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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BAKTHAVATCHALAM, Rajagopal [IN/US]; 125 Berry Drive, Wilmington, DE 19808 (US). ARVANITIS, Argyrios, Georgios [GR/US]; 101 Willow Glen Drive, Kennett Square, PA 19348 (US). BECK, James, Peter [US/US]; 5506 Byron Court, Newark, DE 19702 (US). CAIN, Gary, Avonn [US/US]; 8 Wayne Drive, Wilmington, DE 19809 (US). CHORVAT, Robert, John [US/US]; 1193 Killarney Lane, West Chester, PA 19382 (US). GILLIGAN, Paul, Joseph [US/US]; 2629 Pennington Drive, Wilmington, DE 19810 (US). OLSON, Richard, Eric [US/US]; 600 Silverside Road, Wilmington, DE 19809 (US).

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

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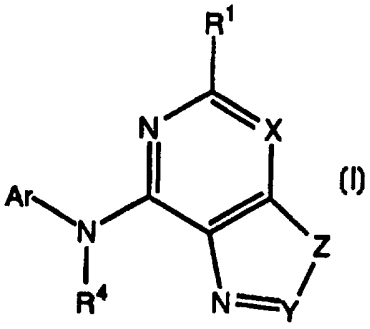
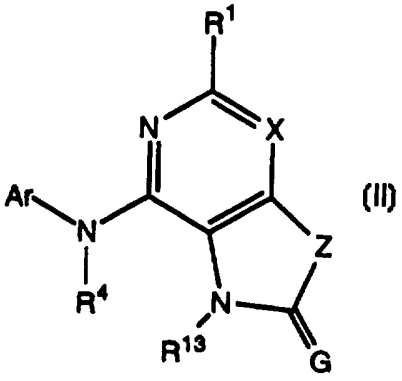
(54) Title: ARYLAMINO FUSED PYRIDINES AND PYRIMIDINES

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I) or formula (II): and their use in treating anxiety, depression, and other psychiatric and neurological disorders.



(I)



(II)

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TITLE

ARYLAMINO FUSED PYRIDINES AND PYRIMIDINES

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and 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

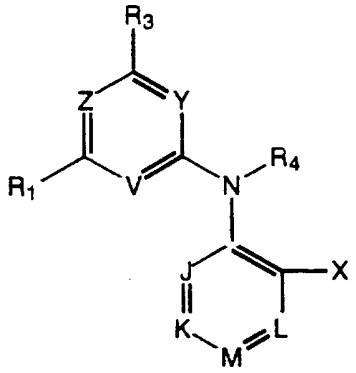
[Grigoriadis et al., *Neuropsychopharmacology* 2:53 (**1989**)].

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**)].

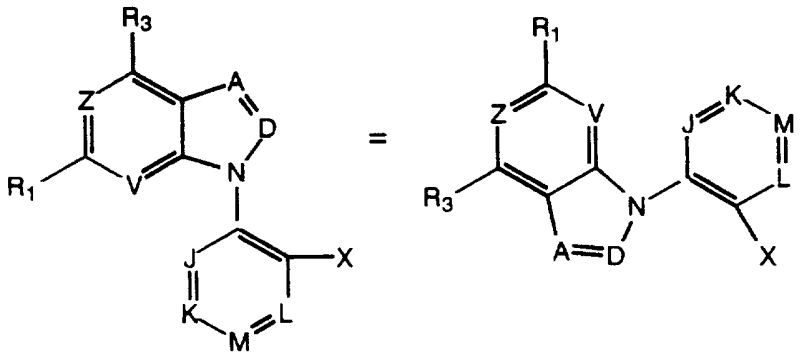
The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are

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 (a-helical CRF$_{9-41}$) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

DuPont Merck PCT application US94/11050 describes corticotropin releasing factor antagonist compounds of the formula:

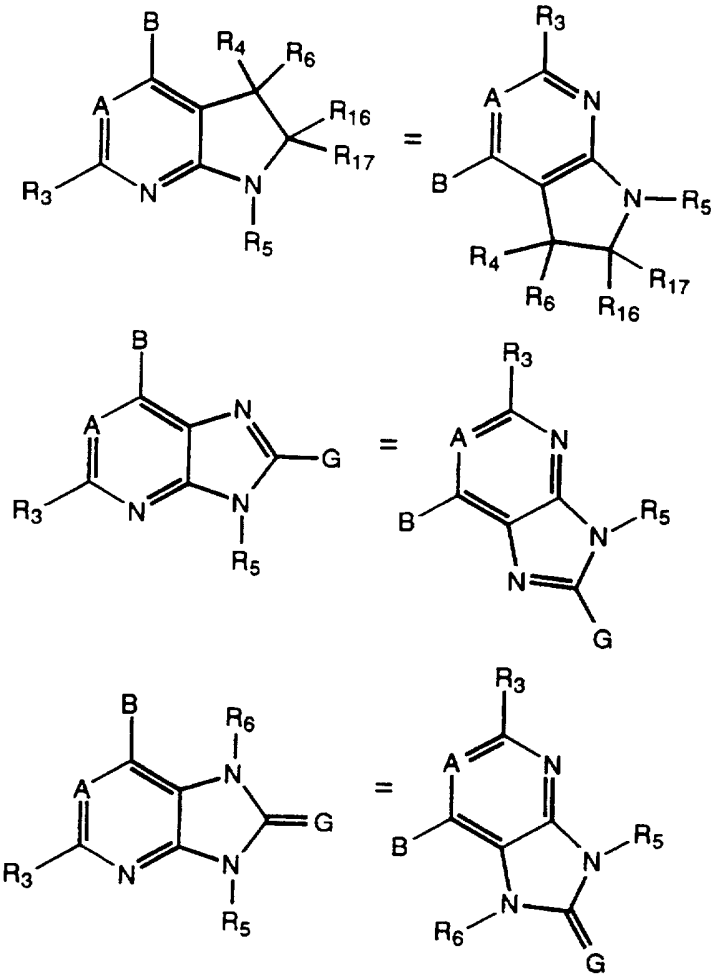


and their use to treat psychiatric disorders and neurological diseases. Included in the description are fused pyridines and pyrimidines of the formula:



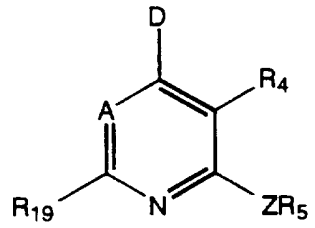
where: V is CR^{1a} or N; Z is CR^{2} or N; A is CR^{30} or N; and D is CR^{28} or N.

Pfizer WO 95/33750 describes corticotropin releasing factor antagonist compounds useful in the treatment of CNS and stress disorders. The description includes compounds of the formulae:



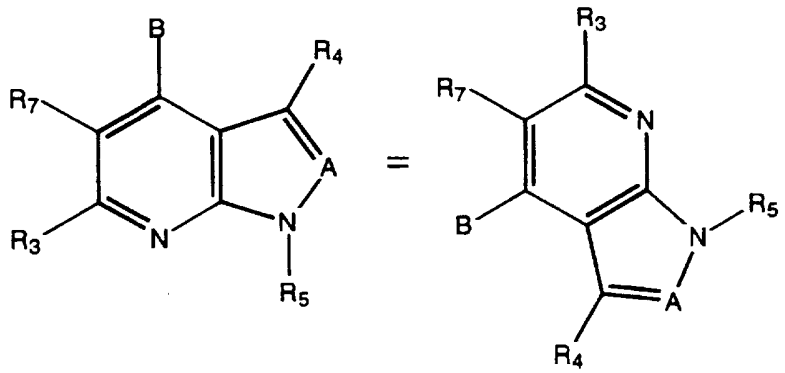
where A is CR_7 or N; B is $-NR_1R_2$; R_1 is substituted or unsubstituted alkyl; R_2 is substituted or unsubstituted alkyl, aryl or heteroaryl; R_3 is methyl, halo, cyano, methoxy, etc.; R_4 is H, substituted or unsubstituted alkyl, halo, amino, nitro, etc.; R_5 is substituted or unsubstituted aryl or heteroaryl; R_6 is H or substituted or unsubstituted alkyl; R_7 is H, methyl, halo, cyano, etc.; R_{16} and R_{17} taken together form an oxo (=O) group; and G is =O, =S, =NH, $=NCH_3$, hydrogen,

methyl, methoxy, etc. Pfizer WO 95/33750 also describes intermediates of the formula:



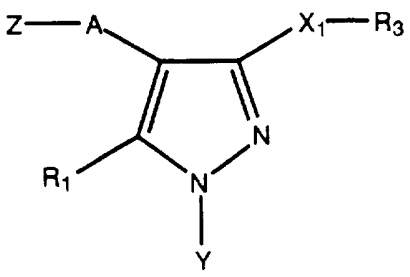
where A can be N, D can be OH, R_4 can be nitro, R_{19} is methyl or ethyl, Z can be NH or $N(CH_3)$, and R_5 is substituted phenyl or substituted pyridyl, each substituted with 2 or 3 substituents selected from C1-C4 alkyl, chloro and bromo.

Pfizer WO 95/34563 describes corticotropin releasing factor antagonist compounds, including compounds of the formula:



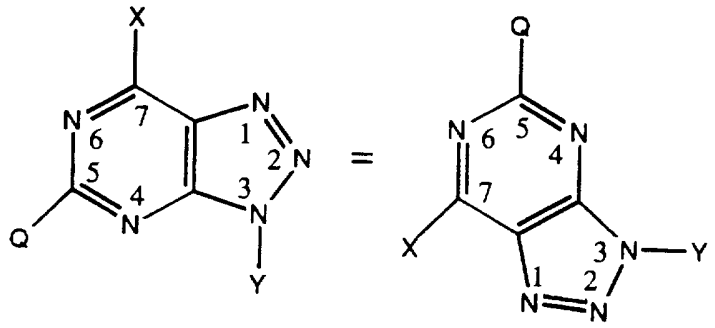
where A, B and the R groups have definitions similar to those in WO 95/33750.

Pfizer WO 95/33727 describes corticotropin releasing factor antagonist compounds of the formula:



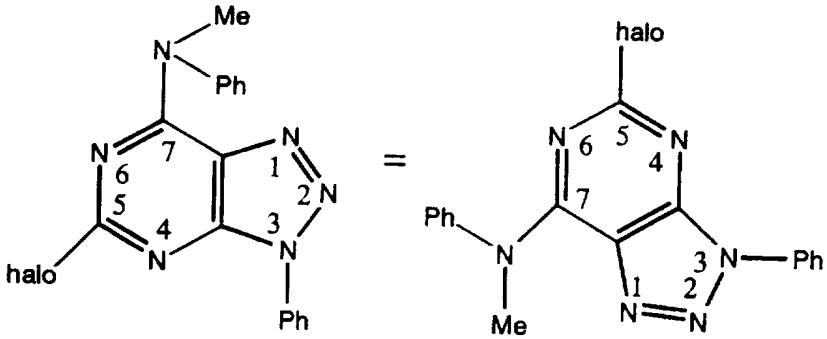
where A is CH_2 and Z can be a heteroaryl moiety.

Ganguly et al., U.S. Patent 4,076,711 describes triazolo[4,5-d]pyrimidines of the formula:



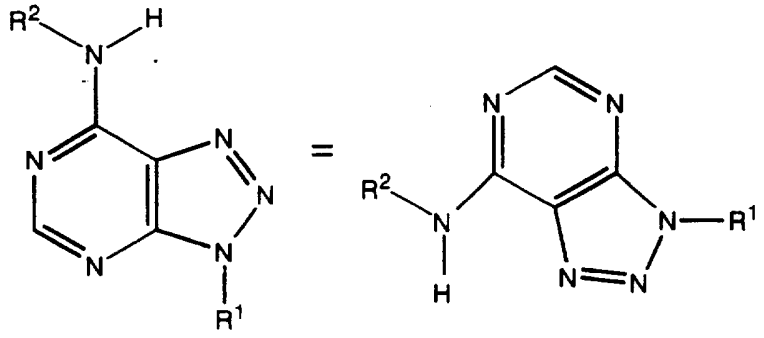
where X is halo, $-NR_1R$ or alkoxy, with R1 and R each being H or alkyl; Y is alkyl, cycloalkyl, hydroxycycloalkyl, phenyl, bicycloalkyl or phenylalkyl or bicycloalkylalkyl; and Q is H or Y. The patent states that the compounds are useful in the treatment of psoriasis.

Tanji et al., Chem. Pharm. Bull. 39(11)3037-3040(1991), describes triazolo[4,5-d]pyrimidines of the formula:



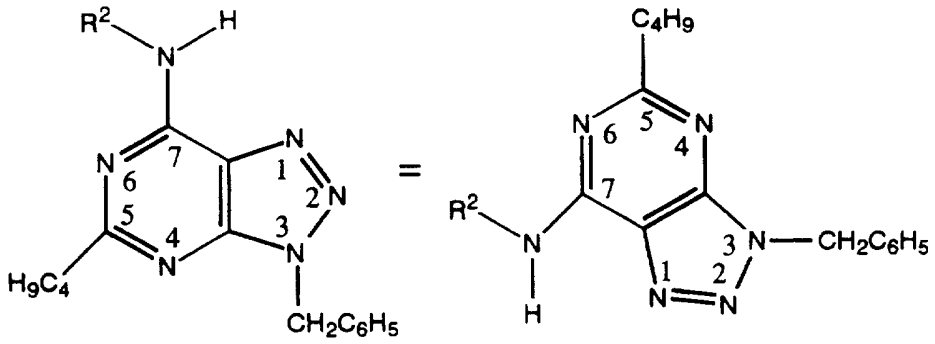
where halo is I, Br or Cl, Ph is phenyl and Me is methyl. No utility for the compounds is described.

Settimo et al., Il Farmaco, Ed. Sc., 35 (4), 308-323 (1980) describes 8-azaadenines (triazolo[4,5-d] pyrimidines) of the formula:



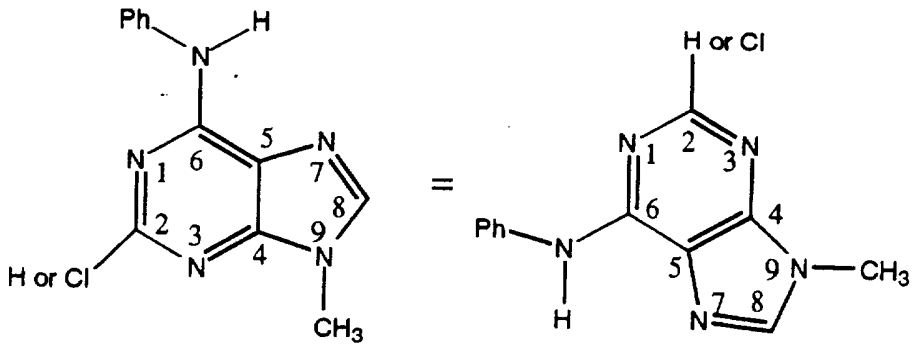
where R1 is H or benzyl and R2 is p-methylphenyl.

Biagi et al., Il Farmaco, 49 (3), 183-186 (1994), describes N(6)-substituted 2-n-butyl-9-benzyl-8-azaadenines of the formula:



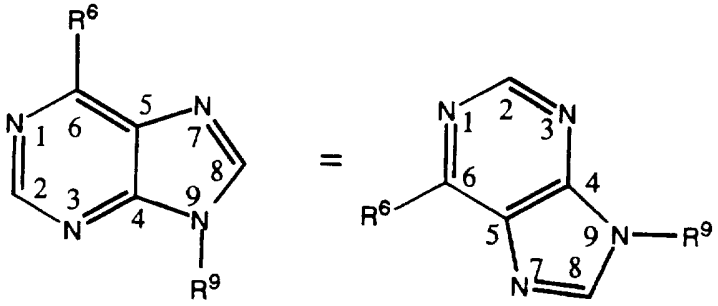
where R^2 can be alkyl, phenyl, or benzyl. The paper states that the compounds have affinity for adenosine receptors.

Thompson et al., J. Med. Chem., 1991, 34, 2877-2882, describes N^6,9-disubstituted adenines of the formula:



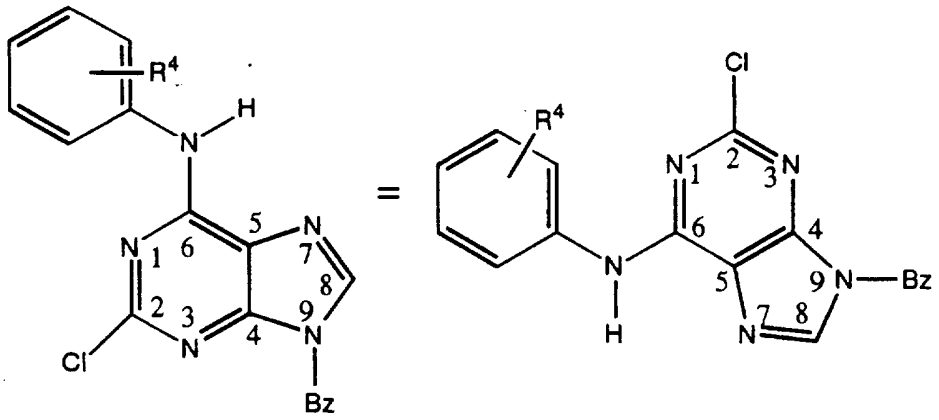
where Ph is phenyl or (when C-2 is unsubstituted) 2-fluorophenyl. The paper states that the compounds have selective affinity for the A_1 adenosine receptor.

Kelley et al., J. Med. Chem. 1990, 31, 606-612, describes the compound



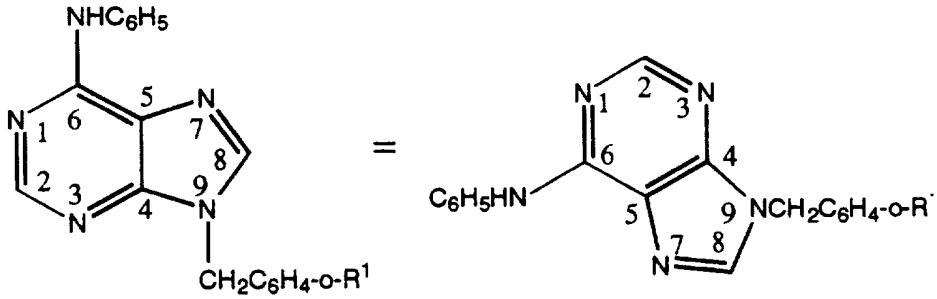
where R^6 is NHC_6H_5 and R^9 is $CH_2C_6H_5$, and reports that the compound was inactive when tested for anticonvulsant activity. The paper reports that various 6-(alkylamino)-9-benzyl-9H-purine analogs of the above compound exhibited anticonvulsant activity.

Kelley et al., J. Med. Chem. 1990, 33, 1360-1363, describes 6-anilino-9-benzyl-2-choro-9H-purines of the formula:



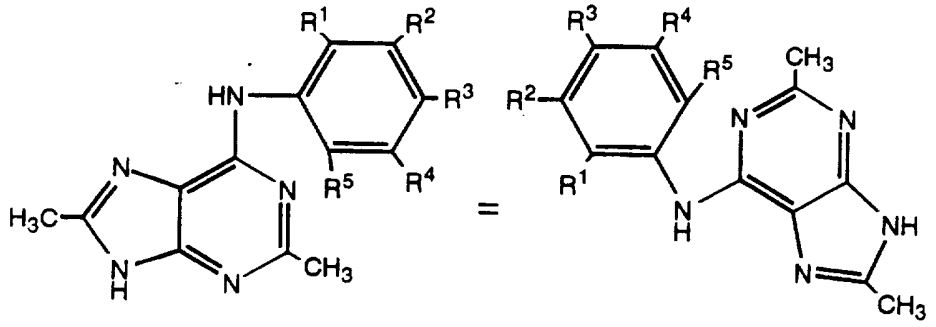
where Bz is benzyl or (when R^4 is H) p-methylbenzyl and R^4 is H or alkyl, alkoxy, halo, cyano, nitro, etc. Tests of the compounds for antirhinoviral activity are reported.

Kelley et al., J. Heterocyclic Chem., 28, 1099 (1991), describes 6-substituted-9-(3-formamidobenzyl)-9H-purines of the formula:



where R1 is NH2 or NHCHO. The compound where R1 is NHCHO was tested for benzodiazepine receptor binding and was inactive, although various analogs were active.

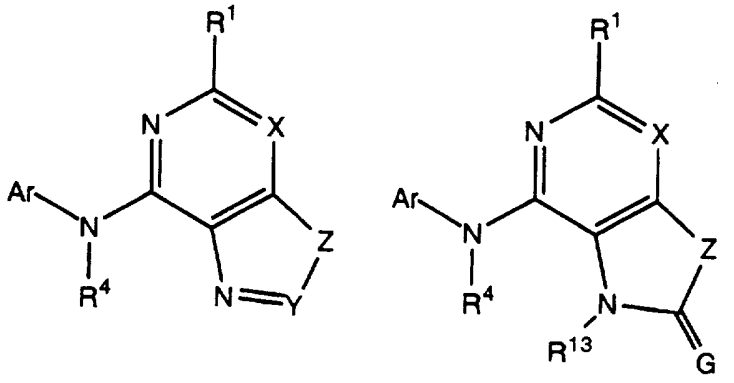
Khairy et al., J. Heterocyclic Chem., 22, 853 (1985), describes synthesis of certain 9-aryl-9H-purin-6-amines of the formula:



where the R groups are H, methyl, ethyl, isopropyl, chloro or fluoro.

SUMMARY OF THE INVENTION

This invention is a class of novel compounds which are CRF receptor antagonists and which can be represented by formula I or formula II:



I II

or a pharmaceutically acceptable salt or pro-drug form thereof, wherein:

X is N or CR^1;

Y is N or CR^2;

Z is NR^3, O, or $S(O)_n$;

G is O or S;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each optionally substituted with 1 to 5 R^5 groups;

R^1 is independently at each occurrence H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, NR^9COR^{10}, $-OR^{11}$, SH or $-S(O)_nR^{12}$;

R^2 is H, C_1-C_4 alkyl, C_1-C_6 cycloalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl or C_4-C_{12} cycloalkylalkyl each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-CONR^6R^7$, aryl, heteroaryl and heterocyclyl, where the aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

R^4 is H, C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl, allyl, or propargyl is optionally substituted with C_3-C_6 cycloalkyl and where C_1-C_4 alkyl is optionally substituted with, $-OR^7$, $-S(O)_nR^{12}$ or $-CO_2R^7$;

R^5 is independently at each occurrence C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NO_2$, halo, $-CN$, C_1-C_4 haloalkyl, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, $-CO(NOR^9)R^7$, CO_2R^7, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, $-CN$, $-NR^6R^7$, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, CO_2R^7, $-CO(NOR^9)R^7$, or $-S(O)_nR^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

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

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl , pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

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

provided that R^4 in formula I is not H:

(a) when X is N, Y is N, Z is NR^3, R^1 is H, R^3 is H or benzyl, and Ar is p-methylphenyl;

(b) when X is N, Y is N, Z is NR^3, R^1 is butyl, R^3 is benzyl, and Ar is phenyl;

(c) when X is N, Y is CH, Z is NR^3, R^3 is methyl, R^1 is H, and Ar is phenyl or 2-fluorophenyl;

(d) when X is N, Y is CH, Z is NR^3, R^3 is methyl, R^1 is Cl and Ar is phenyl;

(e) when X is N, Y is CH, Z is NR^3, R^1 is Cl, R^3 is benzyl, and Ar is phenyl or substituted phenyl;

(f) when X is N, Y is CH, Z is NR^3, R^3 is p-methylbenzyl, and Ar is phenyl;

(g) when X is N, Y is CR^2, Z is NR^3, R^2 is CH_3, R^3 is H, and Ar is phenyl or phenyl substituted with methyl, ethyl, isopropyl, fluoro or chloro;

(h) when X is N, Y is N, Z is NR^3, R3 is cyclopropylmethyl, R1 is H, and Ar is 2-bromo-4-isopropylphenyl, or

(i) when X is N, Y is N, Z is S, R^1 is H, and Ar is 2-bromo-4-isopropylphenyl.

