CI-HRMS: Calcd 446.1946 $(M + H)^+$, Found: 446.1949;
ap) CI-HRMS: Calcd 450.1917 $(M + H)^+$, Found: 450.1913;
aq) CI-HRMS: Calcd 404.1839 $(M + H)^+$, Found: 404.1846;
ar) CI-HRMS: Calcd 390.1678 $(M + H)^+$, Found: 390.1680;
as) CI-HRMS: Calcd 418.2010 $(M + H)^+$, Found: 418.2012;
at) CI-HRMS: Calcd 384.2512 $(M + H)^+$, Found: 384.2506;
au) CI-HRMS: Calcd 414.2617 $(M + H)^+$, Found: 414.2600;
av) CI-HRMS: Calcd 367.2484 $(M + H)^+$, Found: 367.2477;
aw) CI-HRMS: Calcd 354.2406 $(M + H)^+$, Found: 354.2388;
ax) CI-MS 370 $(M + H)^+$;
ay) CI-MS 380 $(M + H)^+$;
az) CI-MS 340 $(M + H)^+$;
ba) CI-HRMS: Calcd 376.1340 $(M + H)^+$, Found: 376.1347;
bb) CI-HRMS: Calcd 378.1497 $(M + H)^+$, Found: 378.1495;
bc) CI-HRMS: Calcd 364.1340 $(M + H)^+$, Found: 364.1333;
bd) CI-HRMS: Calcd 378.1593 $(M + H)^+$, Found: 378.1498;
be) CI-HRMS: Calcd 392.1653 $(M + H)^+$, Found: 392.1649;
bf) CI-HRMS: Calcd 378.1497 $(M + H)^+$, Found: 378.1489;
bg) CI-HRMS: Calcd 406.1810 $(M + H)^+$, Found: 406.1819;

The examples delineated in TABLE 8 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, cPr is cyclopropyl, Ex is Example, EtOAc is ethyl acetate.

TABLE 8



Ex.	R	R^3	Ar	mp (°C)
2000	Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph	
2001	Me	N(Bu)Et	2,4-Cl_2-Ph	
2002	Me	NHCH(Et)CH_2OMe	2,4-Cl_2-Ph	
2003	Me	N(Pr)CH_2CH_2CN	2,4-Cl_2-Ph	
2004	Me	NH-3-pentyl	2,4-Cl_2-Ph	
2005	Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	
2006	Me	$NHCH(Et)_2$	2,4-Me_2-Ph	
2007	Me	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph	
2008	Me	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph	
2009	Me	N(c-Pr)CH_2CH_2CN	2,4-Me_2-Ph	
2010	Me	$N(CH_2CH_2OMe)_2$	2-Cl,4-MePh	
2011	Me	$NHCH(CH_2OMe)_2$	2-Cl,4-MePh	
2012	Me	$NHCH(Et)_2$	2-Cl,4-MePh	
2013	Me	NEt_2	2,4-Me_2-Ph	
2014	Me	N(Pr)CH_2CH_2CN	2,4-Me_2-Ph	
2015	Me	N(Bu)CH_2CH_2CN	2,4-Me_2-Ph	
2016	Me	NHCH(Et)CH_2OMe	2,4-Me_2-Ph	
2017	Me	$NHCH(Et)_2$	2-Me,4-MeOPh	
2018	Me	$NHCH(CH_2OMe)_2$	2-Me,4-MeOPh	
2019	Me	$N(CH_2CH_2OMe)_2$	2-Me,4-MeOPh115-	
116[a]				
2020	Me	(S)-NHCH(CH_2CH_2OMe)-	2-Me,4-MeOPh	

2021		(CH_2OMe)	
2022	Me	(S)-NHCH(CH_2CH_2OMe)-	2,4-Me_2-Ph
2023		(CH_2OMe)	
2024	Me	N(CH_2CH_2OMe)$_2$	2-Me,4-ClPh
2025	Me	NHEt	2,4-Me_2-Ph
2026	Me	NHCH(Et)$_2$	2-Me,4-ClPh
2027	Me	NHCH(CH_2OMe)$_2$	2-Me,4-ClPh
2028	Me	N(Ac)Et	2,4-Me_2-Ph
2029	Me	(S)-NHCH(CH_2CH_2OMe)-	2-Me,4-ClPh
2030		(CH_2OMe)	
2031	Me	N(Pr)CH_2CH_2CN	2-Me,4-MeOPh
2032	Me	NEt_2	2-Me,4-MeOPh
2033	Me	(S)-NHCH(CH_2CH_2OMe)-	2-Cl,4-MePh
2034		(CH_2OMe)	
2035	Me	NEt_2	2-Cl,4-MePh
2036	Me	N(c-Pr)CH_2CH_2CN	2-Me,4-MeOPh
2037	Me	N(c-Pr)CH_2CH_2CN	2-Cl,4-MePh
2038	Me	NHCH(Et)CH_2OMe	2-Me,4-MeOPh
2039	Me	NHCH(Et)CH_2OMe	2-Cl,4-MePh
2040	Me	NHCH(CH_2OMe)$_2$	2-Cl-4-MeOPh
2041	Me	N(CH_2CH_2OMe)$_2$	2-Cl-4-MeOPh
2042	Me	NHCH(Et)CH_2OMe	2-Cl-4-MeOPh
2043	Me	N(c-Pr)CH_2CH_2CN	2-Cl-4-MeOPh
2044	Me	NEt_2	2-Cl-4-MeOPh
2045	Me	NH-3-pentyl	2-Cl-4-MeOPh
2046	Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4-MeOPh
2047	Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4-MeOPh
2048	Me	NHCH(Et)CH_2CH_2OMe	2-Br-4-MeOPh
2049	Me	NHCH(Me)CH_2CH_2OMe	2-Br-4-MeOPh
2050	Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
2051	Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
2052	Me	NHCH(CH_2OMe)$_2$	2-Cl-4,5-(MeO)$_2$Ph

2053	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
2054	Me	NHCH(Et)CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2055	Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,5-$(MeO)_2$Ph
2056	Me	NEt_2	2-Cl-4,5-$(MeO)_2$Ph
2057	Me	NH-3-pentyl	2-Cl-4,5-$(MeO)_2$Ph
2058	Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2059	Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2060	Me	$NHCH(CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
2061	Me	$N(CH_2CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
2062	Me	NHCH(Et)CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2063	Me	N(c-Pr)CH_2CH_2CN	2-Br-4,5-$(MeO)_2$Ph
2064	Me	NEt_2	2-Br-4,5-$(MeO)_2$Ph
2065	Me	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph
2066	Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2067	Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2068	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
2069	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
2070	Me	NHCH(Et)CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2071	Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,6-$(MeO)_2$Ph
2072	Me	NEt_2	2-Cl-4,6-$(MeO)_2$Ph
2073	Me	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph
2074	Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2075	Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2076	Me	$NHCH(CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
2077	Me	$N(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
2078	Me	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2079	Me	N(c-Pr)CH_2CH_2CN	2-Me-4,6-$(MeO)_2$Ph
2080	Me	NEt_2	2-Me-4,6-$(MeO)_2$Ph
2081	Me	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph
2082	Me	NHCH(Et)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2083	Me	NHCH(Me)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2084	Me	N(c-Pr)CH_2CH_2CN	2-Br-4,6-$(MeO)_2$Ph

2085	Me	NEt_2	2-Br-4,6-$(MeO)_2$Ph
2086	Me	NH-3-pentyl	2-Br-4,6-$(MeO)_2$Ph
2087	Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
2088	Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
2089	Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
2090	Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
2091	Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
2092	Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh
2093	Me	NHCH(Et)CH_2OMe	2-MeO-4-MePh
2094	Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
2095	Me	NEt_2	2-MeO-4-MePh
2096	Me	NH-3-pentyl	2-MeO-4-MePh
2097	Me	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh
2098	Me	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
2099	Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
2100	Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh
2101	Me	NHCH(Et)CH_2OMe	2-MeO-4-MePh
2102	Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
2103	Me	NEt_2	2-MeO-4-MePh
2104	Me	NH-3-pentyl	2-MeO-4-MePh
2105	Me	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh
2106	Me	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
2107	Me	NHCH$(CH_2OMe)_2$	2-MeO-4-ClPh
2108	Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-ClPh
2109	Me	NHCH(Et)CH_2OMe	2-MeO-4-ClPh
2110	Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-ClPh
2111	Me	NEt_2	2-MeO-4-ClPh
2112	Me	NH-3-pentyl	2-MeO-4-ClPh
2113	Me	NHCH(Et)CH_2CH_2OMe	2-MeO-4-ClPh
2114	Me	NHCH(Me)CH_2CH_2OMe	2-MeO-4-ClPh
2115	Cl	N$(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph
2116	Cl	N(Bu)Et	2,4-Cl_2-Ph

2117	Cl	NHCH(Et)CH_2OMe	2,4-Cl_2-Ph	
2118	Cl	N(Pr)CH_2CH_2CN	2,4-Cl_2-Ph	
2119	Cl	NH-3-pentyl	2,4-Cl_2-Ph	
2120	Cl	NHCH(CH_2OMe)$_2$	2,4-Cl_2-Ph	
2121	Cl	NHCH(Et)$_2$	2,4-Me_2-Ph	
2122	Cl	NHCH(CH_2OMe)$_2$	2,4-Me_2-Ph	
2123	Cl	N(CH_2CH_2OMe)$_2$	2,4-Me_2-Ph	
2124	Cl	N(c-Pr)CH_2CH_2CN	2,4-Me_2-Ph	
2125	Cl	N(CH_2CH_2OMe)$_2$	2-Cl,4-MePh	
2126	Cl	NHCH(CH_2OMe)$_2$	2-Cl,4-MePh	
2127	Cl	NHCH(Et)$_2$	2-Cl,4-MePh	
2128	Cl	NEt_2	2,4-Me_2-Ph	
2129	Cl	N(Pr)CH_2CH_2CN	2,4-Me_2-Ph	
2130	Cl	N(Bu)CH_2CH_2CN	2,4-Me_2-Ph	
2131	Cl	NHCH(Et)CH_2OMe	2,4-Me_2-Ph	
2132	Cl	NHCH(Et)$_2$	2-Me,4-MeOPh	
2133	Cl	NHCH(CH_2OMe)$_2$	2-Me,4-MeOPh	74-76[b]
2134	Cl	N(CH_2CH_2OMe)$_2$	2-Me,4-MeOPh	
2135	Cl	(S)-NHCH(CH_2CH_2OMe)-	2-Me,4-MeOPh	
2136		(CH_2OMe)		
2137	Cl	(S)-NHCH(CH_2CH_2OMe)-	2,4-Me_2-Ph	
2138		(CH_2OMe)		
2139	Cl	N(CH_2CH_2OMe)$_2$	2-Me,4-ClPh	
2140	Cl	NHEt	2,4-Me_2-Ph	
2141	Cl	NHCH(Et)$_2$	2-Me,4-ClPh	
2142	Cl	NHCH(CH_2OMe)$_2$	2-Me,4-ClPh	
2143	Cl	N(Ac)Et	2,4-Me_2-Ph	
2144	Cl	(S)-NHCH(CH_2CH_2OMe)-	2-Me,4-ClPh	
2145		(CH_2OMe)		
2146	Cl	N(Pr)CH_2CH_2CN	2-Me,4-MeOPh	
2147	Cl	NEt_2	2-Me,4-MeOPh	