Preferred compounds of this invention are compounds of formula I and formula II and pharmaceutically acceptable salts and pro-drug forms thereof, wherein, independently or concurrently:

X is N or CR^1;

Y is N or CR^2;

Z is NR^3, O, or $S(O)_n$;

G is O or S;

Ar is phenyl or pyridyl, each optionally substituted with 1 to 3 R^5 groups;

R^1 is independently at each occurrence H, C_1-C_4 alkyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, $-OR^{11}$ or $-S(O)_nR^{12}$;

R^2 is H, C_1-C_4 alkyl, C_1-C_6 cycloalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, C_1-C_4 haloalkyl, $-OR^7$ or $-S(O)_nR^{12}$;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl or C_4-C_{12} cycloalkylalkyl each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, $-S(O)_nR^{13}$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, aryl and heteroaryl, where the aryl or heteroaryl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, cyano, $-OR^7$, $-S(O)_nR^7$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, and $-NR^6R^7$;

R^4 is H, C_1-C_4 alkyl, allyl, or propargyl;

R^5 is independently at each occurrence C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_8 cycloalkylalkyl, $-NO_2$, halo, -CN C_1-C_4 haloalkyl, $-NR^6R^7$, COR^7 $-OR^7$, $-CONR^6R^7$, $-CO(NOR^9)R^7$, CO_2R^7, or $-S(O)_nR^7$, where C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7, $-CO(NOR^9)R^7$, or $-S(O)_nR^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

aryl is phenyl or naphthyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, cyano, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^8$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{12}$, and $-NR^6R^7$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, cyano, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^8$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{12}$, and $-NR^6R^7$;

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

Of the preferred compounds, more preferred are those of formula I wherein Z is NR^3 and pharmaceutically acceptable salts and pro-drug forms thereof.

Included in this invention is the method of treating 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, or fertility problem in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of formula I or II.

Also included in this invention are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of any one of the above-described compounds.

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

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

DETAILED DESCRIPTION OF INVENTION

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

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. "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 "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural amino acids, modified and unusual amino acids, as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids, such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, ornithine, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, ß-phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The term "amino acid residue" as used herein means that portion of an amino acid (as defined herein) that is present in a peptide.

The term "peptide" as used herein means a compound that consists of two or more amino acids (as defined herein) that are linked by means of a peptide bond. The term "peptide" also includes compounds containing both peptide and non-peptide components, such as pseudopeptide or peptide mimetic residues or other non-amino acid components. Such a compound containing both peptide and non-peptide components may also be referred to as a "peptide analog".

The term "peptide bond" means a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of one amino acid and the amino group of a second amino acid.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of formulas (I) and (II). 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.

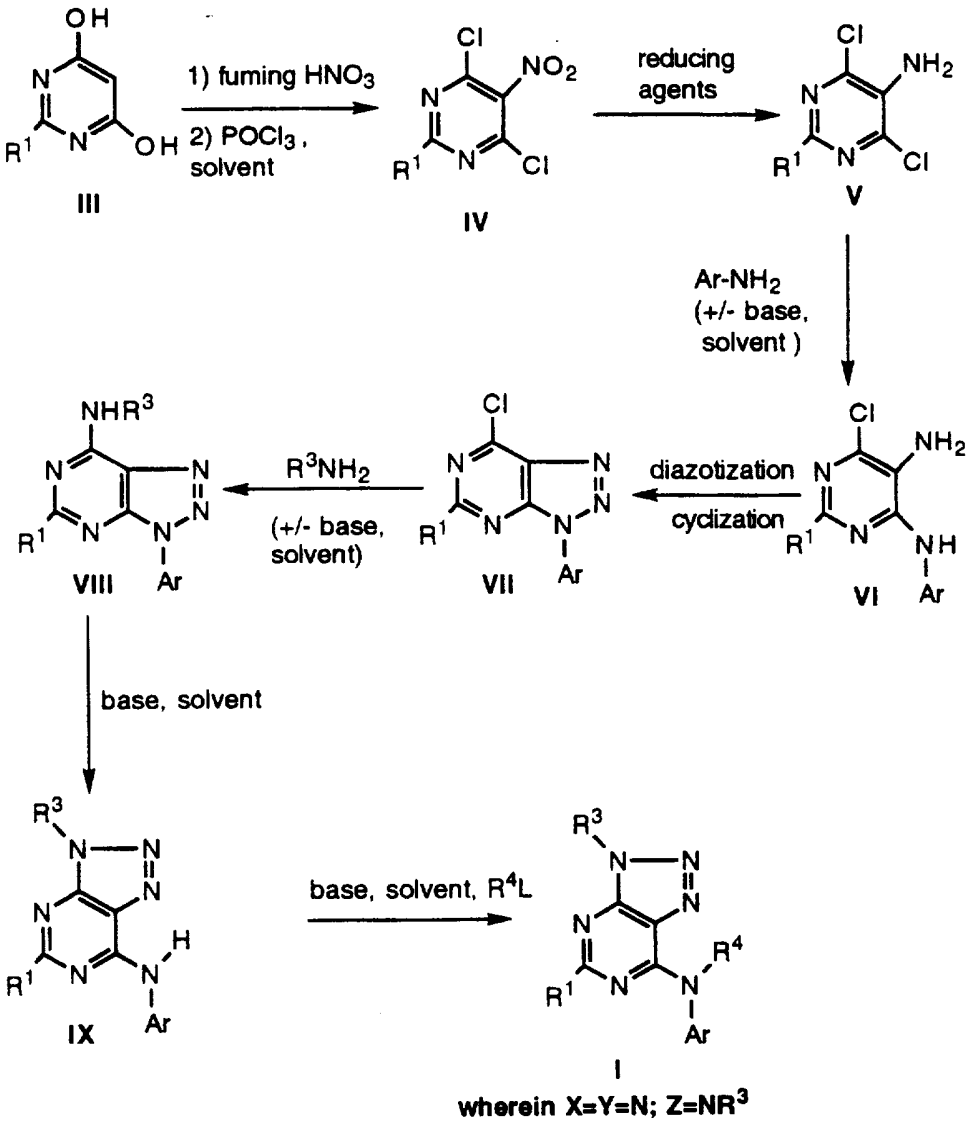
The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

Synthesis

The bicylic fused pyrimidine and pyridines of this invention can be prepared by one of the general schemes outlined below (Scheme 1-9).

Compounds of the Formula (I) wherein X=Y=N and $Z=NR^3$, can be prepared as shown in Scheme 1.

Scheme 1



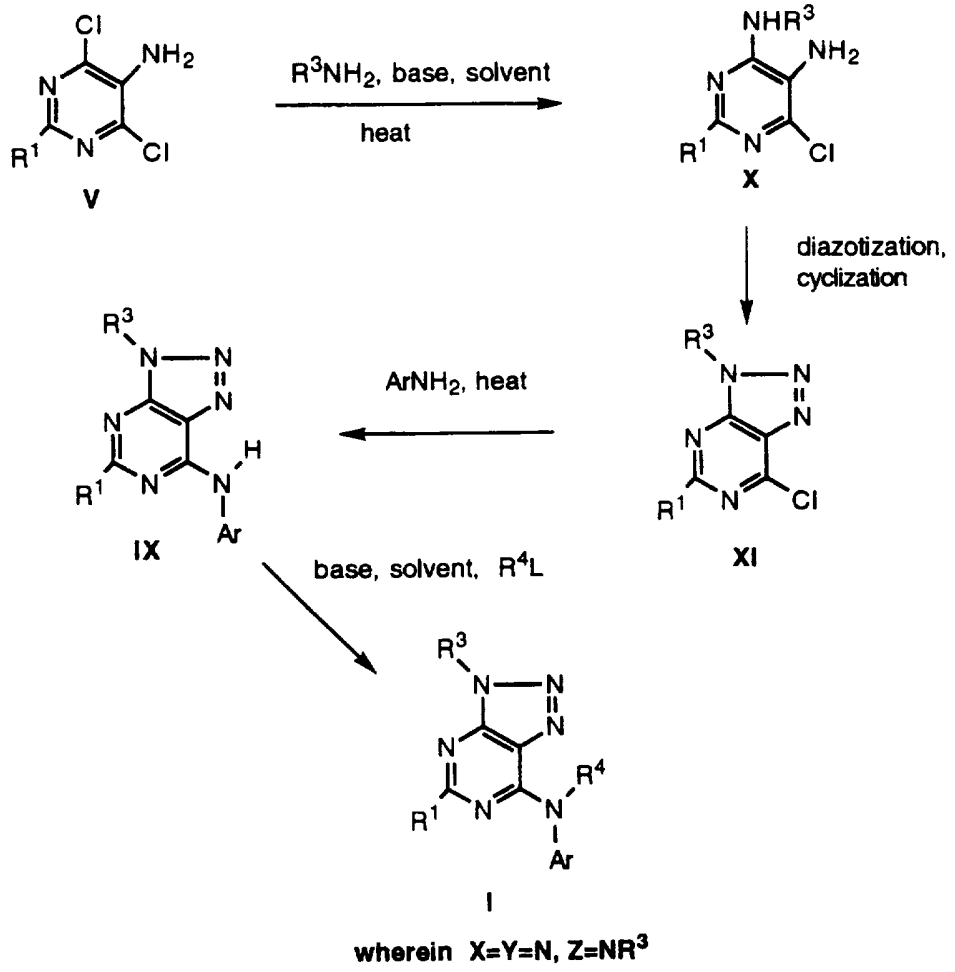
The 4,6-dihydroxypyrimidines (III) can be nitrated using fuming nitric acid and then converted into intermediates (IV) by the action of phosphorous oxychloride with the optional assistance of a catalyst such as dialkylanilines (see: Brown, D.J. et.al. J. *Chem. Soc.*, **1954**, 3832). The amino group of pyrimidines of Formula (V) can be prepared from the corresponding nitro compounds (IV) by treatment with reducing agents such as, but not limited to, sodium dithionate, iron or zinc, or catalytic hydrogenation

(see: Larock, R.C. *Comprehensive Organic Transformations*,. VCH Publishers, New York, **1989**, 411). Reaction with Ar-NH_2 can be used to provide compounds of Formula (VI). Conditions which may facilitate this transformation include the optional presence of protic or aprotic acids, or bases such as alkali metal hydrides, trialkylamines, or alkali metal carbonates, or alkali metal bis(trimethylsilyl)amides wherein the metal can be sodium, lithium, or potassium. These reactions may be conducted neat, or in the optional presence of solvents such as but not limited to cyclic ethers such as tetrahydrofuran, dialkylformamides, ethylene glycol, 2-ethoxyethanol, halocarbons, alkanenitriles, or alkyl alcohols at room temperature or at elevated temperature up to the boiling point of the solvent employed. One skilled in the art of organic synthesis will readily understand the optimal combinations of these conversions to prepare a number of compounds of Formula (VI). Cyclization to triazolopyrimidines of Formula (VII) can then be readily accomplished by diazotization and cyclization of the diamino compounds of Formula (VI) with an alkali metal nitrite in the presence of acid in water with or without an organic cosolvent such as halocarbons, or cyclic ethers. Treatment of compound of Formula (VII) with primary amines then can provide the intermediates (VIII) using reaction conditions similar to those employed for the conversion of (V) to (VI). The rearranged triazolopyrimidine of Formula (IX) may be obtained from the triazolopyrimidine of Formula (VIII) by treatment with base such as but not limited to, alkali metal hydrides, alkaline earth metal hydrides, alkali metal dialkyl amides in inert solvents such as dialkylformamides, dialkylacetamides at temperatures ranging from 0 ° to 200 °C. Finally, reaction with an appropriate R^4L wherein L is a suitable leaving group such as halo, methanesulfonate,

p-toluenesulfonate, or triflate in the presence or absence of bases such as but not limited to, alkali metal hydrides, alkaline earth metal hydrides, alkali metal dialkyl amides in inert solvents such as dialkylformamides or dialkylacetamides at temperatures ranging from 0 ° to 200 °C can be used to generate compounds of Formula (I).

Alternatively, compounds of Formula (I) wherein X=Y=N and Z=NR^3, of this invention can be prepared as outlined in Scheme 2:

Scheme 2



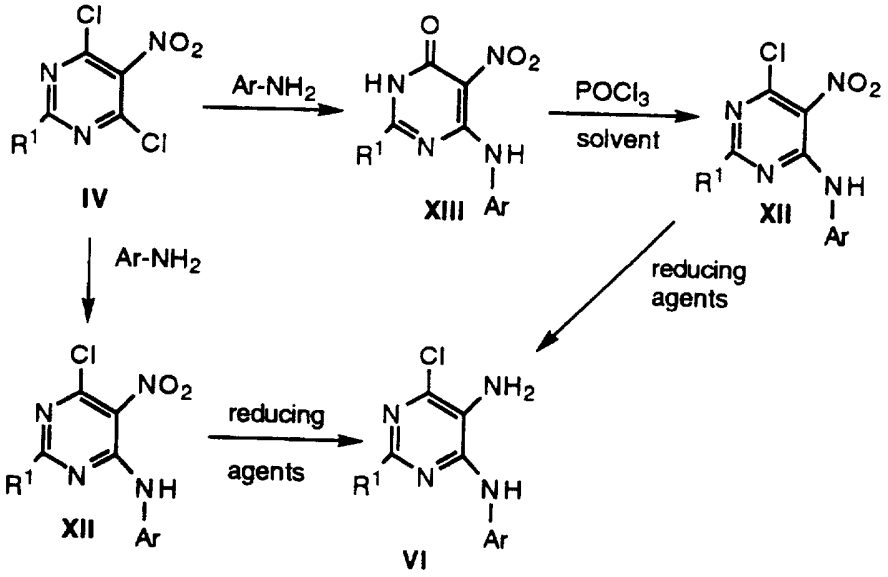
wherein X=Y=N, Z=NR^3

Treatment of compound of Formula (V) with primary amines can provide the diamino substituted pyrimidines

(X). Conditions which facilitate this transformation are detailed previously for the conversion of (VII) to (VIII). Cyclization to triazolopyrimidines of Formula (XI) can then be readily accomplished by following the conditions already described for the conversion of (VI) to (VII) in Scheme 1. The leaving group such as, but not limited to, halogen can then be displaced by addition of Ar-NH_2 to provide compounds of Formula (IX) by utilizing the conditions described for the conversion of (V) to (VI). Compounds of Formula (IX) can be converted to (I) in the same way as outlined in Scheme 1.

Compounds of the Formula (VI) can also prepared by an another approach (Scheme 3) involving addition of Ar-NH_2 to (IV) to afford compounds of Formula (XII).

Scheme 3

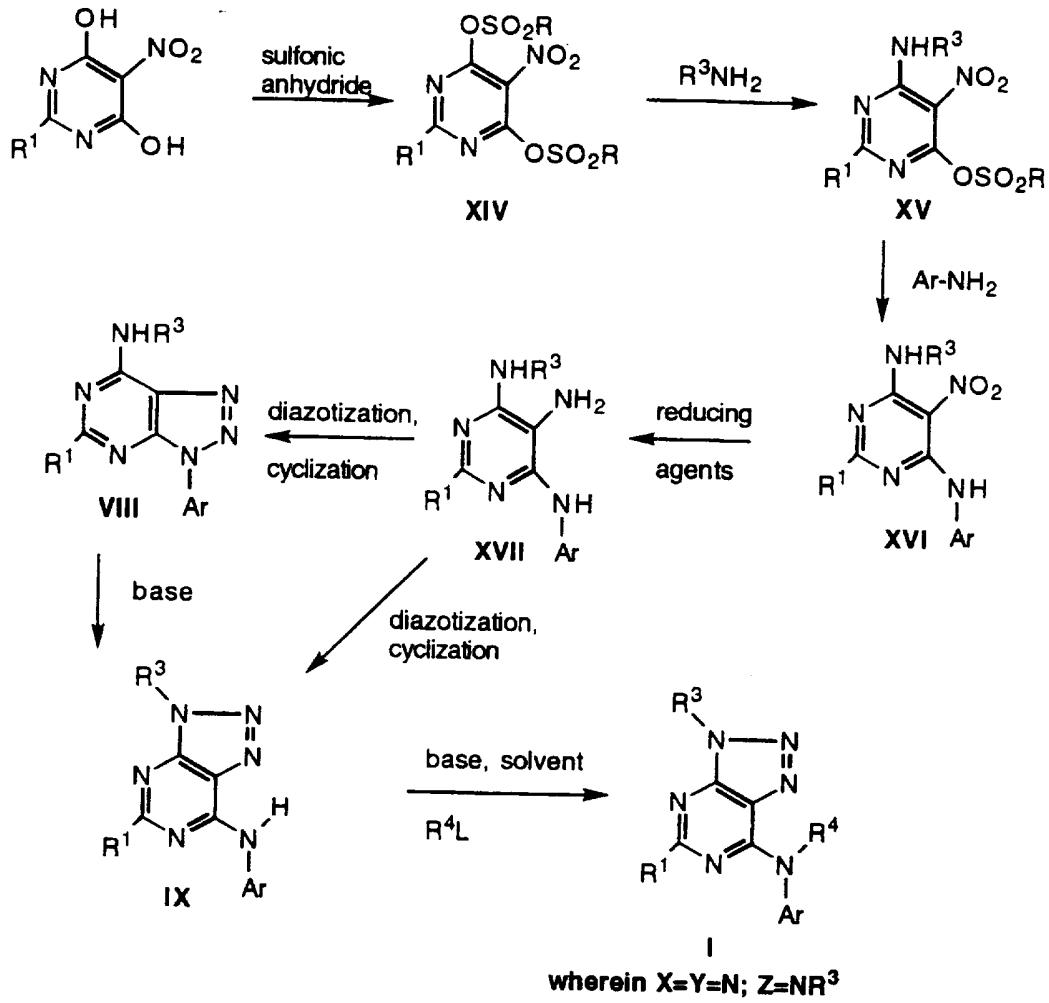


The nitro group in (XII) can be reduced to give compounds of Formula (VI) under conditions similar to those described for the transformation of (IV) to (V) in Scheme 1. Alternatively, as shown in Scheme 3, addition of Ar-NH_2 to compounds of Formula (IV) can

generate in-situ the pyrimidones (XIII). For example, treatment of dichloropyrimidines of Formula (IV) with one equivalent of Ar-NH_2 in the presence of solvents such as (but not limited to) dialkylsulfoxides, dialkylformamides, and alkyl alcohols readily generate pyrimidones (XIII). Compounds of Formula (XIII) can be converted into (IV) by the action of phosphorous oxychloride with the optional assistance of a catalyst such as dialkylanilines with or without an inert solvent. Compounds of Formula (VI) are elaborated to structures of Formula (I) as previously shown in Scheme 1.

Scheme 4 outlines another route to fused triazolopyrimidine type of compounds of this invention.

Scheme 4

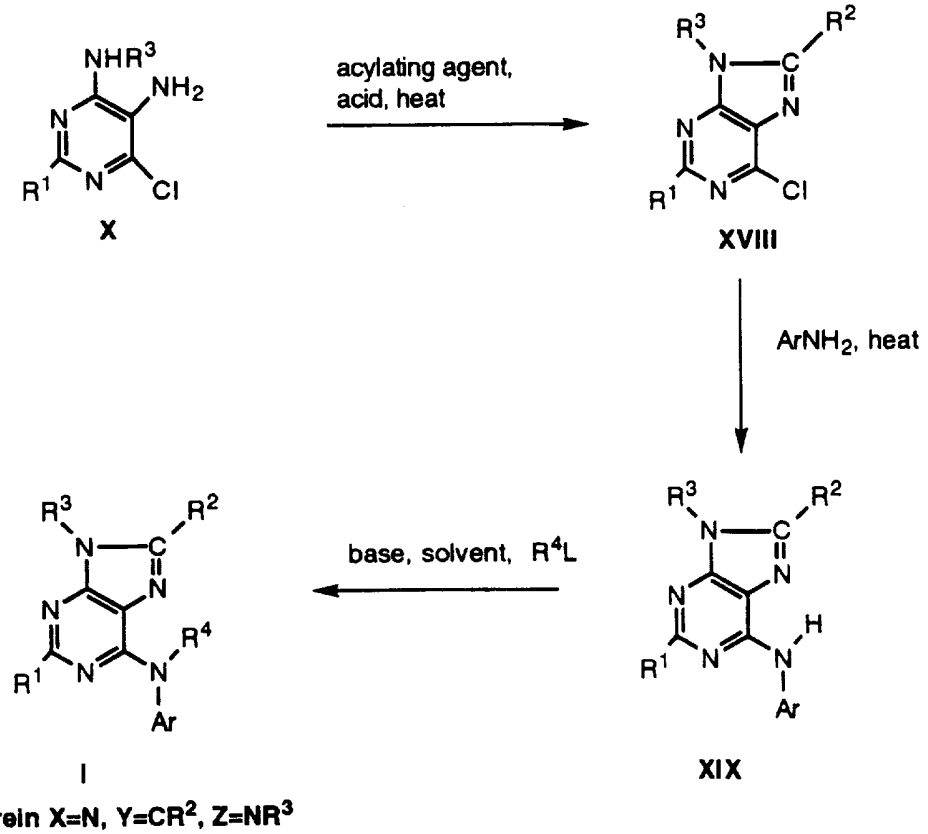


4,6-dihydroxy-5-nitropyrimidines can be treated with aryl sulfonic anhydrides, aryl sulfonyl chlorides, alkyl sulfonic anhydrides or alkyl sulfonyl chlorides in the presence or absence of bases such as alkali metal hydrides, alkaline earth metal hydrides, alkali metal dialkyl amides in inert solvents such as dialkylformamides, dialkylacetamides at temperatures ranging from 0 ° to 200 °C to give intermediates of Formula (XIV). Compounds of Formula (XIV) are treated with primary amines to give aminonitropyrimidines (XV). Treatment of (XV) with Ar-NH_2 can provide compounds of Formula (XVI). Compounds of the formula (XVI) can be reduced to amino derivatives (XVII) using

the reagents described for the conversion of (IV) to (V) in Scheme 1.. Intermediate (XVII) can be converted to a mixture of (VIII) and (IX) by diazotization and cyclization. Compounds of the Formula (VIII) can be converted to (IX) by treatment with base such as but not limited to, alkali metal hydrides, alkaline earth metal hydrides, alkali metal dialkyl amides in an inert solvent. Compounds of Formula (IX) are elaborated to give (I) as delineated in Scheme 1.

Fused imidazolopyrimidines of the Formula (I) wherein X=N, Y=CR^2, and Z=NR^3, can be prepared from compound (X) as shown in Scheme 5.