2148	Cl	(S)-NHCH(CH_2CH_2OMe)-	2-Cl,4-MePh
2149		(CH_2OMe)	
2150	Cl	NEt_2	2-Cl,4-MePh
2151	Cl	N(c-Pr)CH_2CH_2CN	2-Me,4-MeOPh
2152	Cl	N(c-Pr)CH_2CH_2CN	2-Cl,4-MePh
2153	Cl	NHCH(Et)CH_2OMe	2-Me,4-MeOPh
2154	Cl	NHCH(Et)CH_2OMe	2-Cl,4-MePh
2155	Cl	NHCH($CH_2OMe)_2$	2-Cl-4-MeOPh
2156	Cl	N($CH_2CH_2OMe)_2$	2-Cl-4-MeOPh
2157	Cl	NHCH(Et)CH_2OMe	2-Cl-4-MeOPh
2158	Cl	N(c-Pr)CH_2CH_2CN	2-Cl-4-MeOPh
2159	Cl	NEt_2	2-Cl-4-MeOPh
2160	Cl	NH-3-pentyl	2-Cl-4-MeOPh
2161	Cl	NHCH(Et)CH_2CH_2OMe	2-Cl-4-MeOPh
2162	Cl	NHCH(Me)CH_2CH_2OMe	2-Cl-4-MeOPh
2163	Cl	NHCH(Et)CH_2CH_2OMe	2-Br-4-MeOPh
2164	Cl	NHCH(Me)CH_2CH_2OMe	2-Br-4-MeOPh
2165	Cl	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
2166	Cl	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
2167	Cl	NHCH($CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
2168	Cl	N($CH_2CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
2169	Cl	NHCH(Et)CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2170	Cl	N(c-Pr)CH_2CH_2CN	2-Cl-4,5-$(MeO)_2$Ph
2171	Cl	NEt_2	2-Cl-4,5-$(MeO)_2$Ph
2172	Cl	NH-3-pentyl	2-Cl-4,5-$(MeO)_2$Ph
2173	Cl	NHCH(Et)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2174	Cl	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2175	Cl	NHCH($CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
2176	Cl	N($CH_2CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
2177	Cl	NHCH(Et)CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2178	Cl	N(c-Pr)CH_2CH_2CN	2-Br-4,5-$(MeO)_2$Ph
2179	Cl	NEt_2	2-Br-4,5-$(MeO)_2$Ph

2180	Cl	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph
2181	Cl	NHCH(Et)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2182	Cl	NHCH(Me)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2183	Cl	NHCH$(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
2184	Cl	N$(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
2185	Cl	NHCH(Et)CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2186	Cl	N(c-Pr)CH_2CH_2CN	2-Cl-4,6-$(MeO)_2$Ph
2187	Cl	NEt_2	2-Cl-4,6-$(MeO)_2$Ph
2188	Cl	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph
2189	Cl	NHCH(Et)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2190	Cl	NHCH(Me)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2191	Cl	NHCH$(CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
2192	Cl	N$(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
2193	Cl	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2194	Cl	N(c-Pr)CH_2CH_2CN	2-Me-4,6-$(MeO)_2$Ph
2195	Cl	NEt_2	2-Me-4,6-$(MeO)_2$Ph
2196	Cl	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph
2197	Cl	NHCH(Et)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2198	Cl	NHCH(Me)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2199	Cl	N(c-Pr)CH_2CH_2CN	2-Br-4,6-$(MeO)_2$Ph
2200	Cl	NEt_2	2-Br-4,6-$(MeO)_2$Ph
2201	Cl	NH-3-pentyl	2-Br-4,6-$(MeO)_2$Ph
2202	Cl	NHCH(Et)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
2203	Cl	NHCH(Me)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
2204	Cl	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
2205	Cl	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
2206	Cl	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
2207	Cl	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh
2208	Cl	NHCH(Et)CH_2OMe	2-MeO-4-MePh
2209	Cl	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
2210	Cl	NEt_2	2-MeO-4-MePh
2211	Cl	NH-3-pentyl	2-MeO-4-MePh

2212	Cl	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh
2213	Cl	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
2214	Cl	NHCH(CH_2OMe)$_2$	2-MeO-4-MePh
2215	Cl	N(CH_2CH_2OMe)$_2$	2-MeO-4-MePh
2216	Cl	NHCH(Et)CH_2OMe	2-MeO-4-MePh
2217	Cl	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
2218	Cl	NEt_2	2-MeO-4-MePh
2219	Cl	NH-3-pentyl	2-MeO-4-MePh
2220	Cl	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh
2221	Cl	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
2222	Cl	NHCH(CH_2OMe)$_2$	2-MeO-4-ClPh
2223	Cl	N(CH_2CH_2OMe)$_2$	2-MeO-4-ClPh
2224	Cl	NHCH(Et)CH_2OMe	2-MeO-4-ClPh
2225	Cl	N(c-Pr)CH_2CH_2CN	2-MeO-4-ClPh
2226	Cl	NEt_2	2-MeO-4-ClPh
2227	Cl	NH-3-pentyl	2-MeO-4-ClPh
2228	Cl	NHCH(Et)CH_2CH_2OMe	2-MeO-4-ClPh
2229	Cl	NHCH(Me)CH_2CH_2OMe	2-MeO-4-ClPh
2230	F	N(CH_2CH_2OMe)$_2$	2,4-Cl_2-Ph
2231	F	N(Bu)Et	2,4-Cl_2-Ph
2232	F	NHCH(Et)CH_2OMe	2,4-Cl_2-Ph
2233	F	N(Pr)CH_2CH_2CN	2,4-Cl_2-Ph
2234	F	NH-3-pentyl	2,4-Cl_2-Ph
2235	F	NHCH(CH_2OMe)$_2$	2,4-Cl_2-Ph
2236	F	NHCH(Et)$_2$	2,4-Me_2-Ph
2237	F	NHCH(CH_2OMe)$_2$	2,4-Me_2-Ph
2238	F	N(CH_2CH_2OMe)$_2$	2,4-Me_2-Ph
2239	F	N(c-Pr)CH_2CH_2CN	2,4-Me_2-Ph
2240	F	N(CH_2CH_2OMe)$_2$	2-Cl,4-MePh
2241	F	NHCH(CH_2OMe)$_2$	2-Cl,4-MePh
2242	F	NHCH(Et)$_2$	2-Cl,4-MePh
2243	F	NEt_2	2,4-Me_2-Ph

2244	F	N(Pr)CH_2CH_2CN	2,4-Me_2-Ph
2245	F	N(Bu)CH_2CH_2CN	2,4-Me_2-Ph
2246	F	NHCH(Et)CH_2OMe	2,4-Me_2-Ph
2247	F	NHCH(Et)$_2$	2-Me-4-MeOPh
2248	F	NHCH(CH_2OMe)$_2$	2-Me-4-MeOPh
2249	F	N(CH_2CH_2OMe)$_2$	2-Me-4-MeOPh
2250	F	(S)-NHCH(CH_2CH_2OMe)-	2-Me-4-MeOPh
2251		(CH_2OMe)	
2252	F	(S)-NHCH(CH_2CH_2OMe)-	2,4-Me_2-Ph
2253		(CH_2OMe)	
2254	F	N(CH_2CH_2OMe)$_2$	2-Me,4-ClPh
2255	F	NHEt	2,4-Me_2-Ph
2256	F	NHCH(Et)$_2$	2-Me,4-ClPh
2257	F	NHCH(CH_2OMe)$_2$	2-Me,4-ClPh
2258	F	N(Ac)Et	2,4-Me_2-Ph
2259	F	(S)-NHCH(CH_2CH_2OMe)-	2-Me,4-ClPh
2260		(CH_2OMe)	
2261	F	N(Pr)CH_2CH_2CN	2-Me,4-MeOPh
2262	F	NEt_2	2-Me,4-MeOPh
2263	F	(S)-NHCH(CH_2CH_2OMe)-	2-Cl,4-MePh
2264		(CH_2OMe)	
2265	F	NEt_2	2-Cl,4-MePh
2266	F	N(c-Pr)CH_2CH_2CN	2-Me,4-MeOPh
2267	F	N(c-Pr)CH_2CH_2CN	2-Cl,4-MePh
2268	F	NHCH(Et)CH_2OMe	2-Me,4-MeOPh
2269	F	NHCH(Et)CH_2OMe	2-Cl,4-MePh
2270	F	NHCH(CH_2OMe)$_2$	2-Cl-4-MeOPh
2271	F	N(CH_2CH_2OMe)$_2$	2-Cl-4-MeOPh
2272	F	NHCH(Et)CH_2OMe	2-Cl-4-MeOPh
2273	F	N(c-Pr)CH_2CH_2CN	2-Cl-4-MeOPh
2274	F	NEt_2	2-Cl-4-MeOPh
2275	F	NH-3-pentyl	2-Cl-4-MeOPh

2276	F	NHCH(Et)CH_2CH_2OMe	2-Cl-4-MeOPh
2277	F	NHCH(Me)CH_2CH_2OMe	2-Cl-4-MeOPh
2278	F	NHCH(Et)CH_2CH_2OMe	2-Br-4-MeOPh
2279	F	NHCH(Me)CH_2CH_2OMe	2-Br-4-MeOPh
2280	F	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
2281	F	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
2282	F	NHCH$(CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
2283	F	N$(CH_2CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
2284	F	NHCH(Et)CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2285	F	N(c-Pr)CH_2CH_2CN	2-Cl-4,5-$(MeO)_2$Ph
2286	F	NEt_2	2-Cl-4,5-$(MeO)_2$Ph
2287	F	NH-3-pentyl	2-Cl-4,5-$(MeO)_2$Ph
2288	F	NHCH(Et)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2289	F	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
2290	F	NHCH$(CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
2291	F	N$(CH_2CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
2292	F	NHCH(Et)CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2293	F	N(c-Pr)CH_2CH_2CN	2-Br-4,5-$(MeO)_2$Ph
2294	F	NEt_2	2-Br-4,5-$(MeO)_2$Ph
2295	F	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph
2296	F	NHCH(Et)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2297	F	NHCH(Me)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
2298	F	NHCH$(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
2299	F	N$(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
2300	F	NHCH(Et)CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2301	F	N(c-Pr)CH_2CH_2CN	2-Cl-4,6-$(MeO)_2$Ph
2302	F	NEt_2	2-Cl-4,6-$(MeO)_2$Ph
2303	F	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph
2304	F	NHCH(Et)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2305	F	NHCH(Me)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
2306	F	NHCH$(CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
2307	F	N$(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph