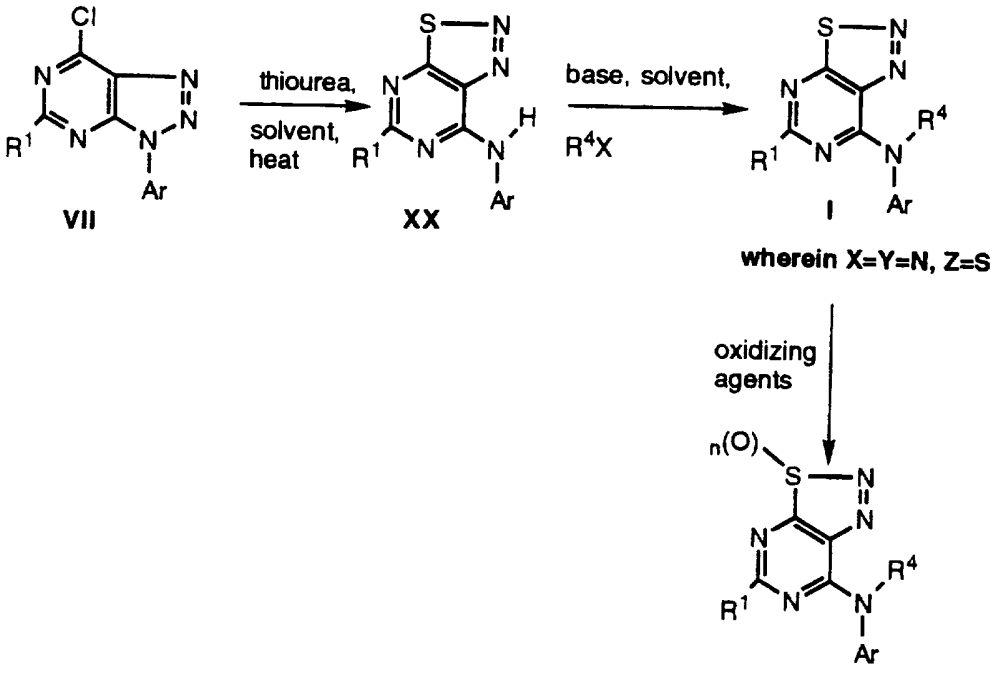
Scheme 5



Treatment of (X) with an acylating agent such as, but not limited to, alkyl anhydrides, haloalkyl anhydrides, alkylamides, haloalkyl amides, trialkylorthoesters $R^2(OR)_3$ (where R is C_1-C_4 alkyl), guanidines, cyanogen bromide, R^2COOH, urea or thiourea in the presence or absence of an acid (such as HOAc, HCl, H_2SO_4) in the presence or absence of an organic cosolvent such as alkyl alcohols, cyclic ethers, or aromatic solvents at temperatures ranging from 0 ° to 200 °C. Treatment of (XVIII) with Ar-NH_2 can provide compounds of Formula (XIX). Finally, alkylation of compound (XIX) can provide imidazolopyrimidine (I, wherein X=N, Y=CR^2, Z=NR^3).

The 1,2,3-thiadiazolo[5,4-d]pyrimidines of the formula (I) (wherein X=Y=N and Z=S), can be prepared as shown in Scheme 6.

Scheme 6

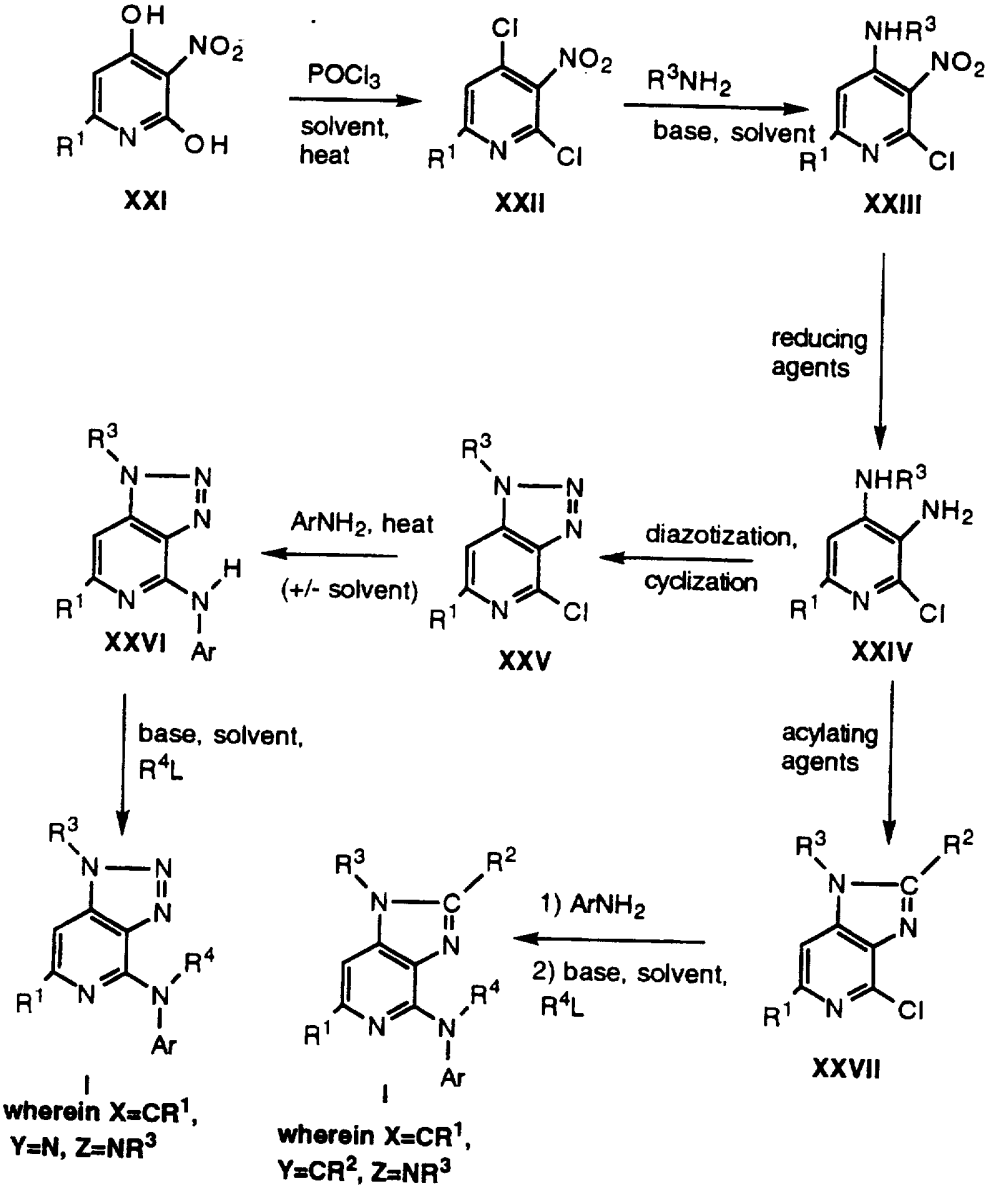


Compounds of the formula (VII) with thiourea can react upon heating in presence of solvents such as but not limited to, cyclic ethers such as tetrahydrofuran,

dialkylformamides such as dimethylformamide, dialkyl acetamides, ethylene glycol, 2-ethoxyethanol, halocarbons such as methylene chloride, alkanenitriles such as acetonitrile, or alkyl alcohols such as methanol, ethanol to give compound (XX) which is alkylated to afford thiadiazolpyrimidine (I) (wherein X=Y=N and Z=S). Compounds of Formula (I) can be converted to sulfoxides as well sulfones under a variety of oxidizing agents such as but not limited to , $NaIO_4$, $KMnO_4$ or m-chloroperbenzoic acid.

The method of synthesis of the triazolopyridines of this invention is shown in Scheme 7.

Scheme 7



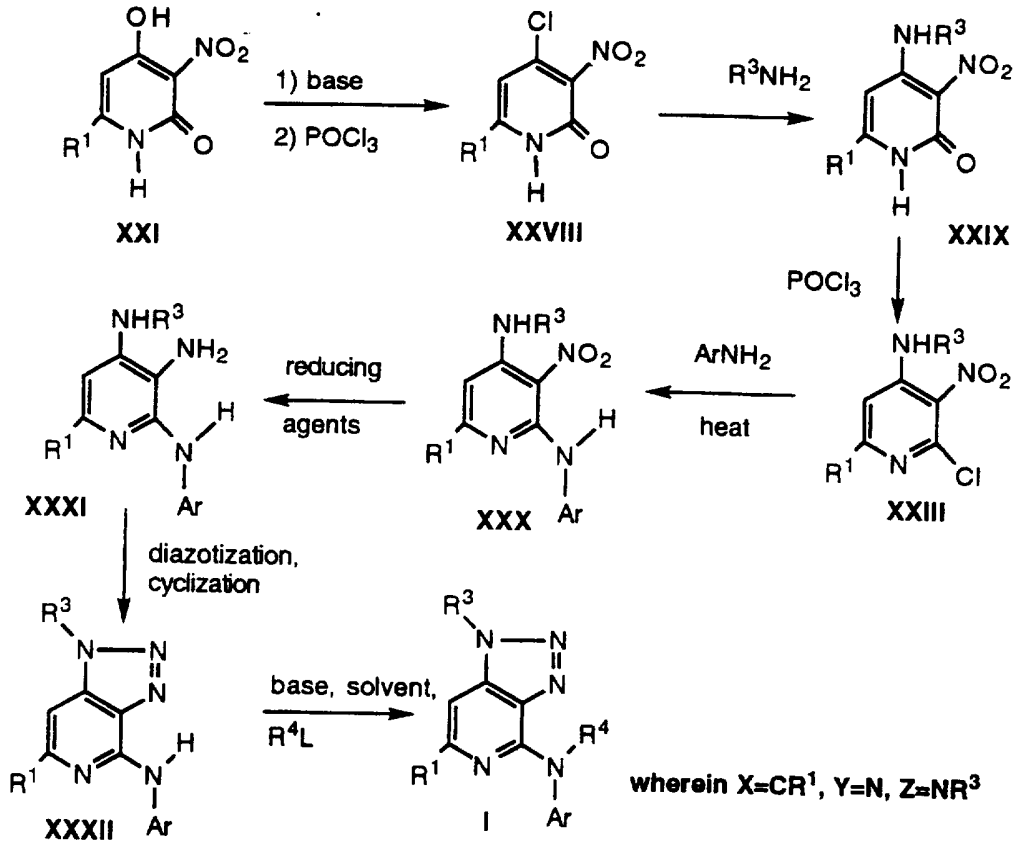
The hydroxy groups in (XXI) can be converted into chloro groups by the action of phosphorous oxychloride with the optional assistance of a catalyst such as dialkylaniline (see: Brown, D.J. et.al. J. *Chem. Soc.*, **1954**, 3832) to afford compounds of Formula (XXII). Addition of primary amines to compound (XXII) can provide alkylaminonitropyridines (XXIII). The nitro group in (XXIII) can be reduced using the conditions employed for the transformation of (IV) to

(V) to give (XXIV). Diazotization and cyclization of (XXIV) can provide chlorotriazolopyridine derivatives (XXV) as was described for the conversion of (VI) to (VII) in Scheme 1. The chloro group can then be displaced by addition of Ar-NH_2 to afford compounds (XXVI) and then treated with R^4L to give (I).

Imidazolopyridines of the present invention can be prepared from compound (XXIV) as shown in Scheme 7 by following the conditions outlined for the conversion of (X) to (XVIII) in Scheme 5. Treatment of compound (XXVII) with Ar-NH_2 using the conditions outlined in Scheme 1 can provide compounds of Formula (I, where R^4=H). Alkylation with R^4L can afford imidazolopyridines of formula I (where R^4 is not equal to H).

Alternatively, the triazolopyridines can be synthesized as shown in Scheme 8.

Scheme 8

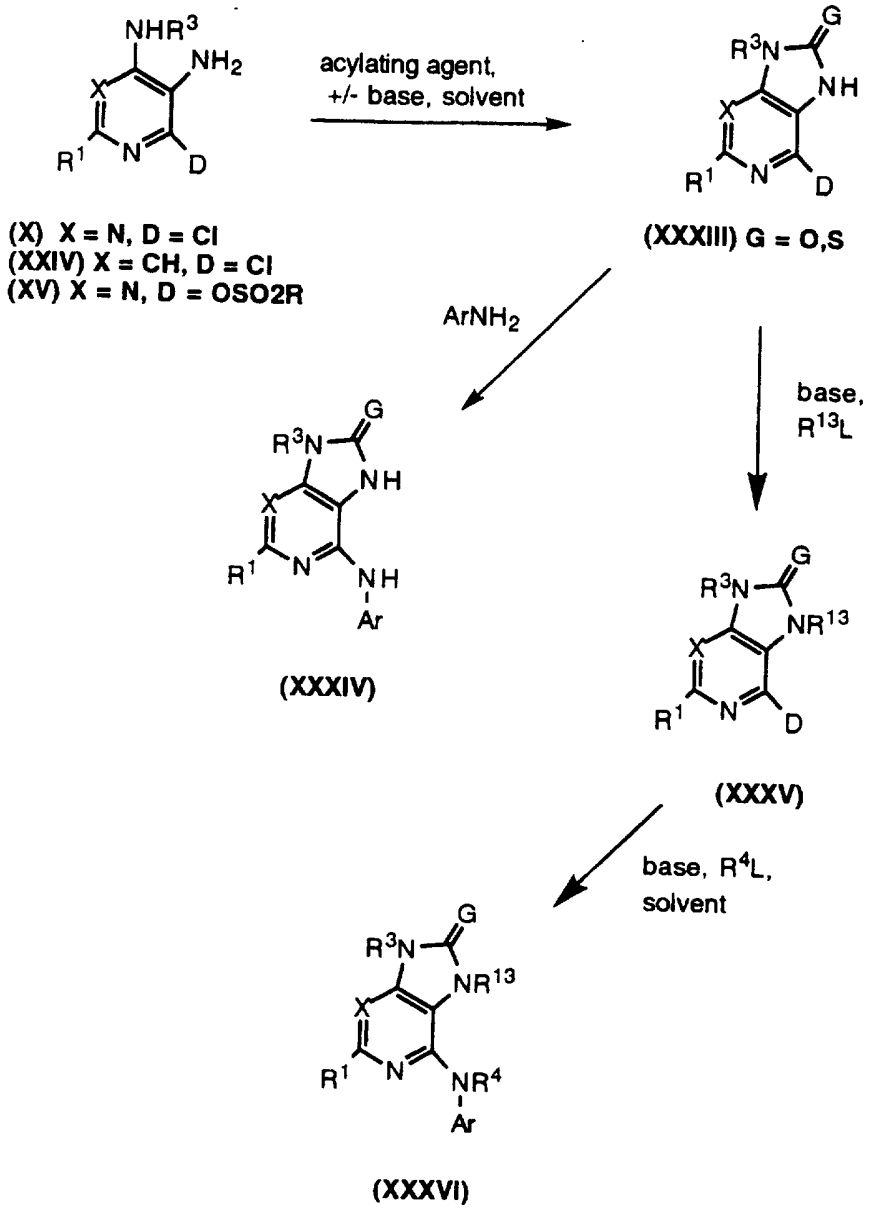


Treatment of compounds of Formula (XXI) with an aliphatic or aromatic amine in the appropriate organic solvent but not limited to, alkyl alcohols such as methanol, ethanol, propanol, butanol, alkyl alkanoates such as ethyl acetate, alkanenitriles such as acetonitrile, dialkyl formamides such as DMF gives the corresponding ammonium salt, which upon treatment with $POCl_3$ at temperatures from 25 to 120 °C, give compounds of Formula (XXVIII). Treatment of compounds of Formula (XXVIII) with appropriate primary amines in an organic solvent such as but not limited to, alkyl alcohols such as methanol, ethanol, propanol, butanol, alkyl alkanoates such as ethyl acetate, alkanenitriles such as acetonitrile, dialkyl formamides such as DMF, dialkylsulfoxides at temperatures from 25 to 120 °C to give (XXIX). This was converted to (XXIII) by

treatment with $POCl_3$ at temperatures from 25 to 120 °C. Compounds of Formula (XXIII) could be coupled with Ar-NH_2 with or without the presence of solvent at temperatures from 25 to 200 °C to give product (XXX). These could be converted to intermediates (XXXI) by reduction of the nitro group under a variety of reducing conditions, such as those used for the conversion of (IV) to (V) in Scheme 1. The final cyclizaton was carried out as described for the conversion of (VI) to (VII) in Scheme 1.

Compounds of general formula (II) may be prepared according to the procedures outlined in Scheme 9.

Scheme 9



Intermediates of formula (X), (XV) or (XXIV) may be converted to compounds of formula (XXXIII) by treatment with an acylating agent in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -78 °C to 200 °C. Acylating agents include, but are not limited to, phosgene, thiophosgene, diphosgene, triphosgene, carbonyl diimidazole, thiocarbonyl diimidazole,

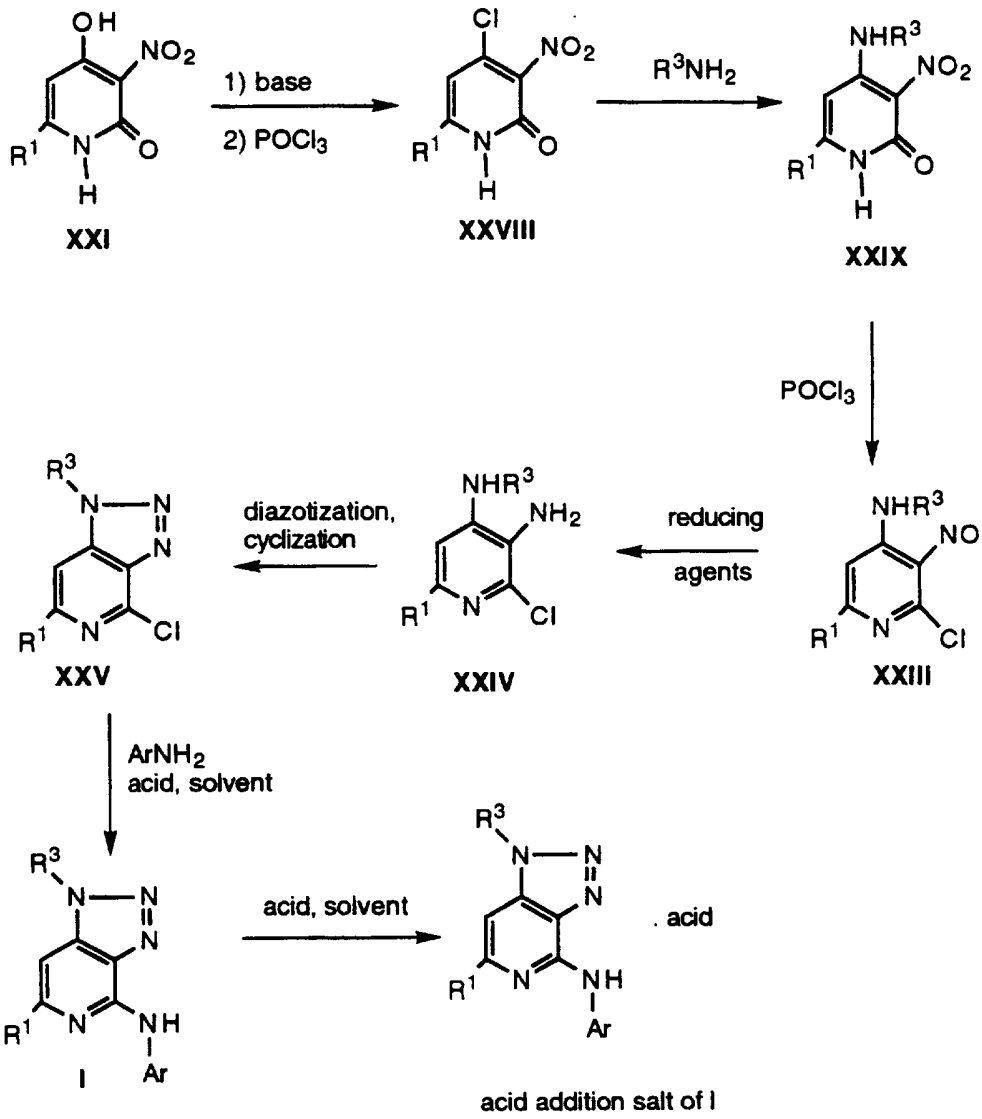
dialkylcarbonates (such as diethyl carbonate) or $R^aR^bN(C=G)OR^c$ (where G= O,S; R^a, R^b, and R^c are independently C1-C8 alkyl). Bases include, but are not limited to, alkali metal alkoxides, akali metal hydrides, trialkyl amines, pyridine, 4-dimethylaminopyridine, alkali metal dialkyl amides or alkali metal bis(trimethylsilyl)amides. Inert solvents include, but are not limited to, halocarbons, alkanenitriles, dialkylformamides, dialkylacetamides, dialkyl ethers, cyclic ethers such as tetrahydrofuran or dioxane, or alkyl alcohols. Intermediates of (XXXIII) may be converted to compounds of formula (XXXIV) (Formula (II) where R^4 = H) by reaction with $ArNH_2$, using the conditions described for the conversion of compound (V) to (VI) in Scheme 1.

Compounds of Formula (XXXV) may be prepared from compounds of structure (XXXIII) by reaction with $R^{13}L$ (where L is a leaving group such as halide, alkanesulfonate or arylsulfonate) in the presence or absence of a base in an inert solvent. Bases and inert solvents may be the same as those listed above for the preparation of (XXXIII). Intermediates of Formula (XXXV) can be reacted with $ArNH_2$ to give compounds of formula (XXXVI) (Formula (II), where R^4 = H) using the conditions described for the conversion of compound (V) to (VI) in Scheme 1. Compounds of Formula (XXXVI) may be converted to compounds of (XXXVII) (Formula (II), where R^4 does not equal H) by treatment with R^4L (where L is a leaving group such as halide, alkanesulfonate or arylsulfonate) in the presence or absence of a base in an inert solvent. Bases and inert solvents may be the same as those listed above for the preparation of (XXXIII).

As illustrated in Scheme 10, treatment of compounds of Formula (XXI) with an aliphatic or

aromatic amine in an appropriate organic solvent (such as but not limited to, alkyl alcohols such as methanol, ethanol, propanol, butanol, alkyl alkanoates such as ethyl acetate, alkanenitriles such as acetonitrile, dialkyl formamides such as DMF) gives the corresponding ammonium salt, which upon treatment with $POCl_3$ at temperatures from 25 to 120 °C, give compounds of Formula (XXVIII). Treatment of compounds of Formula (XXVIII) with appropriate primary amines R^3NH_2 in an organic solvent (such as but not limited to, alkyl alcohols such as methanol, ethanol, propanol, butanol, alkyl alkanoates such as ethyl acetate, alkanenitriles such as acetonitrile, dialkyl formamides such as DMF, dialkylsulfoxides) at temperatures from 25 to 120 °C provides compounds of Formula (XXIX). These can be converted to (XXIII) by treatment with $POCl_3$ at temperatures from 25 to 120 °C. Compounds of Formula (XXIII) can be converted to intermediates (XXIV) by reduction of the nitro group under a variety of reducing conditions, such as those used for the conversion of (IV) to (V) in Scheme 1. Diazotization and cyclization of (XXIV) can provide chlorotriazolopyridine (XXV) as was described for the conversion of of (VI) to (VII) in Scheme I. The chloro group can then be displaced by addition of $Ar\text{-}NH_2$ in the presence of an acid such as but not limited to HCl, H_2SO_4, AcOH, methanesulfonic acid, p-toluenesulfonic acid in inert solvents such as toluene, xylenes at temperatures ranging from 0 ° to 200 °C to afford product I. Salts of I are prepared by combining the free base with appropriate acid in a suitable organic solvent.