2308	F	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2309	F	N(c-Pr)CH_2CH_2CN	2-Me-4,6-$(MeO)_2$Ph
2310	F	NEt_2	2-Me-4,6-$(MeO)_2$Ph
2311	F	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph
2312	F	NHCH(Et)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2313	F	NHCH(Me)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
2314	F	N(c-Pr)CH_2CH_2CN	2-Br-4,6-$(MeO)_2$Ph
2315	F	NEt_2	2-Br-4,6-$(MeO)_2$Ph
2316	F	NH-3-pentyl	2-Br-4,6-$(MeO)_2$Ph
2317	F	NHCH(Et)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
2318	F	NHCH(Me)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
2319	F	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
2320	F	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
2321	F	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
2322	F	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh
2323	F	NHCH(Et)CH_2OMe	2-MeO-4-MePh
2324	F	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
2325	F	NEt_2	2-MeO-4-MePh
2326	F	NH-3-pentyl	2-MeO-4-MePh
2327	F	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh
2328	F	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
2329	F	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
2330	F	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh
2331	F	NHCH(Et)CH_2OMe	2-MeO-4-MePh
2332	F	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
2333	F	NEt_2	2-MeO-4-MePh
2334	F	NH-3-pentyl	2-MeO-4-MePh
2335	F	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh
2336	F	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
2337	F	NHCH$(CH_2OMe)_2$	2-MeO-4-ClPh
2338	F	N$(CH_2CH_2OMe)_2$	2-MeO-4-ClPh
2339	F	NHCH(Et)CH_2OMe	2-MeO-4-ClPh

2340	F	N(c-Pr)CH_2CH_2CN	2-MeO-4-ClPh
2341	F	NEt_2	2-MeO-4-ClPh
2342	F	NH-3-pentyl	2-MeO-4-ClPh
2343	F	NHCH(Et)CH_2CH_2OMe	2-MeO-4-ClPh
2344	F	NHCH(Me)CH_2CH_2OMe	2-MeO-4-ClPh
2345	Me	NMe(CH_2CH_2OMe)	2,4-Cl_2-Ph
2346	Me	NEt(CH_2CH_2OMe)	2,4-Cl_2-Ph
2347	Me	NPr(CH_2CH_2OMe)	2,4-Cl_2-Ph
2348	Me	NH-2-butyl	2,4-Cl_2-Ph
2349	Me	cyclobutylamino	2,4-Cl_2-Ph
2350	Me	2-ethylpiperidinyl	2,4-Cl_2-Ph
2351	Me	NMe(propargyl)	2,4-Cl_2-Ph
2352	Me	NEt(propargyl)	2,4-Cl_2-Ph
2353	Me	NEtMe	2,4-Cl_2-Ph
2354	Me	NEtPr	2,4-Cl_2-Ph
2355	Me	NMeBu	2,4-Cl_2-Ph
2356	Me	NMe(CH_2cPr)	2,4-Cl_2-Ph
2357	Me	NEt(CH_2cPr)	2,4-Cl_2-Ph
2358	Me	NPr(CH_2cPr)	2,4-Cl_2-Ph
2359	Me	NMe(CH_2CH_2OMe)	2-Me-4-MeOPh
2360	Me	NEt(CH_2CH_2OMe)	2-Me-4-MeOPh
2361	Me	NPr(CH_2CH_2OMe)	2-Me-4-MeOPh
2362	Me	NH-2-butyl	2-Me-4-MeOPh
2363	Me	cyclobutylamino	2-Me-4-MeOPh
2364	Me	2-ethylpiperidinyl	2-Me-4-MeOPh
2365	Me	NMe(propargyl)	2-Me-4-MeOPh
2366	Me	NEt(propargyl)	2-Me-4-MeOPh
2367	Me	NEtMe	2-Me-4-MeOPh
2368	Me	NEtPr	2-Me-4-MeOPh
2360	Me	NMeBu	2-Me-4-MeOPh
2370	Me	NMe(CH_2cPr)	2-Me-4-MeOPh
2371	Me	NEt(CH_2cPr)	2-Me-4-MeOPh
2372	Me	NPr(CH_2cPr)	2-Me-4-MeOPh

2373	Me	NMe(CH_2CH_2OMe)	2,4-Me_2-Ph
2374	Me	NEt(CH_2CH_2OMe)	2,4-Me_2-Ph
2375	Me	NPr(CH_2CH_2OMe)	2,4-Me_2-Ph
2376	Me	NH-2-butyl	2,4-Me_2-Ph
2377	Me	cyclobutylamino	2,4-Me_2-Ph
2378	Me	2-ethylpiperidinyl	2,4-Me_2-Ph
2379	Me	NMe(propargyl)	2,4-Me_2-Ph
2380	Me	NEt(propargyl)	2,4-Me_2-Ph
2381	Me	NEtMe	2,4-Me_2-Ph
2382	Me	NEtPr	2,4-Me_2-Ph
2383	Me	NMeBu	2,4-Me_2-Ph
2384	Me	NMe(CH_2cPr)	2,4-Me_2-Ph
2385	Me	NEt(CH_2cPr)	2,4-Me_2-Ph
2386	Me	NPr(CH_2cPr)	2,4-Me_2-Ph
2387	Me	NMe(CH_2CH_2OMe)	2-Cl-4-MeOPh
2388	Me	NEt(CH_2CH_2OMe)	2-Cl-4-MeOPh
2389	Me	NPr(CH_2CH_2OMe)	2-Cl-4-MeOPh
2390	Me	NH-2-butyl	2-Cl-4-MeOPh
2391	Me	cyclobutylamino	2-Cl-4-MeOPh
2392	Me	2-ethylpiperidinyl	2-Cl-4-MeOPh
2393	Me	NMe(propargyl)	2-Cl-4-MeOPh
2394	Me	NEt(propargyl)	2-Cl-4-MeOPh
2395	Me	NEtMe	2-Cl-4-MeOPh
2396	Me	NEtPr	2-Cl-4-MeOPh
2397	Me	NMeBu	2-Cl-4-MeOPh
2398	Me	NMe(CH_2cPr)	2-Cl-4-MeOPh
2399	Me	NEt(CH_2cPr)	2-Cl-4-MeOPh
2400	Me	NPr(CH_2cPr)	2-Cl-4-MeOPh
2401	Me	NMe(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2402	Me	NEt(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2403	Me	NPr(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2404	Me	NH-2-butyl	2,5-Me_2-4-MeOPh

2405	Me	cyclobutylamino	2,5-Me_2-4-MeOPh
2406	Me	2-ethylpiperidinyl	2,5-Me_2-4-MeOPh
2407	Me	NMe(propargyl)	2,5-Me_2-4-MeOPh
2408	Me	NEt(propargyl)	2,5-Me_2-4-MeOPh
2409	Me	NEtMe	2,5-Me_2-4-MeOPh
2410	Me	NEtPr	2,5-Me_2-4-MeOPh
2411	Me	NMeBu	2,5-Me_2-4-MeOPh
2412	Me	NMe(CH_2cPr)	2,5-Me_2-4-MeOPh
2413	Me	NEt(CH_2cPr)	2,5-Me_2-4-MeOPh
2414	Me	NPr(CH_2cPr)	2,5-Me_2-4-MeOPh
2415	Cl	NMe(CH_2CH_2OMe)	2,4-Cl_2-Ph
2416	Cl	NEt(CH_2CH_2OMe)	2,4-Cl_2-Ph
2417	Cl	NPr(CH_2CH_2OMe)	2,4-Cl_2-Ph
2418	Cl	NH-2-butyl	2,4-Cl_2-Ph
2419	Cl	cyclobutylamino	2,4-Cl_2-Ph
2420	Cl	2-ethylpiperidinyl	2,4-Cl_2-Ph
2421	Cl	NMe(propargyl)	2,4-Cl_2-Ph
2422	Cl	NEt(propargyl)	2,4-Cl_2-Ph
2423	Cl	NEtMe	2,4-Cl_2-Ph
2424	Cl	NEtPr	2,4-Cl_2-Ph
2425	Cl	NMeBu	2,4-Cl_2-Ph
2426	Cl	NMe(CH_2cPr)	2,4-Cl_2-Ph
2427	Cl	NEt(CH_2cPr)	2,4-Cl_2-Ph
2428	Cl	NPr(CH_2cPr)	2,4-Cl_2-Ph
2429	Cl	NMe(CH_2CH_2OMe)	2-Me-4-MeOPh
2430	Cl	NEt(CH_2CH_2OMe)	2-Me-4-MeOPh
2431	Cl	NPr(CH_2CH_2OMe)	2-Me-4-MeOPh
2432	Cl	NH-2-butyl	2-Me-4-MeOPh
2433	Cl	cyclobutylamino	2-Me-4-MeOPh
2434	Cl	2-ethylpiperidinyl	2-Me-4-MeOPh
2435	Cl	NMe(propargyl)	2-Me-4-MeOPh
2436	Cl	NEt(propargyl)	2-Me-4-MeOPh

2437	Cl	NEtMe	2-Me-4-MeOPh
2438	Cl	NEtPr	2-Me-4-MeOPh
2439	Cl	NMeBu	2-Me-4-MeOPh
2440	Cl	NMe(CH_2cPr)	2-Me-4-MeOPh
2441	Cl	NEt(CH_2cPr)	2-Me-4-MeOPh
2442	Cl	NPr(CH_2cPr)	2-Me-4-MeOPh
2443	Cl	NMe(CH_2CH_2OMe)	2,4-Me_2-Ph
2444	Cl	NEt(CH_2CH_2OMe)	2,4-Me_2-Ph
2445	Cl	NPr(CH_2CH_2OMe)	2,4-Me_2-Ph
2446	Cl	NH-2-butyl	2,4-Me_2-Ph
2447	Cl	cyclobutylamino	2,4-Me_2-Ph
2448	Cl	2-ethylpiperidinyl	2,4-Me_2-Ph
2449	Cl	NMe(propargyl)	2,4-Me_2-Ph
2450	Cl	NEt(propargyl)	2,4-Me_2-Ph
2451	Cl	NEtMe	2,4-Me_2-Ph
2452	Cl	NEtPr	2,4-Me_2-Ph
2453	Cl	NMeBu	2,4-Me_2-Ph
2454	Cl	NMe(CH_2cPr)	2,4-Me_2-Ph
2455	Cl	NEt(CH_2cPr)	2,4-Me_2-Ph
2456	Cl	NPr(CH_2cPr)	2,4-Me_2-Ph
2457	Cl	NMe(CH_2CH_2OMe)	2-Cl-4-MeOPh
2458	Cl	NEt(CH_2CH_2OMe)	2-Cl-4-MeOPh
2459	Cl	NPr(CH_2CH_2OMe)	2-Cl-4-MeOPh
2460	Cl	NH-2-butyl	2-Cl-4-MeOPh
2461	Cl	cyclobutylamino	2-Cl-4-MeOPh
2462	Cl	2-ethylpiperidinyl	2-Cl-4-MeOPh
2463	Cl	NMe(propargyl)	2-Cl-4-MeOPh
2464	Cl	NEt(propargyl)	2-Cl-4-MeOPh
2465	Cl	NEtMe	2-Cl-4-MeOPh
2466	Cl	NEtPr	2-Cl-4-MeOPh
2467	Cl	NMeBu	2-Cl-4-MeOPh
2468	Cl	NMe(CH_2cPr)	2-Cl-4-MeOPh
2469	Cl	NEt(CH_2cPr)	2-Cl-4-MeOPh