Scheme 10

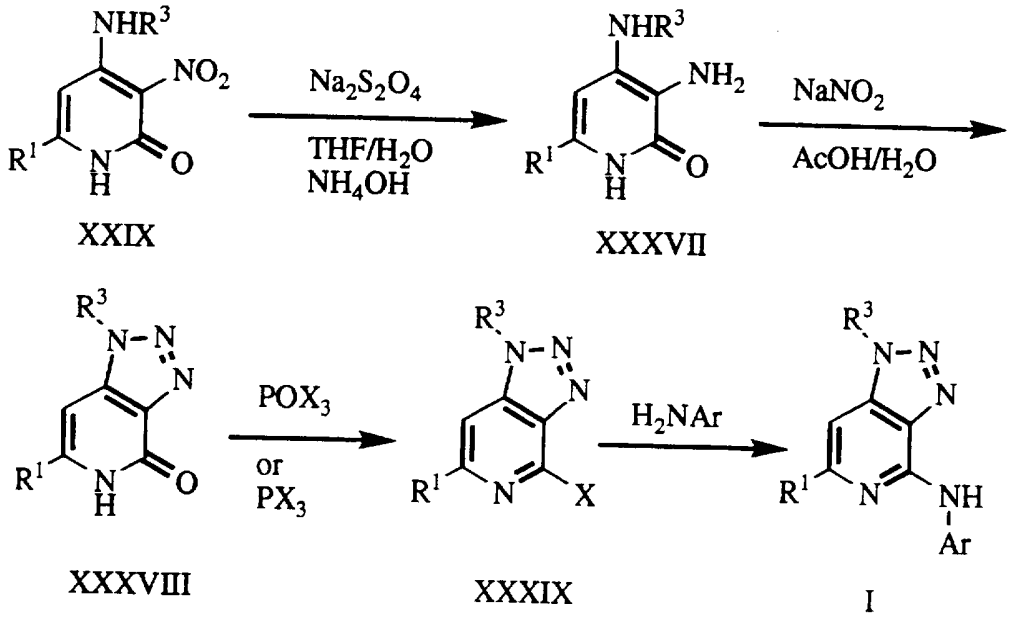


wherein X=CR^1, Y=N, Z=NR^3

As shown in Scheme 11, reaction of a 4-amino-3-nitro-pyridone of formula (XXIX) with a reducing agent, such as $Na_2S_2O_4$ affords the corresponding 4-amino-3-amino-pyridone of formula (XXXVII). This transformation can be effected under a variety of reducing conditions, such as catalytic hydrogenation, reducing metal reaction (Fe, Sn, Zn), hydride reaction ($NaBH_4$, $LiAlH_4$) etc., which are known to those skilled in the art. The 4-amino-3-amino-pyridone can be converted to the

triazolopyridone of formula (XXXVIII) by treatment with an alkali metal nitrite, such as $NaNO_2$, under acidic conditions. The resulting triazolopyridone can be converted to the corresponding halo-triazolopyridine of formula (XXXIX)(X= Cl, Br), by treatment with a halogenating agent such as $POCl_3$, PBr_3, $POBr_3$. Alternatively X can be an appropriate leaving group resulting from treatment of the triazolopyridone with triflic, tosic or mesyl anhydride in the presence of a base. The triazolopyridine can be coupled with arylamines $ArNH_2$ under acidic, basic or thermal catalysis to compounds of Formula I.

Scheme 11



Example 1

***N*-[2-bromo-4-(1-methylethyl)phenyl]-5-methyl-3-propyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

Part A: 4,6-Dihydroxy-2-methylpyrimidine (60 g) was added in portions to fuming nitric acid (120 mL) at 0 °C while cooling the reaction flask. After completion of addtion, the reaction was stirred an additional 1 h at 0 °C followed by another 1 h at room temperature. The reaction mixture was then poured over ice (200 g) and the ice was allowed to melt. A light pink solid was isolated by filteration and washed with cold water (100 mL). The solid was dried in a vacuum oven overnight to yield 4,6-dihydroxy-2-methyl-5-nitropyrimidine (72.5 g).

Part B: The product of Part A was added portionwise to phosphorous oxychloride (400 mL) under a nitrogen atmosphere followed by dropwise addition of N,N-diethylaniline (80 mL). The reaction mixture was refluxed for 2 1/2 h with stirring, cooled to room temperature, poured over ice (2.0 Kg) and stirred for 1 hr. The aqueous layer was extracted with diethyl ether (4 x 500 mL) and the extracts combined. The combined extracts were washed with brine (500 mL), dried over anhydrous magnesium sulfate, filtered and stripped down to afford 4,6-dichloro-2-methyl-5-nitropyrimidine as a yellow solid (68.8 g) which has an unpleasant odor.

Part C: The product of Part B (42 g) was added to acetic acid (77 mL) and methanol (350 mL). To this mixture was added iron powder (42 g) in portions, stirred for 2 h at 60-65 °C, cooled to room

temperature, and filtered. The filterate was stripped to a brown solid, which was extracted with ethyl acetate (2 x 500 mL), washed with 1N NaOH (250 mL), and brine (500 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and stripped down to yield 5-amino-4,6-dichloro-2-methylpyrimidine as a pale yellow solid (25.4 g).

Part D: The product of Part C (14.2 g) and 2-bromo-4-isopropylaniline (17.1 g) were dissolved in 2-ethoxyethanol (60 mL) and refluxed at 135 °C for 30 h. The reaction mixture was cooled, removed the solvent, extracted the residue with dichloromethane, washed with water, dried over anhydrous magnesium sulfate. Filtered the extract, removed the solvent and residue was purified by flash column chromatography on a silica gel using methanol + CH_2Cl_2 (1:100) to yield 5-amino-4-(2-bromo-4-isopropylphenyl)- amino-6-chloro-2-methylpyrimidine as a cream colored solid (16.05 g).

Part E: The product of Part D (12.5 g) was dissolved in dichloromethane (125 mL) and 50 % aqueous acetic acid (125 mL). To this stirred mixture was added sodium nitrite (2.55 g) in water (10 mL) dropwise at room temperature. After completion of addition, the reaction was stirred for an additional 15 mins. The organic layer was separated, washed with water, dried with anhydrous magnesium sulfate, and stripped down to a residue. The residue was purified by flash column chromatography (CH_2Cl_2) to afford light brown oil. The oil was crystallized from 1:1 hexane + pentane (15 mL) to yield 3-[2-bromo-4-(1-methylethyl)phenyl]-7-chloro-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidine as an off-white solid (12.15 g).

Part F: The product of Part E (0.65 g) was dissolved in dichloromethane (20 mL) and then added 1.0 g of 1-propylamine at room temperature. The reaction mixture was stirred at room temperature for 1 h, washed with water, dried with anhydrous magnesium sulfate, and stripped down to a white solid. The crude solid was recrystallized from 2-propanol (2 mL) to furnish 3-[2-bromo-4-(1-methylethyl)phenyl]-5-methyl-*N*-propyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white needles (0.58 g; mp 156-157 °C). Elemental analysis for $C_{17}H_{21}BrN_6$: Theory C: 52.45, H: 5.45, N: 21.59. Found: C: 52.47, H: 5.33, N: 21.46.

Part G: Rearrangement of Product F: The product of Part F (0.40 g) was dissolved in dry DMF (10 mL) and added NaH (0.103 g, 60% in oil) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 14 h and partitioned between ethyl acetate (25 mL) and water (25 mL). The organic layer was washed with brine, dried, and stripped in vacuum to a solid. The solid was recrystallized from 2-propanol (0.5 mL) to afford the title compound as a white crystalline solid (0.35 g; mp 80-81 °C). Elemental analysis for $C_{17}H_{21}BrN_6$: Theory C: 52.45, H: 5.45, N: 21.59. Found: C: 52.19, H: 5.37, N: 21.48.

Example 2

N-[2-bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-5-methyl-3-propyl-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

The title compound from Example 1 (0.30 g) was dissolved in dry DMF (10 mL) and added NaH (62 mg; 60 % in oil) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 5 mins., and then added EtI (0.2 mL) and continued for

an additional 24 h. The reaction mixture was partitioned between ethyl acetate (25 mL) and water (25 mL), washed the organic layer with brine, dried, and stripped in vacuum to yield a pale yellow oil. The sample was purified by flash column chromatography (1:100 MeOH + CH_2Cl_2) to afford the title compound as a colorlesss oil (0.16 g). Elemental analysis for $C_{19}H_{25}BrN_6$: Theory C: 54.68, H: 6.05 Found: C: 54.66, H: 6.02.

Example 3

***N*-[2-bromo-4-(1-methylethyl)phenyl]-3-butyl-*N*-ethyl-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

Part A: The product of Part E from Example 1 was treated with 1-butylamine in the same manner as outlined in Part F to afford 3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-butyl-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white solid (mp 149-151 °C). Elemental analysis for $C_{18}H_{23}BrN_6$: Theory C: 53.60, H: 5.76, N: 20.84. Found: C: 53.46, H: 5.62, N: 20.80.

Part B: The product of Part A from Example 3 (0.34 g) was dissolved in dry DMF (10 mL) and added NaH (67 mg; 60% in oil) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 24 h, then added EtI (0.1 mL) and continued for another 24 hrs. The title compound was isolated in the same way as described in Example 2 to afford colorless oil (0.21 g). Elemental analysis for $C_{20}H_{27}BrN_6$: Theory C: 55.69, H: 6.32, N: 19.48. Found: C: 55.61, H: 6.19, N: 19.23.

Example 4

N-[2-bromo-4-(1-methylethyl)phenyl]-3-(cyclopropylmethyl)-N-ethyl-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product of Part E from Example 1 was reacted with aminomethylcyclopropane in the same way as outlined in Part F to furnish 3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-(cyclopropyl-methyl)-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white needles (mp 166-167 °C). Elemental analysis for $C_{18}H_{21}BrN_6$: Theory C: 53.87, H: 5.27, N: 20.94. Found: C: 54.11, H: 5.32, N: 21.08.

Part B: Using the procedure for Part G in Example 1, the product of Part A in Example 4 was rearranged to yield the title compound as a white crystalline solid (mp 100-101 °C). Elemental analysis for $C_{18}H_{21}BrN_6$: Theory C: 53.87, H: 5.27, N: 20.94. Found: C: 53.93, H: 5.28, N: 20.78.

Part C: Using the procedure for Example 2, the product of Part B from above was alkylated to furnish the title compound as a colorless oil. Elemental analysis for $C_{20}H_{25}BrN_6$: Theory C: 55.95, H: 5.88, N: 19.57. Found: C: 56.11, H: 6.04, N: 19.23.

Example 5

N-[2-bromo-4-(1-methyl)ethylphenyl]-5-methyl-3-[(1-methoxymethyl)-2-methoxyethyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: Serinol (3.42 g) was added to a solution of trityl chloride (8.36 g) and triethylamine in 75 mL of dry DMF. After stirring at room temperature overnight, the reaction was poured into water and extracted twice with toluene. The combined organic layers were dried over potassium carbonate and

concentrated to dryness. Recrystallization from boiling 1:1 benzene/hexane (two crops) afforded N-triphenylmethylserinol (7.59 g).

Part B: Methyl iodide (2.60 mL) was added to a suspension of N-triphenylmethylserinol (6.34 g) and powdered sodium hydroxide (7.60 g) in 95 mL of dry DMSO. After stirring overnight, more methyl iodide was added (0.35 mL). After stirring for an additional 24 h, the reaction was added to water and extracted with toluene, toluene/ether, and then ether. The combined organic layers were dried over potassium carbonate and concentrated to afford 1,3-dimethoxy-2-triphenylmethylaminopropane (7.00 g) as a thick viscous oil.

Part C: To a solution of the product of Part B (1.45 g) in methanol (32 mL) was added 1 M HCl in ether (8.4 mL). After stirring overnight, the reaction was added to hexane and extracted with 1:1 methanol/water. The methanol/water layer was washed twice with hexane and concentrated to dryness to afford 1,3-dimethoxy-2-aminopropane hydrochloride (600 mg) as a waxy solid.

Part D: The product of Part C (576 mg), 3-[2-bromo-4-(1-methyl)ethylphenyl]-7-chloro-5-methyl-3H-1,2,3-triazolo[4,5-d] pyrimidine (0.733 g, from Example 1, Part E) and triethylamine (0.56 mL) were stirred overnight at room temperature. The reaction mixture was added to aqueous sodium dihydrogen phosphate and extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated. Recrystallization from ether/hexane and then boiling methanol afforded N-(1-methoxymethyl-2-methoxyethyl)-3-[2-bromo-4-(1-methyl)ethylphenyl]-5-methyl-3H-1,2,3-

triazolo[4,5-d]pyrimidin-7-amine (855 mg) as crystals melting 156.0-158.5°. Calculated for C19H25N6O2Br: C, 50.79%; H, 5.62%; N, 18.70%. Found: C, 50.48%; H, 5.65%; N, 18.41%.

Part E: The product of Part D (449 mg), dry t-butanol (8 mL) and 1 M potassium t-butoxide (2 mL) were heated at reflux for 2 h. The reaction mixture was added to saturated aqueous ammonium chloride and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated to dryness. The residue crystallized after partial evaporation of a dichloromethane/ether/hexane solution, affording the title compound (403 mg) as an amorphorus white solid melting 53.5-60.0°. Calculated for C19H25N6O2Br: C, 50.79%; H, 5.62%; N, 18.70%. Found: C, 50.92%; H, 5.62%; N, 18.77%.

Example 6

N-[2-bromo-4-(1-methylethyl)phenyl]-3-(2-methoxyethyl)-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product of Part E from Example 1 was reacted with 2-methoxyethylamine in the same way as outlined in Part F to furnish 3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-(2-methoxyethyl)-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white solid (mp 134-136 °C). Elemental analysis for $C_{17}H_{21}BrN_6O$: Theory C: 50.38, H: 5.22, N: 20.74. Found: C: 50.37, H: 5.32, N: 20.52.

Part B: Using the procedure for Part G in Example 1, the product of Part A in Example 6 was rearranged to yield the title compound as a white crystalline solid (mp 94-95 °C). Elemental analysis

for $C_{17}H_{21}BrN_6O$: Theory C: 50.38, H: 5.22, N: 20.74. Found: C: 50.40, H: 5.31, N: 20.65.

Example 7

_N_-[2-bromo-4-(1-methylethyl)phenyl]-_N_-ethyl-3-(2-methoxyethyl)-5-methyl-3_H_-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Using the procedure for Example 2, the product of Part B in Example 6 was alkylated to furnish the title compound as a colorless oil. Elemental analysis for $C_{19}H_{25}BrN_6O$: Theory C: 52.66, H: 5.81, N: 19.39. Found: C: 52.85, H: 5.96, N: 19.02.

Example 8

_N_-[2-bromo-4-(1-methylethyl)phenyl]-_N_-ethyl-3-(3-methoxypropyl)-5-methyl-3_H_-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Part A: The product of Part E from Example 1 was treated with 3-methoxyethylamine in the same manner as outlined in Part F to afford 3-[2-bromo-4-(1-methylethyl)phenyl]-_N_-ethyl-_N_-(3-methoxypropyl)-5-methyl-3_H_-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white solid (mp 109-110 °C). Elemental analysis for $C_{18}H_{23}BrN_6O$: Theory C: 51.56, H: 5.54, N: 20.04. Found: C: 51.57, H: 5.40, N: 20.23.

Part B: The product of Part A from Example 8 was rearranged and alkylated in the same way as outlined in Part B of Example 3 to furnish the title compound as a colorless oil. Elemental analysis for $C_{20}H_{27}BrN_6O$: Theory C: 53.69, H: 6.08, N: 18.79. Found: C: 53.63, H: 5.98, N: 18.59.

Example 9

(+/-)-*N*-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Part A: The product of Part E (0.72 g) from Example 1 was dissolved in a mixture of ethanol (10 mL) and triethylamine (0.21 g) and added 2-amino-1-methoxybutane (0.23 g). The reaction mixture was refluxed for 8 h, removed the solvent, partitioned between ethyl acetate (25 mL) and water (25 mL), washed the organic layer with brine, dried and stripped down to a residue. The residue was purified by flash column chromatography (1:100 MeOH + CH_2Cl_2) to afford (+/-)-3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin- 7-amine as a white solid (mp 132-134 °C). Elemental analysis for $C_{19}H_{25}BrN_6O$: Theory C: 52.66, H: 5.81, N: 19.39. Found: C: 52.52, H: 5.72, N: 19.46.

Part B: The product of Part A from Example 9 was rearranged in a manner similar to Part G of Example 1 to furnish the title compound as a white crystalline solid (mp 115-116 °C). Elemental analysis for $C_{19}H_{25}BrN_6O$: Theory C: 52.66, H: 5.81, N: 19.39. Found: C: 52.61, H: 5.70, N: 19.41.

Example 10

(+/-)-*N*-[2-bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-3-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Using the procedure for Example 2, the product of Part B in Example 9 was alkylated to afford the title compound as a colorless oil. Elemental analysis for $C_{21}H_{29}BrN_6O$: Theory C: 54.66, H: 6.35, N: 18.21. Found: C: 54.76, H: 6.86, N: 17.85.

Example 11

(S)-*N*-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-(1-methoxymethyl)-2-phenylethyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Part A: The product of Part E from Example 1 was treated with S-(+)-2-amino-1-methoxy-3-phenylpropane hydrochloride in the same manner as outlined in Part A of Example 9 to afford (S)-3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-[1-(1-methoxymethyl)-2-phenylethyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white solid (mp 67-69 °C). Elemental analysis for $C_{24}H_{27}BrN_6O$: Theory C: 58.18, H: 5.49, N: 16.96. Found: C: 57.79, H: 5.39, N: 16.77.

Part B: The product of Part A from Example 11 was rearranged in the same way as outlined in Part G of Example 1 to furnish the title compound as a colorless oil. Elemental analysis for $C_{24}H_{27}BrN_6O$: Theory C: 58.18, H: 5.49, N: 16.96. Found: C: 57.94, H: 5.49, N: 16.43.

Example 12

(S)-methyl 7-[2-bromo-4-(1-methylethyl)phenyl]-5-methyl-a-[2-(methylthio)ethyl]-3*H*-1,2,3-triazolo[4,5-d] pyrimidine-3-acetate

Part A: The product of Part E from Example 1 was treated with L-methionine methyl ester hydrochloride in the same manner as outlined in Part A of Example 9 to afford (S)-methyl 3-[2-bromo-4-(1-methylethyl)phenyl]-5-methyl-a-[2-(methylthio)ethyl]-3*H*-1,2,3-triazolo[4,5-d] pyrimidine-7-acetate as a white solid (mp 135-137 °C). Elemental analysis for

$C_{20}H_{25}BrN_6O_2S$: Theory C: 48.68, H: 5.12, N: 17.03. Found: C: 48.73, H: 5.21, N: 16.90.

Part B: The product of Part A from Example 12 was rearranged in the same way as described in Part G of Example 1 to furnish the title compound as a colorless oil. Elemental analysis for $C_{20}H_{25}BrN_6O_2S$: Theory C: 48.68, H: 5.12, N: 17.03. Found: C: 48.55, H: 5.19, N: 16.82.

Example 13

(+/-)-*N*-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-ethylpentyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product of Part E from Example 1 was reacted with 3-aminoheptane in the same way as outlined in Part F to yield 3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-[1-ethylpentyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white crystalline solid (mp 137-138 °C). Elemental analysis for $C_{21}H_{29}BrN_6$: Theory C: 56.63, H: 6.56, N: 18.87. Found: C: 56.53, H: 6.54, N: 18.79.

Part B: Using the procedure for Part G in Example 1, the product of Part A in Example 13 was rearranged to yield the title compound as a colorless oil. Elemental analysis for $C_{21}H_{29}BrN_6$: Theory C: 56.63, H: 6.56, N: 18.87. Found: C: 56.78, H: 6.58, N: 18.79.

Example 14

(+/-)-*N*-[2-bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-3-[1-ethylpentyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Using the procedure for Example 2, the product of Part B in Example 13 was alkylated to furnish the title compound as a colorless oil. Mass spec. (ESI): 473.4

Example 15

***N*-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-propylbutyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

Part A: The product of Part E from Example 1 was reacted with 4-aminoheptane in the same manner as outlined in Part A of Example 9 to yield 3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-[1-propylbutyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white crystalline solid (mp 162-163 °C). Elemental analysis for $C_{21}H_{29}BrN_6$: Theory C: 56.63, H: 6.56, N: 18.87. Found: C: 56.64, H: 6.56, N: 18.81.

Part B: Using the procedure for Part G in Example 1, the product of Part A in Example 15 was rearranged to yield the title compound as a white crystalline solid (mp 69-70 °C). Elemental analysis for $C_{21}H_{29}BrN_6$: Theory C: 56.63, H: 6.56, N: 18.87. Found: C: 56.69, H: 6.48, N: 18.97.

Example 16

***N*-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-butylpentyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

Part A: The product of Part E from Example 1 was reacted with 5-aminononane in a manner similar to Part A of Example 9 to yield 3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-[1-butylpentyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white crystalline solid (mp 132-133 °C). Elemental analysis

for $C_{23}H_{33}BrN_6$: Theory C: 58.35, H: 7.04, N: 17.75. Found: C: 58.19, H: 7.00, N: 17.97.

Part B: Using the procedure for Part G in Example 1, the product of Part A in Example 16 was rearranged to yield the title compound as a colorless oil. Elemental analysis for $C_{23}H_{33}BrN_6$: Theory C: 58.35, H: 7.04, N: 17.75. Found: C: 58.58, H: 7.12, N: 17.47.

Example 17

(+/-)-*N*-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-ethylbutyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Part A: The product of Part E from Example 1 was reacted with 3-aminohexane in a manner similar to Part A of Example 9 to yield 3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-[1-ethylbutyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white crystalline solid (mp 154-155 °C). Elemental analysis for $C_{20}H_{27}BrN_6$: Theory C: 55.69, H: 6.32, N: 19.48. Found: C: 55.57, H: 6.31, N: 19.41.

Part B: Using the procedure for Part G in Example 1, the product of Part A in Example 17 was rearranged to yield the title compound as a white crystalline solid (87-88 °C). Elemental analysis for $C_{20}H_{27}BrN_6$: Theory C: 55.69, H: 6.32, N: 19.48. Found: C: 55.70, H: 6.36, N: 19.40.

Example 18

(+/-)-7-[2-bromo-4-(1-methylethyl)phenyl]-5-methyl-a-propyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidine-3-ethanol

Part A: The product of Part E from Example 1 was treated with DL-2-amino-1-pentanol in a manner similar to Part A of Example 9 to furnish 3-[2-bromo-4-(1-methylethyl)phenyl]-5-methyl-a-propyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidine-7-ethanol as a white crystalline solid (mp 154-155 °C). Elemental analysis for $C_{19}H_{25}BrN_6O$: Theory C: 52.66, H: 5.83, N: 19.39. Found: C: 52.54, H: 5.64, N: 19.12.

Part B: Using the procedure for Part G in Example 1, the product of Part A in Example18 was rearranged to afford the title compound as a colorless oil. Elemental analysis for $C_{19}H_{25}BrN_6O$: Theory C: 52.66, H: 5.83, N: 19.39. Found: C: 52.46, H: 5.83, N: 19.18.

Example 19

N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-ethylpropyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product of Part E from Example 1 was reacted with 3-aminopentane in the same manner as outlined in Part A of Example 9 to yield 3-[2-bromo-4-(1-methylethyl)phenyl]-*N*-[1-ethylpropyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine as a white crystalline solid (mp 171-172 °C). Elemental analysis for $C_{19}H_{25}BrN_6$: Theory C: 54.68, H: 6.05, N: 20.14. Found: C: 54.54, H: 5.73, N: 20.18.

Part B: Using the procedure for Part G in Example 1, the product of Part A in Example 19 was rearranged to yield the title compound as a white crystalline solid (mp 117-118 °C). Elemental analysis for $C_{21}H_{29}BrN_6$: Theory C: 56.63, H: 6.56, N: 18.87. Found: C: 54.86, H: 5.93, N: 20.17.

Example 20

***N*-[2-bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-3-[1-ethylpropyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine**

Using the procedure for Example 2, the product of Part B in Example 19 was alkylated to afford the title compound as a colorless oil. Elemental analysis for $C_{21}H_{29}BrN_6$: Theory C: 56.63, H: 6.56, N: 18.87. Found: C: 56.63, H: 6.33, N: 18.78.