2470	Cl	NPr(CH_2cPr)	2-Cl-4-MeOPh
2471	Cl	NMe(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2472	Cl	NEt(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2473	Cl	NPr(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2474	Cl	NH-2-butyl	2,5-Me_2-4-MeOPh
2475	Cl	cyclobutylamino	2,5-Me_2-4-MeOPh
2476	Cl	2-ethylpiperidinyl	2,5-Me_2-4-MeOPh
2477	Cl	NMe(propargyl)	2,5-Me_2-4-MeOPh
2478	Cl	NEt(propargyl)	2,5-Me_2-4-MeOPh
2479	Cl	NEtMe	2,5-Me_2-4-MeOPh
2480	Cl	NEtPr	2,5-Me_2-4-MeOPh
2481	Cl	NMeBu	2,5-Me_2-4-MeOPh
2482	Cl	NMe(CH_2cPr)	2,5-Me_2-4-MeOPh
2483	Cl	NEt(CH_2cPr)	2,5-Me_2-4-MeOPh
2484	Cl	NPr(CH_2cPr)	2,5-Me_2-4-MeOPh
2485	F	NMe(CH_2CH_2OMe)	2,4-Cl_2-Ph
2486	F	NEt(CH_2CH_2OMe)	2,4-Cl_2-Ph
2487	F	NPr(CH_2CH_2OMe)	2,4-Cl_2-Ph
2488	F	NH-2-butyl	2,4-Cl_2-Ph
2489	F	cyclobutylamino	2,4-Cl_2-Ph
2490	F	2-ethylpiperidinyl	2,4-Cl_2-Ph
2491	F	NMe(propargyl)	2,4-Cl_2-Ph
2492	F	NEt(propargyl)	2,4-Cl_2-Ph
2493	F	NEtMe	2,4-Cl_2-Ph
2494	F	NEtPr	2,4-Cl_2-Ph
2495	F	NMeBu	2,4-Cl_2-Ph
2496	F	NMe(CH_2cPr)	2,4-Cl_2-Ph
2497	F	NEt(CH_2cPr)	2,4-Cl_2-Ph
2498	F	NPr(CH_2cPr)	2,4-Cl_2-Ph
2499	F	NMe(CH_2CH_2OMe)	2-Me-4-MeOPh
2500	F	NEt(CH_2CH_2OMe)	2-Me-4-MeOPh
2501	F	NPr(CH_2CH_2OMe)	2-Me-4-MeOPh

2502	F	NH-2-butyl	2-Me-4-MeOPh
2503	F	cyclobutylamino	2-Me-4-MeOPh
2504	F	2-ethylpiperidinyl	2-Me-4-MeOPh
2505	F	NMe(propargyl)	2-Me-4-MeOPh
2506	F	NEt(propargyl)	2-Me-4-MeOPh
2507	F	NEtMe	2-Me-4-MeOPh
2508	F	NEtPr	2-Me-4-MeOPh
2509	F	NMeBu	2-Me-4-MeOPh
2510	F	NMe(CH_2cPr)	2-Me-4-MeOPh
2511	F	NEt(CH_2cPr)	2-Me-4-MeOPh
2512	F	NPr(CH_2cPr)	2-Me-4-MeOPh
2513	F	NMe(CH_2CH_2OMe)	2,4-Me_2-Ph
2514	F	NEt(CH_2CH_2OMe)	2,4-Me_2-Ph
2515	F	NPr(CH_2CH_2OMe)	2,4-Me_2-Ph
2516	F	NH-2-butyl	2,4-Me_2-Ph
2517	F	cyclobutylamino	2,4-Me_2-Ph
2518	F	2-ethylpiperidinyl	2,4-Me_2-Ph
2519	F	NMe(propargyl)	2,4-Me_2-Ph
2520	F	NEt(propargyl)	2,4-Me_2-Ph
2521	F	NEtMe	2,4-Me_2-Ph
2522	F	NEtPr	2,4-Me_2-Ph
2523	F	NMeBu	2,4-Me_2-Ph
2524	F	NMe(CH_2cPr)	2,4-Me_2-Ph
2525	F	NEt(CH_2cPr)	2,4-Me_2-Ph
2526	F	NPr(CH_2cPr)	2,4-Me_2-Ph
2527	F	NMe(CH_2CH_2OMe)	2-Cl-4-MeOPh
2528	F	NEt(CH_2CH_2OMe)	2-Cl-4-MeOPh
2529	F	NPr(CH_2CH_2OMe)	2-Cl-4-MeOPh
2530	F	NH-2-butyl	2-Cl-4-MeOPh
2531	F	cyclobutylamino	2-Cl-4-MeOPh
2532	F	2-ethylpiperidinyl	2-Cl-4-MeOPh
2533	F	NMe(propargyl)	2-Cl-4-MeOPh
2534	F	NEt(propargyl)	2-Cl-4-MeOPh