Example 21

***N*-(2-bromo-4,6-dimethylphenyl)-5-methyl-3-[1-propylbutyl]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

Part A: The product of Part D (9 g) from Example 1 was dissolved in ethanol (100 mL) and N,N-diisopropylethylamine (8 g). To this mixture 4-aminoheptane (7.65 g) was added and refluxed for 7 days. The ethanol was stripped off in vacuum, the residue was partitioned between ethyl acetate (250 mL) and water (150 mL). The ethyl acetate layer was washed with brine (100 mL), dried and stripped in vacuum to a pale yellow solid. Recrystallized from 2-propanol (20 mL) to yield 5-amino-4-chloro-6-(4-heptyl)amino-2-methylpyrimidine as a white crystalline solid (12.5 g; mp162-163 °C). Elemental analysis for $C_{12}H_{21}ClN_4$: Theory C: 56.13, H: 8.24, N: 21.82. Found: C: 55.94 , H: 8.22, N: 21.78.

Part B: Using the procedure for Part E in Example 1, the product of Part A in Example 21 was cyclized to yield 7-chloro-5-methyl-3-[1-propylbutyl]-3*H*-1,2,3-triazolo[4,5-d]pyrimidine as a pale yellow solid (mp 92-93 °C). Elemental analysis for

$C_{12}H_{18}ClN_5$: Theory C: 53.83, H: 6.79, N: 26.16. Found: C: 53.81, H: 6.60, N: 25.98.

Part C : The product of Part B (0.27 g) from above was combined with 4-bromo-2,6-dimethylaniline (0.2 g) and heated at 150 °C for 4h. The reaction mixture was partitioned between dichloromethane (20 mL) and water (20 mL), washed the organic layer with water, dried and stripped in vacuum to a residue. The residue was purified by flash column chromatography (1:100 MeOH + CH_2Cl_2) to afford the title compound as an off-white solid (0.26 g; mp 141-142 °C). Elemental analysis for $C_{20}H_{27}BrN_6$: Theory C: 55.69, H: 6.32, N: 19.48. Found: C: 56.05 , H: 6.26, N: 19.71.

Example 22

5-methyl-*N*-[4-(1-methylethyl)-2-(methylthio)phenyl]-3-[1-propylbutyl]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product of Part B from Example 21 was treated with 4-isopropyl-2-methylthioaniline in a manner similar to Part C in Example 21, to yield the title compound as a pale yellow oil. Elemental analysis for $C_{22}H_{32}N_6S$: Theory C: 64.04, H: 7.83, N: 20.37. Found: C: 64.12, H: 7.54, N: 20.41.

Example 23

***N*-[2-bromo-4-(trifluromethyl)phenyl)]-5-methyl-3-[1-propylbutyl]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

The product of Part B from Example 21 was combined with 2-bromo-4-trifluromethylaniline in a manner similar to Part C in Example 21, to yield the title compound as a white crystalline solid (mp 84-85

°C). Elemental analysis for $C_{19}H_{22}BrF_3N_6$: Theory C: 48.42, H: 4.70, N: 17.83. Found: C: 48.58, H: 4.50, N: 17.78.

Example 24

***N*-[2-bromo-4,6-(dimethoxy)phenyl)]-5-methyl-3-[1-propylbutyl]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

The product of Part B from Example 21 was combined with 2-bromo-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as a white crystalline solid (mp 146-147 °C). Elemental analysis for $C_{20}H_{27}BrN_6O_2$: Theory C: 51.84, H: 5.87, N: 18.14. Found: C: 51.95, H: 5.68, N: 18.15.

Example 25

***N*-[2,6-dimethyl-4-(methylthio)phenyl)]-5-methyl-3-[1-propylbutyl]-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine**

The product of Part B from Example 21 was combined with 2,6-dimethyl-4-methylthioaniline in a manner similar to Part C in Example 21, to yield the title compound as a cream colored solid (mp 139-140 °C). Elemental analysis for $C_{21}H_{30}N_6S$: Theory C: 63.28, H: 7.60, N: 21.09. Found: C: 62.98 , H: 7.32, N: 21.38.

Example 26

***N*-(4-acetyl-2-bromophenyl)-3-[1-ethylpropyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

Part A: The product of Part D from Example 1 was treated with 3-aminopentane in a manner similar

to Part A of Example 21, to yield 5-amino-4-chloro-2-methyl-6-(3-pentyl)aminopyrimidine as a white crystalline solid (mp 155-156 °C). Elemental analysis for $C_{10}H_{17}ClN_4$: Theory C: 52.51, H: 7.49, N: 24.50. Found: C: 52.43, H: 7.31, N: 24.59.

Part B: The product of Part A from above was cyclized in a manner similar to Part E of Example 1 to yield 7-chloro-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidine as a white crystalline solid (mp 96-97 °C). Elemental analysis for $C_{10}H_{14}ClN_5$: Theory C: 50.11, H: 5.90, N: 29.22. Found: C: 50.40, H: 5.78, N: 29.53.

Part C: The product of Part B from above was combined with 4-acetyl-2-bromoaniline in a manner similar to Part C in Example 21, to yield the title compound as a pale yellow solid (mp 153-154 °C). Elemental analysis for $C_{18}H_{21}BrN_6O$: Theory C: 51.81, H: 5.07, N: 20.14. Found: C: 51.86, H: 5.87, N: 19.84.

Example 27

(+/-)-*N*-(4-acetyl-2-bromophenyl)-3-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product of Part D from Example 1 was treated with 2-amino-1-methoxybutane in a manner similar to Part A of Example 21, to yield 5-amino-4-chloro-6-(1-methoxy-2-butyl) amino-2-methylpyrimidine as an orange yellow solid (mp 128-130 °C).

Part B: The product of Part A from above was cyclized in a manner similar to Part E of Example 1 to yield 7-chloro-3-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]

pyrimidine as an off-white crystalline solid (mp 66-87 °C). Elemental analysis for $C_{10}H_{14}ClN_5O$: Theory C: 46.97, H: 5.53, N: 27.39. Found: C: 47.22 , H: 5.43, N: 27.47.

Part C: The product of Part B from above was combined with 4-acetyl-2-bromoaniline in a manner similar to Part C in Example 21, to yield the title compound as a pale yellow solid (mp 133-134 °C). Elemental analysis for $C_{18}H_{21}BrN_6O_2$: Theory C: 49.89, H: 4.90. Found: C: 50.13, H: 4.99.

Example 28

(+/-)-*N*-(4-bromo-2,6-dimethylphenyl)-3-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product of Part B from Example 27 was combined with 4-bromo-2,6-dimethylaniline in a manner similar to Part C in Example 21, to yield the title compound as a white crystalline solid (mp 137-138 °C). Elemental analysis for $C_{18}H_{23}BrN_6O_2$: Theory C: 51.56, H: 5.54, N: 20.04. Found: C: 51.75, H: 5.43, N: 19.99.

Example 29

(+/-)-*N*-[2,6-dimethyl-4-(methylthio)phenyl]-3-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product of Part B from Example 27 was combined with 2,6-dimethyl-4-methylthioaniline in a manner similar to Part C in Example 21, to yield the title compound as a white crystalline solid (mp 128-129 °C). Elemental analysis for $C_{19}H_{26}BrN_6OS$: Theory C: 59.04, H: 6.78. Found: C: 58.49, H: 6.48.

Example 30

(+/-)-*N*-(2-bromo-4,6-dimethoxyphenyl)-3-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product of Part B from Example 27 was treated with 2-bromo-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as a white crystalline solid (mp 154-155 °C). Elemental analysis for $C_{18}H_{23}BrN_6O_3$: Theory C: 47.90, H: 5.14, N: 18.62. Found: C: 48.28 , H: 5.20, N: 18.91.

Example 31

(+/-)-*N*-(2-chloro-4,6-dimethoxyphenyl)-3-[1-(1-methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product of Part B from Example 27 was treated with 2-chloro-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as a white crystalline solid (mp 149-150 °C). Elemental analysis for $C_{18}H_{23}ClN_6O_3$: Theory C: 53.14, H: 5.70 N: 20.66. Found: C: 53.36, H: 5.72, N: 20.49.

Example 32

(+/-)-3-[1-(1-methoxymethyl) propyl]-5-methyl-*N*-(2,4,6-trimethylphenyl)-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: 4,6-Dichloro-2-methyl-5-nitropyrimidine (10 g, 48 mmol) dissolved in DMSO / water (480 ml / 48 ml) followed by addition of 2,4,6-trimethylaniline (7.43 ml, 52.8 mmol) dropwise via syringe over 30 minutes. The reaction was stirred at room temperature for 18 h and filtered. The solid was washed with water until the filtrant volume reached

600 ml. A 150 ml aliquat was removed, diluted with 1.5 liters water; 100 ml saturated brine, and extracted with 4 X 100 ml methylene chloride. This procedure was repeated until the remainder of the filtrant had been worked up. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in-vacuo*. The crude solid was chromatographed on silica gel (350 g, 97/3 methylene chloride / methanol) to give the desired yellow crystalline product, 10.53 g (76%). ^{1}H NMR ($CDCl_3$, 300 MHz) d 12.23 (bs, 1H), 10.60 (s, 1H), 6.95 (s, 2H), 2.34 (2, 3H), 2.33 (s, 3H), 2.16 (s, 6H)

Part B: The product from Part A (3.1 g, 11 mmol) was suspended in phosphorous oxychloride (25 ml) and heated to just under reflux for 1 h, to give a dark homogeneous reaction. The reaction was pipetted slowly and cautiously onto 700 ml ice/water, stirred 30 minutes at room temperature, diluted with 200 ml methylene chloride and transferred to a separatory funnel. The aqueous layer was extracted and reextracted with 3 X 50 ml methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in-vacuo* to constant weight to afford 3.18 g (97%) of the product as a bright yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.79 (bs, 1H), 6.96 (s, 2H), 2.42 (s, 3H), 2.33 (s, 3H), 2.15 (s, 6H).

Part C: The product from Part B (2.73 g, 8.9 mmol) was suspended in 60 ml methanol, followed by addition of acetic acid (3.4 ml), cooling to 0 °C in an ice/acetone bath, and addition of iron (1.84 g). The heterogeneous reaction was stirred 5 minutes at 0 °C, then refluxed 3 h, cooled, and filtered through celite. The celite pad was washed with 500 ml ethyl acetate. The dark filtrate was concentrated *in-vacuo*

to near dryness, redissolved in ethyl acetate / water and extracted. The aqueous layer was reextracted several times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in-vacuo*. Chromatography on silica gel (300 g, 1/1 ethyl acetate / hexanes) gave the product 2.18 g (88%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) d 6.93 (s, 2H), 6.25 (bs, 1H), 3.13 (bs, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 2.17 (s, 6H).

Part D: The product from Part C (1.28 g, 4.60 mmol) was dissolved in methylene chloride (20 ml), followed by addition of 50% aq. acetic acid (14 ml) and sodium nitrite (338 mg, 4.89 mmol) in water (1ml). The reaction was stirred for 3 hours at room temperature, transferred to a separatory funnel, diluted with 100 ml water and 30 ml methylene chloride and extracted. The aqueous layer was reextracted with 3X30 ml methylene chloride. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Chromatography on silica gel (200 g, 2/8 ethyl acetate / hexanes) gave the product 1.32 g (88%) as an off-white crystalline solid, mp 186-188 °C. CI-HRMS calcd. for $C_{14}H_{15}N_5Cl_1$ (M+H): 288.1016. Found: 288.1008.

Part E: The product from Part D (425 mg, 1.48 mmol) was treated with triethylamine (0.247 ml, 1.78 mmol) and 2-amino-1-methoxy butane (0.183 ml, 1.78 mmol) in ethanol (10 ml) at reflux for 2 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (150 g, 1/2 hexanes / ethyl acetate) afforded the purified product, 392 mg (75%) as a crystalline solid, mp 156-157.5 °C. Anal. Calcd. for $C_{19}H_{26}N_6O_1$: C, 64.38; H,

7.39; N, 23.71. Found: C, 64.27; H, 7.47; N, 23.62.

Part F: The product from Part E (250 mg, 0.70 mmol) was treated with sodium hydride (42 mg, 1.40 mmol, 80%) in dry dimethylformamide (5 ml). The reaction was stirred 72 hours at room temperature, and 24 h at 50 °C, followed by dilution with 100 ml water and extraction with 3X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (50 g, 1/2 hexanes / ethyl acetate) afforded the purified product, 239 mg (96%) as a crystalline solid, mp 144.5-147 °C. Anal. Calcd. for $C_{19}H_{26}N_6O_1$: C, 64.38; H, 7.39; N, 23.71. Found: C, 64.32; H, 7.33; N, 23.78.

Example 33

(+/-)-*N*-ethyl-3-[1-(1-methoxy-methyl)propyl]-5-methyl-*N*-(2,4,6-trimethylphenyl)-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product from Example 32, Part F (125 mg, 0.35 mmol) was treated with sodium hydride (13 mg, 0.42 mmol, 80%) and ethyl iodide (42 ml, 0.42 mmol) in dry dimethylformamide (3 ml) and stirred at room temperature for 48 h. The reaction was diluted with 50 ml water, and extracted with 4X30 ml methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to dryness. Chromatography on silica gel (50 g, 3/2 hexanes / ethyl acetate) afforded the desired product, 111 mg (80%) as a clear viscous oil. CI-HRMS calcd. for $C_{21}H_{31}N_6O_1$ (M+H): 383.2559. Found: 383.2567.

Example 34

3-[1-(1-ethyl)propyl]-5-methyl-*N*-(2,4,6-trimethylphenyl)-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Part A: The product from Example 32, Part D (500 mg, 1.74 mmol) was treated with triethylamine (0.29 ml, 2.09 mmol) and 3-aminopentane (0.243 ml, 2.09 mmol) in ethanol (10 ml) at reflux for 2 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (100 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 462 mg (79%) as a crystalline solid, mp 184.5-186.5 °C. Anal. Calcd. for $C_{19}H_{26}N_6$: C, 67.43; H, 7.74; N, 24.83. Found: C, 67.11; H, 7.59; N, 24.57.

Part B: The product from Part A (300 mg, 0.89 mmol) was treated with sodium hydride (53 mg, 1.78 mmol, 80%) in dry dimethylformamide (5 ml). The reaction was stirred 72 hours at 50 °C, followed by dilution with 125 ml water and extraction with 3X40 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (75 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 239 mg (80%) as a crystalline solid, mp 160-162 °C. Anal. Calcd. for $C_{19}H_{26}N_6$: C, 67.43; H, 7.74; N, 24.83. Found: C, 67.07; H, 7.85; N, 24.51.

Example 35

(+/-)-3-[1-(1-ethyl)butyl]-5-methyl-*N*-(2,4,6-trimethylphenyl)-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Part A: The product from Example 32, Part D (525 mg, 1.82 mmol) was treated with triethylamine

(0.305 ml, 3.64 mmol) and 3-aminohexane (0.219 ml, 3.64 mmol) in ethanol (8 ml) at 50°C for 18 hours. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (140 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 450 mg (70%) as a crystalline solid, mp 170.5-172 °C. Anal. Calcd. for $C_{20}H_{28}N_6$: C, 68.15; H, 8.02; N, 23.84. Found: C, 68.10; H, 7.80; N, 23.94.

Part B: The product from Part A (300 mg, 0.85 mmol) was treated with sodium hydride (64 mg, 2.13 mmol, 80%) in dry dimethylformamide (5 ml). The reaction was stirred 24 hours at room temperature, and 24 hours at 50 °C, followed by dilution with 125 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (60 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 266 mg (89%) as a crystalline solid, mp 156-157.5 °C. Anal. Calcd. for $C_{19}H_{26}N_6$: C, 68.15; H, 8.01; N, 23.84. Found: C, 68.51; H, 8.10; N, 23.94.

Example 36

(+/-)-3-[1-(1-ethyl)pentyl]-5-methyl-*N*-(2,4,6-trimethylphenyl)-3*H*-1,2,3-triazolo[4,5-d] pyrimidine-7-amine

Part A: The product from Example 32, Part D (500 mg, 1.74 mmol) was treated with triethylamine (0.290 ml, 4.35 mmol) and 3-aminoheptane (0.343 ml, 4.35 mmol) in ethanol (8 ml) at 50 °C for 18 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (125 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 465 mg (73%) as a crystalline solid, mp

141.5-142.5 °C. Anal. Calcd. for $C_{21}H_{30}N_6$: C, 68.82; H, 8.25; N, 22.93. Found: C, 69.11; H, 8.10; N, 23.04.

Part B: The product from Part A (300 mg, 0.82 mmol) was treated with sodium hydride (49 mg, 1.64 mmol, 80%) in dry dimethylformamide (5 ml). The reaction was stirred 24 hours at 50°C, followed by dilution with 125 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (75 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 236 mg (79%) as a crystalline solid, mp 129-130.5 °C. Anal. Calcd. for $C_{21}H_{30}N_6$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.73; H, 8.23; N, 22.90.

Example 37

5-methyl-3-[1-(1-propyl)butyl]-*N*-(2,4,6-trimethylphenyl)-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Part A: The product from Example 32, Part D (255 mg, 0.87 mmol) was treated with triethylamine (0.145 ml, 1.74 mmol) and 4-aminoheptane (0.120 ml, 1.74 mmol) in ethanol (5 ml) at 50°C for 18 hours. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (60 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 233 mg (73%) as a crystalline solid, mp 145-146.5 °C. Anal. Calcd. for $C_{21}H_{30}N_6$: C, 68.82; H, 8.25; N, 22.93. Found: C, 69.09; H, 8.21; N, 23.04.

Part B: The product from Part A (230 mg, 0.63 mmol) was treated with sodium hydride (47 mg, 1.58

mmol, 80%) in dry dimethylformamide (5 ml). The reaction was stirred 24 hours at room temperature, and 24 h at 50 °C, followed by dilution with 125 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (60 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 211 mg (92%) as a crystalline solid, mp 143-144.5 °C. Anal. Calcd. for $C_{21}H_{30}N_6$: C, 68.82; H, 8.25; N, 22.93. Found: C, 69.08; H, 8.10; N, 23.03.

Example 38

3-(2-methoxyethyl)-5-methyl-*N*-(2,4,6-trimethylphenyl)-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product from Example 32, Part D (1.07 g, 3.70 mmol) was treated with triethylamine (0.620 ml, 4.44 mmol) and 2-methoxyethylamine (0.386 ml, 4.44 mmol) in ethanol (20 ml) at reflux for 3 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (150 g, 1/1 hexanes / ethyl acetate) afforded the purified product, 1.18 g (97%) as a crystalline solid, mp 141.5-143.5 °C. Anal. Calcd. for $C_{17}H_{22}N_6O_1$: C, 62.56; H, 6.79; N, 25.75. Found: C, 62.54; H, 6.78; N, 25.70.

Part B: The product from Part A (325 mg, 1.00 mmol) was treated with sodium hydride (60 mg, 2.00 mmol, 80%) in dry dimethylformamide (5 ml). The reaction was stirred 72 hours at room temperature, and 24 hours at 50 °C, followed by dilution with 125 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness.

Chromatography on silica gel (50 g, 1/2 hexanes / ethyl acetate) afforded the purified product, 321 mg (99%) as a crystalline solid, mp 171.5-173.5 °C. Anal. Calcd. for $C_{17}H_{22}N_6O_1$: C, 62.56; H, 6.79. Found: C, 62.24; H, 6.89.

Example 39

***N*-ethyl-3-(2-methoxyethyl)-5-methyl-N-(2,4,6-trimethylphenyl)-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

The product from Example 38, Part B (150 mg, 0.46 mmol) was treated with sodium hydride (17 mg, 0.55 mmol, 80%) and ethyl iodide (55 ml, 0.69 mmol) in dry dimethylformamide (3 ml) and stirred at room temperature for 48 h. The reaction was diluted with 50 ml water, and extracted with 4X30 ml methylene chloride. The combined organic extracts were dried over anydrous magnesium sulfate, filtered, and concentrated *in vacuo* to dryness. Chromatography on silica gel (50 g, 1/1 hexanes / ethyl acetate) afforded the desired product, 144 mg (88%) as a clear viscous oil. CI-HRMS calcd. for $C_{19}H_{27}N_6O_1$ (M+H): 355.2246. Found: 355.2240.

Example 40

***N*-(2-Methyl-4-bromophenyl)-3-[1-(1-propyl)butyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

Part A: 4,6-Dichloro-2-methyl-5-nitropyrimidine (5.2 g, 25 mmol) dissolved in DMSO (480 ml) followed by addition of 2-methyl-4-bromoaniline (4.65 g, 25 mmol) dropwise via syringe over 30 minutes. The reaction was stirred at RT for 18 h, followed by addition of 800 ml water. The resulting precipitate was filtered and dried to

constant weight affording 7.02 g (83%) of the desired pyrimidone as a yellow solid.

Part B: The product from Part A (6.95 g, 20.5 mmol) was treated with phosphorous oxychloride (120 ml) and brought to reflux for 20 minutes. The reaction was cooled, and slowly quenched on 3 L of ice/water. The resultant precipitate was filtered and dried. Chromatography on silica gel (500 g, 8/2 hexanes / ethyl acetate) gave the purified product, 5.4 g (74%), as a yellow solid.

Part C: The product from Part B (5.4 g, 15.2 mmol) was suspended in 120 ml methanol, followed by addition of acetic acid (6.8 ml), cooling to 0 °C in an ice/acetone bath, and addition of iron (4.23 g) under the same conditions described in Example 32, Part C. The resultant brown solid was used directly in the next reaction.

Part D: The product from Part C (15.2 mmol) was dissolved in methylene chloride (100 ml), followed by addition of 50% aq. acetic acid (50 ml) and sodium nitrite (1.15 g, 16.70 mmol) in water (5ml) under the same conditions described in Example 32, Part D. Chromatography of the crude product on silica gel (400 g, 2/8 ethyl acetate / hexanes) gave the product 3.15 g (62% from Part C) as an off-white crystalline solid, mp 145-147.5 °C.

Part E: The product from Part D (600 mg, 1.78 mmol) was treated with triethylamine (300 ml, 2.14 mmol) and 4-aminoheptane (246 ml, 2.14 mmol) in ethanol (10 ml) at 50 °C for 18 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (125 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 600 mg

(81%) as a crystalline solid, mp 155-156 °C. Anal. Calcd. for $C_{19}H_{25}N_6Br_1$: C, 54.68; H, 6.05; N, 20.14. Found: C, 54.36; H, 5.71; N, 20.24.

Part F: The product from Part E (350 mg, 0.84 mmol) was treated with sodium hydride (63 mg, 2.10 mmol, 80%) in dry dimethylformamide (5 ml). The reaction was stirred 24 h at room temperature, and 24 h at 50 °C, followed by dilution with 125 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (60 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 333 mg (95%) as a crystalline solid, mp 126.5-128 °C. Anal. Calcd. for $C_{19}H_{25}N_6Br_1$: C, 54.68; H, 6.05; N, 20.14. Found: C, 54.90; H, 6.04; N, 20.40.

Example 41

(+/-)-3-[1-(1-ethyl)butyl]-5-methyl-*N*-(2-methyl-4-bromophenyl)-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product from Example 40, Part D (600 mg, 1.78 mmol) was treated with triethylamine (0.300 ml, 2.14 mmol) and 3-aminohexane (0.214 ml, 2.14 mmol) in ethanol (10 ml) at 50 °C for 18 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (75 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 616 mg (86%) as a crystalline solid, mp 117.5-119.5 °C. Anal. Calcd. for $C_{18}H_{23}N_6Br_1$: C, 53.60; H, 5.76; N, 20.84. Found: C, 53.53; H, 5.72; N, 20.95.

Part B: The product from Part A (450 mg, 1.12 mmol) was treated with sodium hydride (84 mg, 2.80

mmol, 80%) in dry dimethylformamide (10 ml). The reaction was stirred 72 hours at room temperature, followed by dilution with 125 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (75 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 425 mg (94%) as a crystalline solid, mp 99-101 °C.

Example 42

(+/-)-*N*-(4-bromo-2-methylphenyl)-3-[1-(1-methoxymethyl) propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product from Example 40, Part D (800 mg, 2.37 mmol) was treated with triethylamine (0.400 ml, 2.84 mmol) and 2-amino-1-methoxybutane (0.341 ml, 2.84 mmol) in ethanol (20 ml) at room temperature for 48 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (150 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 697 mg (72%) as a crystalline solid, mp 144.5-146 °C. Anal. Calcd. for $C_{17}H_{21}N_6Br_1O_1$: C, 50.38; H, 5.22; N, 20.74. Found: C, 50.35; H, 5.23; N, 20.58.

Part B: The product from Part A (550 mg, 1.36 mmol) was treated with sodium hydride (102 mg, 3.40 mmol, 80%) in dry dimethylformamide (8 ml). The reaction was stirred 72 h at room temperature, followed by dilution with 125 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (75 g, 8/2 hexanes / ethyl acetate) afforded the purified product, 520 mg (94%) as a crystalline solid.

Example 43

(+/-)-3-[1-(1-ethyl)pentyl]-5-methyl-*N*-[(2,4,6-trimethyl)-3-pyridyl-]-3*H*-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

Part A: To 2,4-dichloro-2-methyl-5-nitropyrimidine (10.10 g, 48.60 mmol) in dry tetrahydrofuran (200 ml) and triethylamine (6.8 ml, 48.6 mmol) was added 3-amino-2,4,6-trimethylpyridine (3.30 g, 24.3 mmol) in tetrahydrofuran (30 ml) via canulation over 10 minutes at room temperature. The reaction was stirred 72 h, diluted with 1 L of water, and extracted with 4X200 ml ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness *in vacuo*. Chromatography on silica gel (300 g, 1/1 ethyl acetate / hexanes) afforded the purified product, 4.8 g (64%) as a white solid. ^{1}H NMR (300 MHz, CDCl3) d 8.79 (bs, 1H), 6.97 (s, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 2.17 (s, 3H).

Part B: The product from Part A (4.8 g, 15.60 mmol) was treated with iron (4.36 g, 78.00 mmol) in methanol (110 ml) and acetic acid (6 ml) under the same reaction conditions described in Example 32, Part C. Chromatography on silica gel (250 g, 9/1 methylene chloride / methanol) afforded the purified reduction product, 3.1 g, (72%) as a white solid. ^{1}H NMR (300 MHz, CDCl3) d 6.94 (s, 1H), 6.26 (bs, 1H), 3.36 (bs, 1H), 2.52 (s, 3H), 2.41 (s, 3H), 2.35 (s, 3H), 2.16 (s, 3H).

Part C: The product from Part B (2.1 g, 7.56 mmol) was treated with sodium nitrite (574 mg, 8.32 mmol) in methylene chloride (44 ml) and 50% aq. acetic acid (25 ml) under the same reactions conditions described in Example 32, Part D. Chromatography on

silica gel (125 g, 1/1 ethyl acetate / hexanes) afforded the purified cyclized product, 1.7 g (78%) as a white solid, mp 204.5-206°C. Anal. Calcd. for $C_{13}H_{13}N_6Cl_1$: C, 54.08; H, 4.55; N, 29.11. Found: C, 53.94; H, 4.43; N, 28.79.

Part D: The product from Part C (300 mg, 1.04 mmol) was treated with triethylamine (175 ml, 1.25 mmol) and 3-aminoheptane (243 ml, 1.25 mmol) in ethanol (10 ml) at reflux for 2.5 hours. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (20 g, 1/2 hexanes / ethyl acetate) afforded the purified product, 356 mg (93%) as a crystalline solid, mp 122-130°C. Anal. Calcd. for $C_{20}H_{29}N_7$: C, 65.37; H, 7.95; N, 26.68. Found: C, 65.35; H, 7.95; N, 26.82.

Part E: The product from Part D (160 mg, 0.44 mmol) was treated with sodium hydride (27 mg, 0.88 mmol, 80%) in dry dimethylformamide (4 ml). The reaction was stirred 24 hours at room temperature, and 100 hours at 50°C, followed by dilution with 100 ml water and extraction with 3X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Preparative HPLC [(25-65%) acetonitrile : trifluoroacetic acid / water : trifluoroacetic acid, Dynamax C18 column] afforded the purified product, 60 mg (38%) as an amorphous foam. CI-HRMS calcd. for $C_{20}H_{29}N_7$ (M+H): 368.2545. Found: 368.2563.

Example 44

(+/-)-*N*-ethyl-3-[1-(1-ethyl) pentyl]-5-methyl-*N*-[(2,4,6-trimethyl)-3-pyridyl-]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product from Example 43, Part E (29 mg, 0.08 mmol) was treated with sodium hydride (3 mg, 0.1 mmol, 80%) and ethyl iodide (9.6 ml, 0.12 mmol) in dry dimethylformamide (1 ml) and stirred at room temperature for 168 h. The reaction was diluted with 10 ml water, and extracted with 4X5 ml ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to dryness. Chromatography on silica gel (10 g, 1/1 hexanes / ethyl acetate) afforded the desired product, 19.7 mg (63%) as a clear viscous oil. CI-HRMS calcd. for $C_{22}H_{33}N_7$ (M+H): 396.2876. Found: 396.2876.

Example 45

(+/-)-3-[1-(1-ethyl)butyl]-5-methyl-*N*-[(2,4,6-trimethyl)3-pyridyl-]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product from Example 43, Part C (546 mg, 1.89 mmol) was treated with triethylamine (0.316 ml, 2.27 mmol) and 3-aminohexane (0.210 mg, 2.07 mmol) in ethanol (15 ml) at reflux for 2.5 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (50 g, ethyl acetate) afforded the purified product, 530 mg (79%) as a crystalline solid, mp 155.5-158 °C. Anal. Calcd. for $C_{19}H_{27}N_7$: C, 64.56; H, 7.71; N, 27.74. Found: C, 64.59; H, 7.62; N, 27.91.

Part B: The product from Part A (400 mg, 1.13 mmol) was treated with sodium hydride (94 mg, 3.11 mmol, 80%) in dry dimethylformamide (12 ml). The reaction was stirred 72 h at 50 °C, followed by dilution with 100 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and

concentrated to dryness. Chromatography on silica gel (50 g, 1/3 hexanes / ethyl acetate) afforded the purified product, 355 mg (89%) as a crystalline solid, mp 132-140.5 °C. Anal. Calcd. for $C_{19}H_{27}N_7$: C, 64.56; H, 7.71; N, 27.74. Found: C, 64.52; H, 7.58; N, 27.97.

Example 46

***N*-ethyl-3-[1-(1-ethyl)butyl]-5-methyl-*N*-[(2,4,6-trimethyl)-3-pyridyl-]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine**

The product from Example 45, Part B (250 mg, 0.71 mmol) was treated with sodium hydride (26 mg, 0.85 mmol, 80%) and ethyl iodide (0.85 ml, 1.07 mmol) in dry dimethylformamide (7 ml) and stirred at room temperature for 15 h. The reaction was diluted with 150 ml water, and extracted with 3X30 ml ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to dryness. Chromatography on silica gel (20 g, 1/3 hexanes / ethyl acetate) afforded the desired product, 221 mg (81%) as a clear viscous oil.

Example 47

3-[1-(1-propyl)butyl]-5-methyl-*N*-[(2,4,6-trimethyl)-3-pyridyl-]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product from Example 43, Part C (700 mg, 2.42 mmol) was treated with triethylamine (0.405 ml, 2.91 mmol) and 4-aminoheptane (335 mg, 2.91 mmol) in ethanol (20 ml) at reflux for 2.5 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (50 g, 1/3 hexanes / ethyl acetate) afforded the purified

product, 845 mg (96%) as a crystalline solid, mp 135.5-137.5 °C. . Anal. Calcd. for $C_{20}H_{29}N_7$: C, 65.37; H, 7.95; N, 26.68. Found: C, 65.71; H, 7.70; N, 26.95.

Part B: The product from Part A (600 mg, 1.63 mmol) was treated with sodium hydride (147.5 mg, 4.89 mmol, 80%) in dry dimethylformamide (15ml). The reaction was stirred 15 h at 50 °C, followed by dilution with 200 ml water and extraction with 5X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (50 g, 1/3 hexanes / ethyl acetate) afforded the purified product, 560 mg (93%) as a crystalline solid, mp 128-130 °C. CI-HRMS calcd. for $C_{20}H_{29}N_7$ (M+H): 368.2561. Found: 368.2563.

Example 48

_N_-ethyl-3-[1-(1-propyl) butyl]-5-methyl-_N_-[(2,4,6-trimethyl)-3-pyridyl-]-3_H_-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product from Example 47, Part B (400 mg, 1.09 mmol) was treated with sodium hydride (40 mg, 1.31 mmol, 80%) and ethyl iodide (0.130 ml, 1.63 mmol) in dry dimethylformamide (10 ml) and stirred at room temperature for 15 hours. The reaction was diluted with 150 ml water, and extracted with 3X30 ml ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to dryness. Chromatography on silica gel (20 g, 1/3 hexanes / ethyl acetate) afforded the desired product, 373 mg (87%) as a clear viscous oil.

Example 49

(+/-)-3-[1-(1-methoxymethyl) propyl]-5-methyl-*N*-[(2,4,6-trimethyl)-3-pyridyl-]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: The product from Example 43, Part C (700 mg, 2.42 mmol) was treated with triethylamine (0.405 ml, 2.91 mmol) and 2-aminomethoxybutane (0.350 ml, 2.91 mmol) in ethanol (20 ml) at reflux for 2.5 h. The reaction was concentrated directly to dryness *in vacuo*. Chromatography on silica gel (50 g, 1/1 hexanes / tetrahydrofuran) afforded the purified product, 845 mg (98%) as a crystalline solid, mp 132-136.5 °C. Anal. Calcd. for $C_{18}H_{25}N_7O_1$: C, 60.82; H, 7.1; N, 27.58. Found: C, 61.13; H, 6.89; N, 27.54.

Part B: The product from Part A (600 mg, 1.68 mmol) was treated with sodium hydride (151.2 mg, 5.04 mmol, 80%) in dry dimethylformamide (15ml). The reaction was stirred 15 hours at 50 °C, followed by dilution with 100 ml water and extraction with 4X30 ml ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel (50 g, 1/1 hexanes / tetrahydrofuran) afforded the purified product, 500 mg (83%) as a crystalline solid, mp 141.5-144 °C. Anal. Calcd. for $C_{18}H_{25}N_7O_1$: C, 60.82; H, 7.1; N, 27.58. Found: C, 60.94; H, 6.95; N,27.46.

Example 50

(+/-)-*N*-ethyl-3-[1-(1-methoxy methyl)propyl]-5-methyl-*N*-[(2,4,6-trimethyl)-3-pyridyl-]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

The product from Example 49, Part B (350 mg, 0.99 mmol) was treated with sodium hydride (36 mg,

1.19 mmol, 80%) and ethyl iodide (0.119 ml, 1.49mmol) in dry dimethylformamide (10 ml) and stirred at room temperature for 15 h. The reaction was diluted with 150 ml water, and extracted with 3X30 ml ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to dryness. Chromatography on silica gel (20 g, 1/1 hexanes / tetrahydrofuran) afforded the desired product, 338 mg (89%) as a clear viscous oil.

Example 51

N-(2,4-dibromophenyl)-5-methyl-3-(1-propyl)butyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: 4-Aminoheptane (2.5 g) was added to a solution of 4,6-ditosyloxy-2-methyl-5-nitropyrimidine (10.5 g) and N,N-diisopropylethylamine (3.8 mL) in dichloromethane (219 mL). The reaction was stirred under nitrogen for 5 h at room temperature and then extracted with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated to yield *N*-(1-propyl)butyl-2-methyl-5-nitro-4-tosyloxypyrimidin-6-amine as a pale yellow solid (9.1 g)

Part B: The product of part A (9.0 g), anhydrous toluene (200 mL), N,N-diisopropylethylamine (3.8 mL) and 2,4-dibromoaniline (5.5 g) were heated at 65 ^{o}C for 16 h under nitrogen. The reaction was added to saturated aqueous NH_4Cl and extracted with dichloromethane (3 times). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to yield *N*-4-(2,4-dibromophenyl)-*N*-[6-(1-propyl)butyl]-2-methyl-5-nitro-pyrimidin-4,6-diamine as a yellow solid (6.5 g).

Part C: The product of part B (6.5 g), 1,4-dioxane (65 mL), water (65 mL), sodium dithionite (18.0 g) and 40% ammonium hydroxide (6.5 mL) were stirred for 3 h at room temperature. The reaction mixture was added to saturated aqueous NH_4Cl and extracted with ethyl acetate (3 times). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash column chromatography on silica gel using EtOAc/hexane (2:8) to yield *N*-[4-(2,4-dibromophenyl)]-*N*-[6-(1-propyl)butyl]-2-methyl-5-aminopyrimidin-4,6-diamine as a pale yellow solid (5.1 g).

Part D: The product of part C (5.0 g) was dissolved in a 2:1:1 mixture of dichloromethane, acetic acid and water. To this solution was added sodium nitrite (0.9 g) and the resulting solution was stirred for 2 h at room temperature. The reaction was added to an equal volume of water and extracted with dichloromethane (3 times). The combined organic layers were washed with saturated aqueous $NaHCO_3$, then were dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane (2:8) to yield *N*-(1-propyl)butyl-3-(2,4-dibromophenyl)-5-methyl-3*H*-1,2,3- triazolo[4,5-d] pyrimidin-7-amine as a white solid (3.9 g). A small amount of the title compound, *N*-(2,4-dibromophenyl)-5-methyl-3-(1-propyl)butyl-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-7-amine (0.18 g) was also isolated from the chromatography.

Part E: Sodium hydride (0.24 g) was added to a solution of the product of part D (3.9 g) in anhydrous DMF (82 mL). The resulting solution was stirred for 16 h under nitrogen and the partitioned between ethyl

acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The resulting solid was recrystallized from boiling 2-propanol to afford the title compound as a white crystalline solid (3.6 g).

Example 52

N-[4-acetyl-2-bromophenyl]-5-methyl-3-(1-propyl)butyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Bis(triphenylphosphine)palladium dichloride (11.9 mg), tetrakis(triphenylphosphine)palladium (19.6 mg) and 1-ethoxyvinyltributyltin (299 mg) were added to the product of Part E, from Example 51 (0.33 g) dissolved in toluene (5 mL). The reaction was heated to reflux and stirred overnight. The solvent was then removed under vacuum and the residue partitioned between ether and aqueous saturated NaF. The mixture was then filtered and separated. The organic layer was then washed with 1N HCl, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane (2:8) to yield the title compound.

Example 53

N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-(N,N-dimethylamino-methyl)butyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

Part A: A solution of N-CBZ-d, l-norvaline (TCI America) in THF (0.5 M) is treated in sequence with 1-hydroxybenzotriazole hydrate (1.2 eq),

dimethylamine hydrochloride (1.3 eq), triethylamine (1.4 eq), and dicyclohexylcarbodiimide (1.2 eq). After stirring overnight, the mixture is filtered, which is followed by aqueous workup and chromatography, to afford N,N-dimethyl-N'-CBZ-d,l-norvalinamide, as an oil (TLC Rf = 0.10, 30:70 ethyl acetate-hexane).

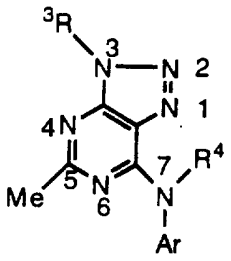
Part B: A solution of the CBZ compound from Part A above is dissolved in methanol (1 M), and 5% Pd on carbon is added. The mixture is submitted to hydrogenation in the usual Parr shaker apparatus (50 PSI, overnight). The resulting mixture is filtered through celite and evaporated to afford sufficiently pure product, N,N-dimethyl-d,l-norvalinamide, as an oil (TLC baseline in 30:70 ethyl acetate-hexane).

Part C: The amine from Part B is elaborated to title compound by using the procedure outlined in Example 32 or 51. Spectral data. ^{1}H NMR (300 MHz, CDCl3): d 8.61 (1H, d, J = 8.4 Hz), 8.20 (1H, br s), 7.48 (1H, d, J =1.8 Hz), 7.26 (1H, dd, J = 8.4, 1.8 Hz), 5.08-4.98 (1H, m), 3.27 (1H, dd, J =12.6, 9.7 Hz), 2.91 (1H, heptet, J = 7.0 Hz), 2.68 (3H, s), 2.67 (1H, dd, J =12.6 Hz), 2.22 (6H, s), 2.21-2.11 (1H, m), 1.99-1.89 (1H, m), 1.29-1.19 (1H, m), 1.27 (6H, d, J = 7.0 Hz), 1.16-1.05 (1H, m), 0.88 (3H, t, J = 7.1 Hz). MS(NH_3-CI): m/e 464 (3), 463 (25), 462 (100), 461 (29), 460 (98).

The compounds of Examples 54-208 can be made by the methods exemplified in Examples 1-53.

Table 1

3*H*-1,2,3-triazolo[4,5-d]pyrimidines:



Ex No.	Ar	R^3	R^4
54	2-Br-4-i-Pr-Ph	$C(Me)_2CH_2$-OCH_3	H
55	2-Br-4-i-Pr-Ph	cyclopentyl	H
56	2-Br-4,6-$(OMe)_2$-Ph	$CH(Bz)CH_2$-OCH_3	H
57	2-Cl-4,6-$(OMe)_2$-Ph	$CH(Bz)CH_2$-OCH_3	H
58	4-i-Pr-2-SMe-Ph	$CH(Bz)CH_2$-OCH_3	H
59	4-i-Pr-2-SO_2Me-Ph	$CH(Bz)CH_2$-OCH_3	H
60	4-(COMe)-2-Br-Ph	$CH(Bz)CH_2$-OCH_3	H
61	2-Br-4-CF_3-Ph	$CH(Bz)CH_2$-OCH_3	H
62	4-Br-2,6-$(Me)_2$-Ph	$CH(Bz)CH_2$-OCH_3	H
63	2,6-$(Me)_2$-4-SO_2Me-Ph	$CH(Bz)CH_2$-OCH_3	H
64	2,4,6-$(Me)_3$Ph	$CH(Bz)CH_2$-OCH_3	H
65	2,6-$(Me)_2$-4-CF_3-Ph	$CH(Bz)CH_2$-OCH_3	H
66	2-Br-4,6-$(Me)_2$-Ph	$CH(Bz)CH_2$-OCH_3	H
67	4-Br-2-Me-Ph	$CH(Bz)CH_2$-OCH_3	H
68	4-$N(Et)_2$-2-Me-Ph	$CH(Bz)CH_2$-OCH_3	H
69	4-I-2-Me-Ph	$CH(Bz)CH_2$-OCH_3	H
70	2-I-4-i-Pr-Ph	$CH(Bz)CH_2$-OCH_3	H
71	2-Br-4-SMe-Ph	$CH(Bz)CH_2$-OCH_3	H
72	2-Br-4-SO_2Me-Ph	$CH(Bz)CH_2$-OCH_3	H
73	2-Br-4-$N(Me)_2$-6-OMe-Ph	$CH(Bz)CH_2$-OCH_3	H
74	2-Br-4,6-$(OMe)_2$-Ph	$CH(Et)Bu^n$	H
75	2-Cl-4,6-$(OMe)_2$-Ph	$CH(Et)Bu^n$	H
76	4-i-Pr-2-SMe-Ph	$CH(Et)Bu^n$	H
77	4-i-Pr-2-SO_2Me-Ph	$CH(Et)Bu^n$	H
78	4-(COMe)-2-Br-Ph	$CH(Et)Bu^n$	H
79	2-Br-4-CF_3-Ph	$CH(Et)Bu^n$	H
80	4-Br-2,6-$(Me)_2$-Ph	$CH(Et)Bu^n$	H

81	2,6-(Me)$_2$-4-SO_2Me-Ph	CH(Et)Bu^n	H
82	2,6-(Me)$_2$-4-SMe-Ph	CH(Et)Bu^n	H
83	2,6-(Me)$_2$-4-CF_3-Ph	CH(Et)Bu^n	H
84	2-Br-4,6-(Me)$_2$-Ph	CH(Et)Bu^n	H
85	4-Br-2-Me-Ph	CH(Et)Bu^n	H
86	4-N(Et)$_2$-2-Me-Ph	CH(Et)Bu^n	H
87	4-I-2-Me-Ph	CH(Et)Bu^n	H
88	2-I-4-i-Pr-Ph	CH(Et)Bu^n	H
89	2-Br-4-SO_2Me-Ph	CH(Et)Bu^n	H
90	2-Br-4-N(Me)$_2$-6-OMe-Ph	CH(Et)Bu^n	H
91	2,4-[SMe]$_2$-Ph	CH(Et)Bu^n	H
92	2,4-[SO_2Me]$_2$-Ph	CH(Et)Bu^n	H
93	2-Br-4,6-(OMe)2-Ph	CH(Et)Pr^n	H
94	2-Cl-4,6-(OMe)$_2$-Ph	CH(Et)Pr^n	H
95	4-i-Pr-2-SMe-Ph	CH(Et)Pr^n	H
96	4-i-Pr-2-SO_2Me-Ph	CH(Et)Pr^n	H
97	4-(COMe)-2-Br-Ph	CH(Et)Pr^n	H
98	4-Br-2-CF_3-Ph	CH(Et)Pr^n	H
99	4-Br-2,6-(Me)$_2$-Ph	CH(Et)Pr^n	H
100	2,6-(Me)$_2$-4-SMe-Ph	CH(Et)Pr^n	H
101	2,6-(Me)$_2$-4-SO_2Me-Ph	CH(Et)Pr^n	H
102	2,6-(Me)$_2$-4-CF_3-Ph	CH(Et)Pr^n	H
103	2-Br-4,6-(Me)$_2$-Ph	CH(Et)Pr^n	H
104	4-N(Et)$_2$-2-Me-Ph	CH(Et)Pr^n	H
105	2-I-4-i-Pr-Ph	CH(Et)Pr^n	H
106	2-Br-4-SMe-Ph	CH(Et)Pr^n	H
107	2-Br-4-SO_2Me-Ph	CH(Et)Pr^n	H
108	2-Br-4,6-(OMe)$_2$-Ph	CH(C_2H_5)$_2$	H
108	(m.p.163-165 °C)		
109	2-Cl-4,6-(OMe)$_2$-Ph	CH(C_2H_5)$_2$	H
109	(m.p.166-167 °C)		
110	4-i-Pr-2-SMe-Ph	CH(C_2H_5)$_2$	H
110	(m.p.89-90 °C)		
111	4-i-Pr-2-SO_2Me-Ph	CH(C_2H_5)$_2$	H
112	4-(COMe)-2-Br-Ph	CH(C_2H_5)$_2$	H
113	2-Br-4-CF_3-Ph	CH(C_2H_5)$_2$	H
114	4-Br-2,6-(Me)$_2$-Ph	CH(C_2H_5)$_2$	H