2535	F	NEtMe	2-Cl-4-MeOPh
2536	F	NEtPr	2-Cl-4-MeOPh
2537	F	NMeBu	2-Cl-4-MeOPh
2538	F	NMe(CH_2cPr)	2-Cl-4-MeOPh
2539	F	NEt(CH_2cPr)	2-Cl-4-MeOPh
2540	F	NPr(CH_2cPr)	2-Cl-4-MeOPh
2541	F	NMe(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2542	F	NEt(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2543	F	NPr(CH_2CH_2OMe)	2,5-Me_2-4-MeOPh
2544	F	NH-2-butyl	2,5-Me_2-4-MeOPh
2545	F	cyclobutylamino	2,5-Me_2-4-MeOPh
2546	F	2-ethylpiperidinyl	2,5-Me_2-4-MeOPh
2547	F	NMe(propargyl)	2,5-Me_2-4-MeOPh
2548	F	NEt(propargyl)	2,5-Me_2-4-MeOPh
2549	F	NEtMe	2,5-Me_2-4-MeOPh
2550	F	NEtPr	2,5-Me_2-4-MeOPh
2551	F	NMeBu	2,5-Me_2-4-MeOPh
2552	F	NMe(CH_2cPr)	2,5-Me_2-4-MeOPh
2553	F	NEt(CH_2cPr)	2,5-Me_2-4-MeOPh
2554	F	NPr(CH_2cPr)	2,5-Me_2-4-MeOPh

a) CI-HRMS: Calcd: 367.2498; Found: 367.2468 $(M + H)^+$

b) CI-HRMS: Calcd: 387.1952; Found: 387.1939 $(M + H)^+$

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 µM 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 µg/l aprotinin, 1 µg/ml leupeptin and 1 µg/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 µg/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 µl capacity. To each well is added 50 µl of test drug dilutions (final concentration

of drugs range from 10^{-10} - 10^{-5} M), 100 µl of ^{125}I-ovine-CRF (^{125}I-o-CRF) (final concentration 150 pM) and 150 µl 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.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are 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^{-6}m) and 0.8 mg original wet weight tissue

(approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/[32P]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 [3H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [32P]cAMP from [32P]ATP is performed by sequential elution over Dowex and alumina columns.

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.

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

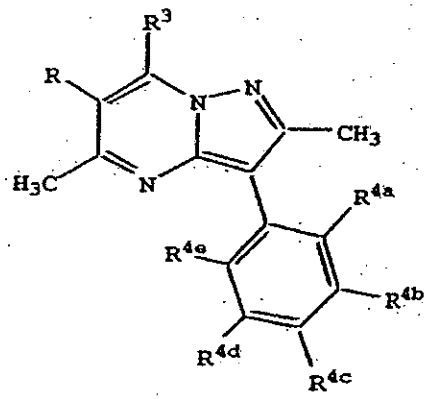
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase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

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

CLAIMS:

1. A compound of Formula (70)



FORMULA (70)

and geometric isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof selected from the group:

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is

H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -

$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - N(Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - N(Bu)(Et), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is

H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is Cl, R^3 is -$N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(n\text{-}Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -

$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is (*S*) -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H

and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is - $NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -

NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is Me, R^3 is -$N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}

is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*)-NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(n-Pr)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*) - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is (*S*) - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is - $N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH-

(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -$NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,

R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Bu)(Et), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH(Et)CH_2OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH$(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH$(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH$(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NHCH$(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NEt_2, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is ME and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH-2-

butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -

N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Pr)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -N(Et)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -

N(Me)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R^3 is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H; and

a compound of Formula (70) wherein R is Me, R^3 is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H.

2. A compound and geometric isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof, wherein said compound is selected from: 7-(diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine and 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

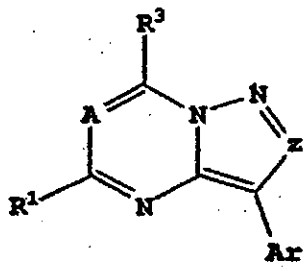
3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claims 1 and 2.

4. The use of a therapeutically effective amount of a compound of claims 1 and 2 for the manufacture of a medicament for treating effective disorder, anxiety, depression, headache, irritable bowel syndrome, post traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals.

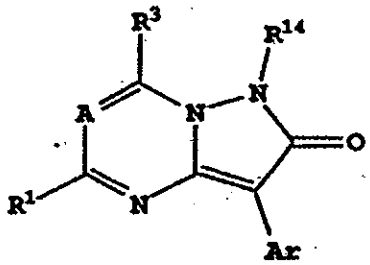
ABSTRACT

AZOLO TRIAZINES AND PYRIMIDINES

Corticotropin releasing factor (CRF) antagonists of formula (I) or (II) and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.



(I)



(II)