114	(m.p.160-162 °C)		
115	2,6-(Me)$_2$-4-SMe-Ph	CH(C$_2$H$_5$)$_2$	H
116	2,6-(Me)$_2$-4-SO$_2$Me-Ph	CH(C$_2$H$_5$)$_2$	H
117	2,6-(Me)$_2$-4-CF$_3$-Ph	CH(C$_2$H$_5$)$_2$	H
118	2-Br-4,6-(Me)$_2$-Ph	CH(C$_2$H$_5$)$_2$	H
119	4-N(Et)$_2$-2-Me-Ph	CH(C$_2$H$_5$)$_2$	H
120	4-I-2-Me-Ph	CH(C$_2$H$_5$)$_2$	H
121	2-I-4-i-Pr-Ph	CH(C$_2$H$_5$)$_2$	H
122	2-Br-4-SMe-Ph	CH(C$_2$H$_5$)$_2$	H
123	2-Br-4-SO$_2$Me-Ph	CH(C$_2$H$_5$)$_2$	H
124	2-Br-4-N(Me)$_2$-6-OMe-Ph	CH(C$_2$H$_5$)$_2$	H
125	2,4-[S(O)$_2$Me]$_2$-Ph	CH(C$_2$H$_5$)$_2$	H
126	2-Cl-4,6-(OMe)$_2$-Ph	CH(n-C$_3$H$_7$)$_2$	H
127	4-i-Pr-2-S(O)$_2$Me-Ph	CH(n-C$_3$H$_7$)$_2$	H
128	4-(COMe)-2-Br-Ph	CH(n-C$_3$H$_7$)$_2$	H
129	4-Br-2-CF$_3$-Ph	CH(n-C$_3$H$_7$)$_2$	H
130	4-Br-2,6-(Me)$_2$-Ph	CH(n-C$_3$H$_7$)$_2$	H
131	2,6-(Me)$_2$-4-S(O)$_n$Me-Ph	CH(n-C$_3$H$_7$)$_2$	H
132	2,6-(Me)$_2$-4-CF$_3$-Ph	CH(n-C$_3$H$_7$)$_2$	H
133	2-Br-4,6-(Me)$_2$-Ph	CH(n-C$_3$H$_7$)$_2$	H
134	4-Cl-2-Me-Ph	CH(n-C$_3$H$_7$)$_2$	H
135	4-N(Et)$_2$-2-Me-Ph	CH(n-C$_3$H$_7$)$_2$	H
136	4-I-2-Me-Ph	CH(n-C$_3$H$_7$)$_2$	H
137	2-I-4-i-Pr-Ph	CH(n-C$_3$H$_7$)$_2$	H
138	2-Br-4-N(Me)$_2$-6-OMe-Ph	CH(n-C$_3$H$_7$)$_2$	H
139	2,4-[SMe]$_2$-Ph	CH(n-C$_3$H$_7$)$_2$	H
140	2,4-[S(O)Me]$_2$-Ph	CH(n-C$_3$H$_7$)$_2$	H
141	2,4-[S(O)$_2$Me]$_2$-Ph	CH(n-C$_3$H$_7$)$_2$	H
142	4-i-Pr-2-S(O)$_n$Me-Ph	CH(Et)CH$_2$-OCH$_3$	H
143	2-Br-4-CF$_3$-Ph	CH(Et)CH$_2$-OCH$_3$	H
144	2,6-(Me)$_2$-4-S(O)Me-Ph	CH(Et)CH$_2$-OCH$_3$	H
145	2,6-(Me)$_2$-4-S(O)$_2$Me-Ph	CH(Et)CH$_2$-OCH$_3$	H
146	2,6-(Me)$_2$-4-CF$_3$-Ph	CH(Et)CH$_2$-OCH$_3$	H
147	2,6-(Et)$_2$-4-Br-Ph	CH(Et)CH$_2$-OCH$_3$	H
148	2-Br-4,6-(Me)$_2$-Ph	CH(Et)CH$_2$-OCH$_3$	H
148	(m.p.156-157 °C)		
149	4-Cl-2-Me-Ph	CH(Et)CH$_2$-OCH$_3$	H

150	4-$N(Et)_2$-2-Me-Ph	$CH(Et)CH_2$-OCH_3	H
151	4-I-2-Me-Ph	$CH(Et)CH_2$-OCH_3	H
151	(m.p.122-123 °C)		
152	2-I-4-i-Pr-Ph	$CH(Et)CH_2$-OCH_3	H
153	2-Br-4-SMe-Ph	$CH(Et)CH_2$-OCH_3	H
154	2-Br-4-$S(O)_2$Me-Ph	$CH(Et)CH_2$-OCH_3	H
155	2-Br-4-NMe_2-Ph	$CH(Et)CH_2$-OCH_3	H
156	2-Me-4-NMe_2-Ph	$CH(Et)CH_2$-OCH_3	H
156	(m.p.159-162 °C)		
157	2,6-$(Me)_2$-4-NMe_2-Ph	$CH(Et)CH_2$-OCH_3	H
158	2-Br-4-OMe-Ph	$CH(Et)CH_2$-OCH_3	H
159	2-$N(Me)_2$-4-Me-Ph	$CH(Et)CH_2$-OCH_3	H
160	2-MeS-4,6-$(Me)_2$-Ph	$CH(Et)CH_2$-OCH_3	H
161	2-MeS(O)-4,6-$(Me)_2$-Ph	$CH(Et)CH_2$-OCH_3	H
162	2-$MeS(O)_2$-4,6-$(Me)_2$-Ph	$CH(Et)CH_2$-OCH_3	H
163	2-(CH_3CO)-4,6-$(Me)_2$-Ph	$CH(Et)CH_2$-OCH_3	H
164	2-Br-4-NMe_2-Ph	$CH(Et)CH_2$-OCH_3	Et
165	2-Me-4-NMe_2-Ph	$CH(Et)CH_2$-OCH_3	Et
166	2,6-$(Me)_2$-4-NMe_2-Ph	$CH(Et)CH_2$-OCH_3	Et
167	2-Br-4-OMe-Ph	$CH(Et)CH_2$-OCH_3	Et
168	2-$N(Me)_2$-4-Me-Ph	$CH(Et)CH_2$-OCH_3	Et
169	2-MeS-4,6-$(Me)_2$-Ph	$CH(Et)CH_2$-OCH_3	Et
170	2-MeS(O)-4,6-$(Me)_2$-Ph	$CH(Et)CH_2$-OCH_3	Et
171	2-$MeS(O)_2$-4,6-$(Me)_2$-Ph	$CH(Et)CH_2$-OCH_3	Et
172	2-(CH_3CO)-4,6-$(Me)_2$-Ph	$CH(Et)CH_2$-OCH_3	Et
173	2-Br-4-NMe_2-Ph	$CH(CH_2$-$OCH_3)_2$	H
174	2-Me-4-NMe_2-Ph	$CH(CH_2$-$OCH_3)_2$	H
175	2,6-$(Me)_2$-4-NMe_2-Ph	$CH(CH_2$-$OCH_3)_2$	H
176	2-Br-4-OMe-Ph	$CH(CH_2$-$OCH_3)_2$	H
177	2-$N(Me)_2$-4-Me-Ph	$CH(CH_2$-$OCH_3)_2$	H
178	2-MeS-4,6-$(Me)_2$-Ph	$CH(CH_2$-$OCH_3)_2$	H
179	2-MeS(O)-4,6-$(Me)_2$-Ph	$CH(CH_2$-$OCH_3)_2$	H
180	2-$MeS(O)_2$-4,6-$(Me)_2$-Ph	$CH(CH_2$-$OCH_3)_2$	H
181	2-(CH_3CO)-4,6-$(Me)_2$-Ph	$CH(CH_2$-$OCH_3)_2$	H
182	2-Br-4-NMe_2-Ph	$CH(CH_2$-$OCH_3)_2$	Et
183	2-Me-4-NMe_2-Ph	$CH(CH_2$-$OCH_3)_2$	Et
184	2,6-$(Me)_2$-4-NMe_2-Ph	$CH(CH_2$-$OCH_3)_2$	Et

185	2-Br-4-OMe-Ph	$CH(CH_2-OCH_3)_2$	Et
186	2-$N(Me)_2$-4-Me-Ph	$CH(CH_2-OCH_3)_2$	Et
187	2-MeS-4,6-$(Me)_2$-Ph	$CH(CH_2-OCH_3)_2$	Et
188	2-MeS(O)-4,6-$(Me)_2$-Ph	$CH(CH_2-OCH_3)_2$	Et
189	2-$MeS(O)_2$-4,6-$(Me)_2$-Ph	$CH(CH_2-OCH_3)_2$	Et
190	2-(CH_3CO)-4,6-$(Me)_2$-Ph	$CH(CH_2-OCH_3)_2$	Et
191	2-Br-4-NMe_2-Ph	$CH(CH_2-CH_2-CH_3)_2$	H
192	2-Me-4-NMe_2-Ph	$CH(CH_2-CH_2-CH_3)_2$	H
193	2,6-$(Me)_2$-4-NMe_2-Ph	$CH(CH_2-CH_2-CH_3)_2$	H
194	2-Br-4-OMe-Ph	$CH(CH_2-CH_2-CH_3)_2$	H
195	2-$N(Me)_2$-4-Me-Ph	$CH(CH_2-CH_2-CH_3)_2$	H
196	2-MeS-4,6-$(Me)_2$-Ph	$CH(CH_2-CH_2-CH_3)$	H
197	2-MeS(O)-4,6-$(Me)_2$-Ph	$CH(CH_2-CH_2-CH_3)_2$	H
198	2-$MeS(O)_2$-4,6-$(Me)_2$-Ph	$CH(CH_2-CH_2-CH_3)_2$	H
199	2-(CH_3CO)-4,6-$(Me)_2$-Ph	$CH(CH_2-CH_2-CH_3)_2$	H
200	2-Br-4-NMe_2-Ph	$CH(CH_2-CH_2-CH_3)_2$	Et
201	2-Me-4-NMe_2-Ph	$CH(CH_2-CH_2-CH_3)_2$	Et
202	2,6-$(Me)_2$-4-NMe_2-Ph	$CH(CH_2-CH_2-CH_3)_2$	Et
203	2-Br-4-OMe-Ph	$CH(CH_2-CH_2-CH_3)_2$	Et
204	2-$N(Me)_2$-4-Me-Ph	$CH(CH_2-CH_2-CH_3)_2$	Et
205	2-MeS-4,6-$(Me)_2$-Ph	$CH(CH_2-CH_2-CH_3)$	Et
206	2-MeS(O)-4,6-$(Me)_2$-Ph	$CH(CH_2-CH_2-CH_3)_2$	Et
207	2-$MeS(O)_2$-4,6-$(Me)_2$-Ph	$CH(CH_2-CH_2-CH_3)_2$	Et
208	2-(CH_3CO)-4,6-$(Me)_2$-Ph	$CH(CH_2-CH_2-CH_3)_2$	Et

Example 209

_N_-[2-bromo-4-(1-methylethyl)phenyl]-2-methyl-9-(1-propylbutyl)-9_H_-purin-6-amine

Part A: The product of Part A (0.74 g) from Example 21 was treated with triethyl orthoformate (7.68 g) and con. H_2SO_4 (3 drops) and heated to 100 °C for 4h. The excess triethyl orthoformate was removed in vacuum, and the residue was purified by flash column chromatography to yield 6-chloro-2-methyl-9-(1-propylbutyl)-9_H_-purine as a colorless liquid (0.32 g).

Part B: The product of Part A from above was combined with 2-bromo-4-isopropylaniline in a manner similar to Part C of Example 21 to afford the title compound as a brown oil. Elemental analysis for $C_{22}H_{30}BrN_5$: Theory C: 59.46, H: 6.80 N: 15.76. Found: C: 59.56, H: 6.83, N: 15.67.

Example 210

(+/-)-*N*-[2-bromo-4-(1-methylethyl)phenyl]-9-(1-ethylpentyl)-2-methyl-9*H*-purin-6-amine

Part A: The product of Part D from Example 1 was treated with 3-aminoheptane in a manner similar to Part A of Example 21, to yield 5-amino-4-chloro-6-(3-heptyl)amino-2-methylpyrimidine as a white crystalline solid (mp 116-117 °C). Elemental analysis for $C_{12}H_{21}ClN_4$: Theory C: 56.13, H: 8.24, N: 21.82. Found: C: 56.16, H: 8.26, N: 21.82

Part B: The product of Part A from above was treated with triethyl orthoformate in a manner similar to Part A of Example 209 to yield 6-chloro-9-(1-ethylpentyl)-2-methyl-9*H*-purine as a pale yellow liquid.

Part C: The product of Part B from above was combined with 2-bromo-4-isopropylaniline in a manner similar to Part C of Example 21 to afford the title compound as a colorless oil. Elemental analysis for $C_{22}H_{30}BrN_5$: Theory C: 59.46, H: 6.80 N: 15.76. Found: C: 59.30, H: 6.82, N: 15.50.

Example 211

(+/-)-*N*-[2-bromo-4-(trifluromethyl)phenyl]-9-[1-(methoxymethyl)propyl]-2-methyl-9*H*-purin-6-amine

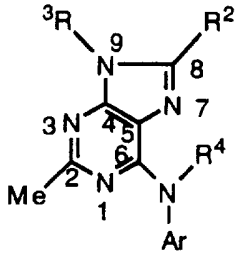
Part A: The product of Part A from Example 27 was treated with triethyl orthoformate in a manner similar to Part A of Example 209 to yield 6-chloro-9-[1-(methoxymethyl)propyl]-2-methyl-9*H*-purine as a white crystalline solid (mp 105-106 °C). Elemental analysis for $C_{11}H_{15}ClN_4O$: Theory C: 51.87, H: 5.95 N: 22.00. Found: C: 51.85, H: 5.81, N: 21.96.

Part B: The product of Part A from above was combined with 2-bromo-4-trifluromethylaniline in a manner similar to Part C of Example 21 to afford the title compound as a off-white solid (mp 123-124 °C). Elemental analysis for $C_{18}H_{19}BrF_3N_5O$: Theory C: 47.18, H: 4.19, N: 15.28. Found: C: 47.28, H: 3.97, N: 15.50.

The compounds of Examples 212-217 can be made by methods exemplified in Examples 209-211.

Table 2

9H-imidazo[4,5-d]pyrimidines:



Ex. No.	Ar	R^2	R^3	R^4
212	2-Br-4-i-Pr-Ph	Me	$CH(n\text{-}C_3H_7)_2$	H
213	2,4,6-$(Me)_3$-Ph	Me	$CH(n\text{-}C_3H_7)_2$	H
214	4-Br-2,6-$(Me)_2$-Ph	Me	$CH(n\text{-}C_3H_7)_2$	H
215	2-Br-4-i-Pr-Ph	Me	$CH(Et)CH_2OCH_3$	H
216	2,4,6-$(Me)_3$-Ph	Me	$CH(Et)CH_2OCH_3$	H
217	4-Br-2,6-$(Me)_2$-Ph	Me	$CH(Et)CH_2OCH_3$	H

Example 218

***N*-[2-bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-5-methyl-[1,2,3]thiadiazolo[5,4-d]pyrimidin-7-amine**

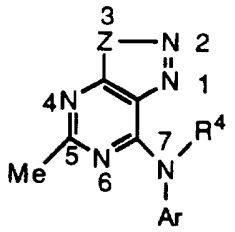
Part A: The product of Part E (1.1 g) from Example 1 was dissolved in ethanol (15 mL) and added thiourea (0.27 g). The reaction mixture was refluxed for 1h, removed the solvent in vacuum, partitioned between CH_2Cl_2 and water, washed with brine, dried and stripped down to a residue. The residue was purified by flash column chromatography (CH_2Cl_2) to furnish the title compound as a white crystalline solid (1.01 g, mp 81-82 °C). Elemental analysis for $C_{14}H_{14}BrN_5S$: Theory C: 46.16, H: 3.87, N: 19.23, S: 8.80. Found: C: 46.15, H: 3.85, N: 19.09, S: 8.60.

Part B: Using the procedure for Example 2, the product of Part A was alkylated to afford the title compound as a pale yellow oil. Elemental analysis for $C_{16}H_{18}BrN_5S$: Theory C: 48.98, H: 4.62, N: 17.85. Found: C: 49.23, H: 4.71, N: 17.72.

The compounds of Examples 219 and 220 can be made by the method of Example 218.

Table 3

[1,2,3]-Thiadiazolo[5,4-d]pyrimidines:



Ex. No.	Ar	Z	R^4
219	2-Br-4-i-Pr-Ph	S	n-C_3H_7
220	2-Br-4-i-Pr-Ph	S	CH_2-CH=CH_2

Example 221

***N*-[2-bromo-4-(1-methylethyl)phenyl]-1-(1-ethylpropyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine**

Part A: 2,4-Dihydroxy-6-methyl-3-nitropyridine was added to phosphorous oxychloride in a manner similar to Part B of Example 1 to afford 2,4-dichloro-3-nitro-6-methylpyridine as a pale yellow solid (mp 69-70 °C).

Part B: The product of Part A (10.35 g) from above was dissolved in ethanol (100 mL) and then added triethylamine (5.05 g) followed by 3-aminopentane at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 days, ethanol was removed in vacuum, the residue was partitioned between ethyl acetate (150 mL) and water (150 mL). The organic layer was washed with brine, dried, stripped down to a residue and purified by flash column chromatography to furnish 2-chloro-6-methyl-3-nitro-4-(3-pentyl)aminopyridine as a pale yellow solid (2.8 g; 84-85 °C). Elemental analysis for $C_{11}H_{16}ClN_3O_2$: Theory C: 51.27, H: 6.27, N: 16.30. Found: C: 51.28 , H: 6.09, N: 16.07.

Part C: The product of Part B from above was reduced in a manner similar to Part C of Example 1 to afford 3-amino-2-chloro-6-methyl-4-(3-pentyl)aminopyridine as a cream colored solid (mp 165-166 °C). Elemental analysis for $C_{11}H_{18}ClN_3$: Theory C: 58.01, H: 7.98, N: 18.45. Found: C: 57.86, H: 7.83, N: 18.44.

Part D: The product of Part C from above was cyclized in a manner similar to Part E of Example 1 to afford 4-chloro-1-(1-ethylpropyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridine as a light pink solid (mp 78-79 °C).

Part E: The product of Part D from above was combined with 2-bromo-4-isopropylaniline in a manner similar to Part C in Example 21, to yield the title compound as a cream colored solid (mp 144-145 °C). Elemental analysis for $C_{20}H_{26}BrN_5$: Theory C: 57.69, H: 6.29, N: 16.82 Found: C: 57.82 , H: 6.29, N: 16.90.

Example 222

***N*-(2-bromo-4,6-dimethoxyphenyl)-1-(1-ethylpropyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine**

The product of Part D from Example 221 was combined with 2-bromo-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as a off-white solid (mp 166-167 °C). Elemental analysis for $C_{19}H_{24}BrN_5O_2$: Theory C: 52.54, H: 5.58, N: 16.12 Found: C: 52.63, H: 5.53, N: 16.16.

Example 223

***N*-(2-chloro-4,6-dimethoxyphenyl)-1-(1-ethylpropyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine**

The product of Part D from Example 221 was combined with 2-chloro-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as an off-white solid (mp 168-169 °C).

Example 224

***N*-(2-bromo-4,6-dimethoxyphenyl)-6-methyl-1-(1-propylbutyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine**

Part A: The product of Part A from Example 221, was treated with 4-aminoheptane in the same manner as outlined in Part B of Example 221 to furnish 2-chloro-4-(4-heptyl)amino-6-methyl-3-nitropyridine as an yellow oil. Elemental analysis for $C_{13}H_{20}ClN_3O_2$: Theory C: 54.64, H: 7.05, N: 14.70. Found: C: 54.93, H: 7.03, N: 14.62.

Part B: The product of Part A from above was reduced in a manner similar to Part C of Example 1 to afford 3-amino-2-chloro-4-(4-heptyl)amino-6-methylpyridine as a cream colored solid (mp 139-140 °C).

Part C: The product of Part B from above was cyclized in a manner similar to Part E of Example 1 to afford 4-chloro-6-methyl-1-(1-propylbutyl)-1*H*-1,2,3-triazolo[4,5-c]pyridine as an orange yellow solid (mp 90-91 °C).

Part D: The product of Part C from above was combined with 2-bromo-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as a brick red colored solid (mp 140-141 °C). Elemental analysis for $C_{21}H_{28}BrN_5O_2$: Theory C: 54.55, H: 6.10, N: 15.15 Found: C: 54.83, H: 5.95, N: 15.11.

Example 225

N-(2-chloro-4,6-dimethoxyphenyl)-6-methyl-1-(1-propylbutyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

The product of Part C from Example 224 was combined with 2-chloro-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as a brick red colored solid (mp 157-158 °C). Elemental analysis for $C_{21}H_{28}ClN_5O_2$: Theory C: 60.35, H: 6.75, N: 16.76 Found: C: 60.43, H: 6.74, N: 16.99.

Example 226

(+/-)-*N*-[2-bromo-4-(1-methylethyl)phenyl]-1-(1-ethylpentyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

Part A: The product of Part A from Example 221, was treated with 3-aminoheptane in the same manner as outlined in Part B of Example 221 to furnish 2-chloro-4-(3-heptyl)amino-6-methyl-3-nitropyridine as an yellow solid (mp 48-49 °C). Elemental analysis for $C_{13}H_{20}ClN_3O_2$: Theory C: 54.64, H: 7.05, N: 14.70. Found: C: 54.79, H: 6.95, N: 14.67.

Part B: The product of Part A from above was reduced in a manner similar to Part C of Example 1 to afford 3-amino-2-chloro-4-(3-heptyl)amino-6-methylpyridine as a cream colored solid (mp 139-140 °C).

Part C: The product of Part B from above was cyclized in a manner similar to Part E of Example 1 to afford 4-chloro-1-(1-ethylpropyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridine as a colored liquid. Elemental analysis for $C_{13}H_{19}ClN_4$: Theory C: 58.53, H: 7.19, N: 21.00. Found: C: 58.69, H: 7.06, N: 20.76.

Part D: The product of Part C from above was combined with 2-bromo-4-isopropylaniline in a manner similar to Part C in Example 21, to yield the title compound as a light pink colored solid (mp 73-74 °C). Elemental analysis for $C_{22}H_{30}BrN_5$: Theory C: 59.46, H: 6.80, N: 15.76, Found: C: 59.56, H: 6.70, N: 15.70.

Example 227

(+/-)-*N*-(2-bromo-4,6-dimethoxyphenyl)-1-(1-ethylpentyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

The product of Part C from Example 226 was combined with 2-bromo-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as a brick red colored solid (mp 127-128 °C). Elemental analysis for $C_{21}H_{28}BrN_5O_2$: Theory C: 54.55, H: 6.10, N: 15.15. Found: C: 54.78, H: 5.84, N: 14.92.

Example 228

(+/-)-*N*-(2-chloro-4,6-dimethoxyphenyl)-1-(1-ethylpentyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

The product of Part C from Example 226 was combined with 2-chloro-4,6-dimethoxyaniline in a manner similar to Part C in Example 21, to yield the title compound as a brick red colored solid (mp 155-156 °C). Elemental analysis for $C_{21}H_{28}ClN_5O_2$: Theory C: 60.35, H: 6.75, N: 16.76. Found: C: 60.36, H: 6.65, N: 16.84.

Example 229

***N*-[2-bromo-4-(1-methylethyl)phenyl]-6-methyl-1-(1-propylbutyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine**

Part A: 4-Chloro-6-methyl-3-nitropyridone: 4-Hydroxy-6-methyl-3-nitropyridone (4.0 g, 23,52 mmol) was treated with cyclohexylamine (2.8 mL, 24.46 mmol) in MeOH (50 mL) until all dissolved. The MeOH was stripped in vacuo and the resulting salt was dried and treated with $POCl_3$ (30 mL) at 25 °C for 30 h. The reaction was then poured into ice/water (400 mL) and extracted with EtOAc

(2x200 mL). The combined EtOAc extracts were washed with water (100 mL), 1 N NaOH (20 mL), water (100 mL) and brine, dried ($MgSO_4$) and stripped in vacuo. The residue was washed with 20% EtOAc/hexanes (2x30 mL) to give the product (2.9 g).

Part B: 6-Methyl-3-nitro-4-(1-propylbutylamino) pyridone: 4-Chloro-6-methyl-3-nitropyridone (2.9 g, 15.40 mmol) was treated with 1-propylbutylamine (4 mL, 26.8 mmol) in CH_3CN (30 mL) at 25 °C for 64 h and at reflux for 2 h. The reaction mixture was partitioned between EtOAc (200 mL) and water (50 mL). The EtOAc was washed with water (2x50 mL), brine, dried ($MgSO_4$) and stripped in vacuo. The residue was washed with 20% EtOAc/hexanes (2x20 mL) to give the product (3.7 g).

Part C: 2-Chloro-6-methyl-3-nitro-*N*-(1-propyl-butyl)pyridin-4-amine: 6-Methyl-3-nitro-4-(1-propylbutylamino) pyridone (3.7 g, 13.84 mmol), was treated with $POCl_3$ (14 mL) at 25 °C for 20 h. Then it was poured into ice/water (200 mL) and extracted with EtOAc (300 mL). The EtOAc was washed with water, brine, dried ($MgSO_4$) and stripped in vacuo. The residue was chromatographed on silica gel (20% EtOAc/hexanes eluting solvent) to give the product (3.3 g).

Part D: *N*-[2-Bromo-4-(1-methylethyl)phenyl]-6-methyl-3-nitro-*N*-(1-propylbutyl)pyridin-2,4-diamine: 2-Chloro-6-methyl-3-nitro-*N*-(1-propylbuty)pyridin-4-amine (0.5 g, 1.75 mmol) and 2-bromo-4-isopropylaniline (0.74 g, 3.5 mmol) were heated at 140 °C for 4.5 h. After cooling it was dissolved in CH_2Cl_2 and filtered through a short column of silica gel. The filtrate was concentrated and chromatographed on silica gel (5%

EtOAc/hexanes eluting solvent) to give the product (0.7 g).

Part E: *N*-[2-Bromo-4-(1-methylethyl)phenyl]-6-methyl-*N*-(1-propylbuty) pyridine-2,3,4-triamine: *N*-[2-Bromo-4-(1-methylethyl)phenyl]-6-methyl-3-nitro-*N*-(1-propyl-butyl)pyridin-2,4-diamine (0.7 g, 1.51 mmol), was suspended between dioxane (30 mL) and water (30 mL) containing conc.NH_4OH (1.2 mL). To that $Na_2S_2O_4$ was added (2.1 g, 12.06 mmol) and the mixture was stirred at 25 °C for 2h. Then an additional 1g $Na_2S_2O_4$ was added followd by 10 mL dioxane and 10 mL water. After stirring for 1 h at 25 °C the mixture was patritioned between EtOAc (120 mL) and water (20 mL). The EtOAc was washed with water (100 mL), brine, dried ($MgSO_4$) and stripped in vacuo. The residue was chromatographed on silica gel (20% EtOAc/hexanes eluting solvent) to give the product (0.5 g).

Part F: *N*-[2-bromo-4-(1-methylethyl)phenyl]-6-methyl-1-(1-propylbutyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine: N-[2-Bromo-4-(1-methylethyl)phenyl]-6-methyl-N-(1-propylbutyl) pyridine-2,3,4-triamine (0.5 g, 1.15 mmol), dissolved in CH_2Cl_2 (6 mL) and 50% AcOH (4 mL) was treated with $NaNO_2$ (0.0846 g, 1.22 mmol) at 25 °C for 16 h. The mixture was patritioned between EtOAc (100 mL) and water (20 mL) The EtOAc was washed with water (20 mL), brine, dried and stripped in vacuo. The residue was chromatographed on silica gel (20% EtOAc/hexanes eluting solvent) to give the product (0.2 g). Anal. Calcd. for $C_{22}H_{30}BrN_5$: C, 59.46; H, 6.80; N, 15.76; Br, 17.98. Found: C, 59.76; H, 6.83; N, 15.67; Br, 18.17.

Example 231

N-[4-(1-methylethyl)-2-sulfonylmethylphenyl]-6-methyl-1-(1-propylbutyl)-1*H*-1,2,3-triazolo[4,5-c] pyridin-4-amine

N-[4-(1-methylethyl)-2-thiomethylphenyl]-6-methyl-1-(1-propylbutyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine (0.15 g, 1 equiv.) (Example 231), synthesized under the same general conditions of Example 229, was dissolved in methanol (3 mL) and water (2 mL) was added, followed by $NaIO_4$ (0.114 g, 1.5 equiv.). The mixture was stirred at 25 °C for 20 h and then was extracted with EtOAc (80 mL). The EtOAc was washed with water, brine, dried and stripped in vacuo. The residue was dissolved in CH_2Cl_2 and a solution of $KMnO_4$ (0.15 g, 2.5 equiv.) in water (2 mL) was added, followed by benzyltriethylammonium chloride (0.15 g, 1.5 equiv.). The mixture was stirred at 25 °C for 20 h and then extracted with EtOAc (80 mL) and the EtOAc was washed with water, brine, dried and stripped in vecuo. The residue was chromatographed on silica gel (10% EtOAc/hexanes eluting solvent) to give the product (0.2 g). Anal. Calcd. for $C_{23}H_{33}BrN_5O_2S$: C, 62.27; H, 7.51; N, 15.79; S, 7.24. Found: C, 62.62; H, 7.38; N, 15.58 S, 7.44.

Example 232

N-[4-(4-acetyl-2-bromophenyl]-6-methyl-1-(1-propyl- butyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

PART A: Used the standard procedure for the coupling of the nitropyridine (0.8 g, 2.9 mmoles) and 2-Bromo-4-iodoaniline (1.7 g, 5.7 mmoles). Preabsorbed the crude material on 12 g. of silica gel before chromatographing on silica gel (5% EtOAc/hexane eluen) to give an orange solid, 1.47 g. of the desired product.

PART B: To the coupled 2-Bromo-4-iodoanilinonitropyridine (0.60 g, 1.1 mmoles) in a dried flask, under nitrogen, was added Bis(triphenylphosphine)palladium(II)chloride (18 mg, 0.026 mmoles) and anhydrous toluene (5 mL). Added 1-Ethoxyvinyltributyltin (0.46 ml, 1.36 mmoles) and stirred at reflux temperature for 1 1/2 hours. Dissolved into ethyl acetate then filtered off the insolubles through celite. Washed the solids 2 x with ethyl acetate. Concentrated in-vacuo the filtrates to near dryness. Stirred the residue with 70 ml 1M hydrochloric acid for 1/2 hour. Added some ethyl acetate and separated the layers., extracted the water layer with 2 x 20 ml ethyl acetate. Concentrated the combined organics to near dryness. Stirred the residue in a saturated potassium fluoride (20 ml) for 1/2 hour. Separated the layers. Extracted the water layer with 2 x 20 ml ethyl acetate. Washed the combined extracts with 10 ml water and 20 ml brine. Chromatographed the crude material on silica gel to give a solid, 0.37 g (73 %) of the desired product.

PART C: Using the product obtained from Part B (0.70 g, 1.5 mmoles), 10 ml tetrahydrofuran, 10 ml water, 0.70 ml ammonium hydroxide solution (38-40%) and sodium dithionite (2.1 g, 12 mmoles) followed the standard procedure to reduce the nitroanilinopyridine. Obtained the crude solid, 0.65 g, which was of sufficient purity for further reaction.

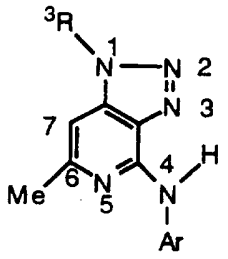
PART D: Followed the standard procedure to cyclize the product obtained in Part C (0.63 g, 1.45 mmoles), using 10 ml methylene chloride, 10 ml acetic acid/water (50%), and sodium nitrite (0.18 g, 2.59 mmoles) in 1 ml water. Chromatographed on silica gel

(10% ethyl acetate / hexane) to give a white solid, 0.31 g, (48%) of desired product, mp 165-166 °C. Anal. Calcd. for $C_{21}H_{26}BrN_5O$: C, 56.76; H, 5.91; N, 15.76; Br, 17.98. Found: C, 56.75; H, 5.76; N, 15.71; Br, 17.72. Obtained the isomer of the desired product, a white solid, 90 mg, mp 133-136 °C. Anal. Calcd: Found: C, 57.11; H, 5.82; N, 15.69; Br, 18.23.

The rest of the examples shown in Table 4 were prepared by following the general procedure outlined in Example 229.

Table 4

1*H*-1,2,3-triazolo[4,5-c]pyridines:



Ex. No.	R^3	Ar	Mp °C
233	CH(Et)CH_2-OCH_3	2-Br-4-i-Pr-Ph	121-123
234	CH(Et)CH_2-OCH_3	4-i-Pr-2-SMe-Ph	97-100
235	CH(i-C_3H_7)$_2$	2-Br-4-(iC_3H_7)Ph	96-96
236	CH(i-C_3H_7)$_2$	4-(i-C_3H_7)-2-SMe-Ph	
237	CH(C_2H_5)$_2$	4-(i-C_3H_7)-2-SMe-Ph	
238	CH(n-C_3H_7)$_2$	2-Br-4-I-Ph	161-164
239	CH(n-C_3H_7)$_2$	2,4-(Br)$_2$-Ph	125-127
240	CH(Et)CH_2-OCH_3	2,4,6-Me_3-Ph	
241	i-Pr	2-Br-4-i-Pr-Ph	
242	i-Pr	4-i-Pr-2-SMe-Ph	
243	c-Pr	2-Br-4-i-Pr-Ph	

244	c-Pr	4-i-Pr-2-SMe-Ph
245	i-Pr	2,4-$(Br)_2$-Ph
246	c-Pr	2,4-$(Br)_2$-Ph
247	$CH(Et)CH_2$-OCH_3	2,4-$(Br)_2$-Ph
248	$CH(Et)_2$	2,4-$(Br)_2$-Ph
249	$CH(Et)CH_2$-OCH_3	2-COMe-4-Br-Ph
250	$CH(Et)_2$	4-COMe-2-Br-Ph
251	$CH(Et)_2$	2-Br-4-SO_2Me-Ph
252	$CH(Et)_2$	2,4,6-Me_3-Ph
253	$CH(CH_2CN)_2$	2-Br-4-(i-C_3H_7)Ph
254	$CH(Et)CH_2CN$	2-Br-4-(i-C_3H_7)Ph
255	$CH(Et)CH_2CONMe_2$	2-Br-4-(i-C_3H_7)Ph
256	$CH(CH_2CN)_2$	2-Br-4,6-$(OMe)_2$Ph
257	$CH(Et)CH_2CN$	2-Br-4,6-$(OMe)_2$Ph
258	$CH(Et)CH_2CONMe_2$	2-Br-4,6-$(OMe)_2$Ph

Example 259

***N*-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-methoxyethyl]-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine:**

Part A: Serinol (24 g) was added to a solution of trityl chloride (65 g) and triethylamine (51.0 g) in 600 mL of dry DMF. After stirring at room temperature for 48 h, the reaction was poured into water and extracted several times with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to dryness to afford N-triphenylmethylserinol (71.0 g).

Part B: Methyl iodide (90 mL) was added to a suspension of N-triphenylmethylserinol (37.0 g) and powdered sodium hydroxide (45.0 g) in 400 mL of dry DMSO. After stirring at room temperature for 24-36 h, the reaction was added to water (800 mL) and extracted with diethyl ether (3 X 500 mL). The combined organic layers was washed with water (4 X 250 mL),

dried over anhydrous magnesium sulfate and concentrated to afford 1,3-dimethoxy-2-triphenylmethylaminopropane (36.0 g) as a thick viscous oil.

Part C: To a solution of the product of Part B (36.0 g) in methanol (400 mL) was added 1 M HCl in ether (350 mL). After stirring overnight, the reaction was poured over water (800 mL) extracted with hexane (3 X 250 mL). The methanol/water layer was concentrated to dryness to afford 1,3-dimethoxy-2-aminopropane hydrochloride (14.0 g) as a waxy solid.

Part D: 4-Chloro-6-methyl-3-nitro-2-pyridone: 4-Hydroxy-6-methyl-3-nitro-2-pyridone (50.0 g) was treated with cyclohexylamine (40 g) in MeOH (300 mL) and heated until all dissolved. The MeOH was stripped in vacuum and the resulting salt was dried and treated with $POCl_3$ (360 mL) at 25 °C for 48 h. The excess $POCl_3$ was removed under vacuum and the residue was poured into ice/water (1000 mL) and extracted with EtOAc (4x250 mL). The combined EtOAc extracts were washed with aq. $NaHCO_3$, brine (3 *100 mL), dried ($MgSO_4$) and stripped in vacuum. The residue was washed with 20% EtOAc/hexanes (2x100 mL) to afford the product as a yellow solid(41.3 g; mp 225 °C).

Part E: 4-[1-methoxymethyl-(2-methoxyethyl]amino-6-methyl-3-nitro-2-pyridone: 4-Chloro-6-methyl-3-nitro-2-pyridone (12.12 g; from part D) was treated with 1,3-dimethoxy-2-aminopropane hydrochloride (10.0 g; from part C) in CH_3CN (200 mL) and diisopropylethylamine (20.0 g) at 25 °C for 24 h and at reflux for 3 h. The reaction mixture was partitioned between EtOAc (200 mL) and water (50 mL). The EtOAc was washed with water (2x50 mL), brine, dried ($MgSO_4$) and stripped in vacuum to give the product as a yellow solid(9.4 g; m.p.172-173 °C).

Part F: 2-Chloro-N-[1-methoxymethyl-(2-methoxyethyl]-6-methyl-3-nitro-pyridin-4-amine: 4-[1-methoxymethyl-(2-methoxyethyl]amino-6-methyl-3-nitro-2-pyridone (9.4 g from part E), was treated with $POCl_3$ (55 mL) at 25 °C for 24 h. The excess $POCl_3$ was removed under vacuum, and the residue was poured into ice/water (200 mL) and extracted with CH_2Cl_2 (3 X 150 mL). The combined CH_2Cl_2 extract was washed with water, dried ($MgSO_4$) and stripped in vacuum to give the product as a yellow solid (9.0 g; m.p. 85-87 °C).

Part G: 2-Chloro-4-[1-methoxymethyl-(2-methoxyethyl]amino-6-methylpyridin-3-amine: The product of Part F (9.0 g) was added to acetic acid (80 mL) and methanol (400 mL). To this mixture was added iron powder (9.0 g) in portions, stirred for 5 h at 60-65 °C, cooled to room temperature, and filtered through celite. The filtrate was stripped to a brown solid, which was extracted with ethyl acetate (2 x 150 mL), washed with $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and stripped down to yield the product as a pale yellow solid (5.6 g; m.p. 100 °C).

Part H: 4-Chloro-1-[1-methoxymethyl-(2-methoxyethyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridine: The product of Part G (5.4 g) was dissolved in dichloromethane (100 mL) and 50 % aqueous acetic acid (100 mL). To this stirred mixture was added sodium nitrite (1.7 g) in water (10 mL) dropwise at room temperature. After completion of addition, the reaction was stirred for an additional 15 mins. The organic layer was separated, washed with water, dried with anhydrous magnesium sulfate, and stripped

down to a residue. The residue was purified by flash column chromatography (CH_2Cl_2) to afford the product as a pale yellow solid (5.4 g; m.p. 49-50 °C).

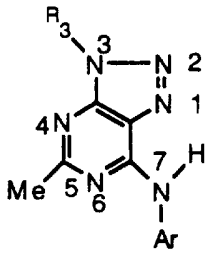
Part I: *N*-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-methoxyethyl]-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine: The product of Part H (2.0 g) from above was combined with 2-chloro-4,6-dimethylaniline (1.4 g) in the presence of p-toluenesulfonic acid (1.7 g) in toluene (25.0 mL) at 110 °C for 4h. The reaction mixture was partitioned between EtOAC (50 mL) and aq. $NaHCO_3$ (50 mL), washed the organic layer with brine, dried and stripped in vacuum to a residue. The residue was purified by flash column chromatography (1:100::MeOH: CH_2Cl_2) to afford the title compound as white solid (1.7 g; mp 83-84 °C) after crystallization from ether/pentane. Elemental analysis for $C_{19}H_{24}ClN_5O_2$: Theory C: 58.53, H: 6.20, N: 17.96, Cl: 9.09. Found: C: 58.69, H: 6.32, N: 17.97, Cl:9.18.

Part J: Mesylate salt of *N*-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-methoxyethyl]-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine: The product of Part I (850 mg) was dissolved in dichloromethane (5.0 mL) and then added methanesulfonic acid (250 mg). The solvent was removed and the residue was crystallized from 2-propanol (2.5 mL) to afford the mesylate salt (920 mg; m.p. 179-180 °C) as a white crystalline solid. Elemental analysis for $C_{20}H_{28}ClN_5O_5S$: Theory C: 49.43, H: 5.82, N: 14.41. Found: C: 49.42, H: 5.79, N: 14.37.

The compounds listed in Tables 5 and 6 were prepared by the methods exemplified in Examples 1-53 and 526.

Table 5

3*H*-1,2,3-triazolo[4,5-d]pyrimidines:



Ex. No.	Ar	R^3	m.p. (°C)
260	2-Br-2,6-$(Me)_2$-Ph	$CH(Et)_2$	134-135
261	2-Cl-2,6-$(Me)_2$-Ph	$CH(Et)_2$	133-134
262	4-Br-2-Cl-6-Me-Ph	$CH(Et)_2$	132-133
263	2,4-$(Cl)_2$-6-Me-Ph	$CH(Et)_2$	132-133
264	2,4-$(Br)_2$-6-F-Ph	$CH(Et)_2$	186-188
265	4-Br-2-Me-Ph	$CH(Et)_2$	125-127
266	4-NMe_2-2-Me-Ph	$CH(Et)_2$	136-137
267	4-Cl-2-Me-Ph	$CH(Et)_2$	116-118
268	4-I-2-Me-Ph	$CH(Et)_2$	139-140
269	4-NMe_2-2,6-$(Me)_2$-Ph	$CH(Et)_2$	160-161
270	2-Cl-4-Me-Ph	$CH(Et)_2$	100-101
271	2-Br-4-OMe-Ph	$CH(Et)_2$	146-147
272	2-Br-4-NMe_2-Ph	$CH(Et)_2$	166-167
273	2-Me-4-CH_2OMe-Ph	$CH(Et)_2$	oil
274	2-CN-4-Me-Ph	$CH(Et)_2$	221-223
275	4-CN-2-Me-Ph	$CH(Et)_2$	216-218
276	2,4,6-Me_3-Ph	CH(nPr)Me	140.5-142
277	4-Br-2,6-Me_2-Ph	CH(nPr)Me	131-133
278	2-Cl-4,6-Me_2-Ph	CH(nPr)Me	amorph.
279	2-Cl-4,6-$(OMe)_2$-Ph	CH(nPr)Me	144-145
280	2,4,5-Me_3-Ph	CH(nPr)Me	110-112
281	4-Cl-2-Me-Ph	CH(nPr)Me	99-101
282	4-Br-2-Me-Ph	CH(nPr)Me	83-84.5
283	4-I-2-Me-Ph	CH(nPr)Me	104-105
284	2,4-Me_2-Ph	CH(nPr)Me	74.5-76.5

285	2-Br-4-$CH(Me)_2$-Ph	CH(nPr)Me	amorph.
286	2-Br-4-Cl-Ph	CH(nPr)Me	104-108
287	2-Br-4-NMe_2-Ph	CH(nPr)Me	Amorph.
288	4-NMe_2-2-Me-Ph	CH(nPr)Me	amorph.
289	2,4-$(Me)_2$-Ph	CH(Et)n-Pr	88-89
290	4-OMe-2-Me-Ph	CH(Et)n-Pr	111-112
291	2,4-$(SMe)_2$-Ph	CH(Et)n-Pr	65-66
292	2-Br-4-CF_3-Ph	CH(Et)n-Pr	91-92
293	4-Ac-2-Br-Ph	CH(Et)n-Pr	138-139
294	4-NMe_2-2-Me-Ph	CH(Et)n-Pr	116.5-118
295	4-Cl-2-Me-Ph	CH(Et)n-Pr	amorph.
296	4-I-2-Me-Ph	CH(Et)n-Pr	110-111.5
297	2,6-Me_2-4-I-Ph	CH(Et)n-Pr	158-160
298	4-Ac-2-Me-Ph	CH(Et)n-Pr	107-110.5
299	2-NMe_2-4-Me-Ph	CH(Et)n-Pr	106-107
300	4-NMe_2-2,6-$(Me)_2$-Ph	CH(Et)n-Pr	146-148
301	2,4-$(SMe)_2$-Ph	$CH(n\text{-}Pr)_2$	105-106
302	4-OMe-2-Me-Ph	$CH(n\text{-}Pr)_2$	109-110
303	2-Br-4-$N(Me)_2$-Ph	$CH(n\text{-}Pr)_2$	102-103
304	2,4-$(Me)_2$-Ph	$CH(n\text{-}Pr)_2$	97-98
305	4-Ac-2,6-$(Me)_2$-Ph	$CH(n\text{-}Pr)_2$	162-164
306	4-Cl-2-Me-Ph	$CH(n\text{-}Pr)_2$	126-127.5
307	4-NMe_2-2-Me-Ph	$CH(n\text{-}Pr)_2$	129-130.5
308	4-I-2-Me-Ph	$CH(n\text{-}Pr)_2$	98.5-101
309	2-Me-4-CH_2OMe-Ph	$CH(n\text{-}Pr)_2$	oil
310	4-Br-2,6-Me_2-Ph	$CH(Et)CH_2OMe$	140-141
311	4-Br-2,6-Me_2-Ph	$CH(Et)CH_2OMe$	139-140
312	2-Cl-4,6-$(Me)_2$-Ph	$CH(Et)CH_2OMe$	141-142
313	4-Br-2-Cl-6-Me-Ph	$CH(Et)CH_2OMe$	121-122
314	2,4-$(Cl)_2$-6-Me-Ph	$CH(Et)CH_2OMe$	109-110
315	2,4-$(Br)_2$-6-F-Ph	$CH(Et)CH_2OMe$	147-148
316	2-Br-3,4,6-$(Me)_3$-Ph	$CH(Et)CH_2OMe$	166-167
317	3-Br-2,4,6-$(Me)_3$-Ph	$CH(Et)CH_2OMe$	147-148
318	4-Br-2,6-$(F)_2$-Ph	$CH(Et)CH_2OMe$	148-149
319	2-Br-4-Cl-6-F-Ph	$CH(Et)CH_2OMe$	139-140
320	2-Br-4,6-$(F)_2$-Ph	$CH(Et)CH_2OMe$	124-125
321	4-CN-2,6-$(Cl)_2$-Ph	$CH(Et)CH_2OMe$	180-181

322	2,4-$(SMe)_2$-Ph	CH(Et)CH_2OMe	75-77
323	2-Br-4-$N(Me)_2$-Ph	CH(Et)CH_2OMe	110-112
324	2-Cl-4-CN-6-Me-Ph	CH(Et)CH_2OMe	145-146
325	2-Cl-4-CN-Ph	CH(Et)CH_2OMe	140
326	2,4,5-$(Me)_3$-Ph	CH(Et)CH_2OMe	108-109
327	2,4-$(Me)_2$-Ph	CH(Et)CH_2OMe	104-105
328	4-Br-2,6-$(Et)_2$-Ph	CH(Et)CH_2OMe	151-152
329	4-Br-2,6-$(Cl)_2$-Ph	CH(Et)CH_2OMe	109-110
330	2-Br-4,6-$(Cl)_2$-Ph	CH(Et)CH_2OMe	113-114
331	2,6-$(Br)_2$-4-Cl-Ph	CH(Et)CH_2OMe	153-154
332	4-Br-2-Me-6-NO_2-Ph	CH(Et)CH_2OMe	150-151
333	4-OMe-2-Me-Ph	CH(Et)CH_2OMe	128-129
334	2,5-Cl_2-4-NMe_2-Ph	CH(Et)CH_2OMe	84-85
335	2,4-Cl_2-Ph	CH(Et)CH_2OMe	114-116
336	2-Br-4-Cl-Ph	CH(Et)CH_2OMe	133.5-135
337	4-Cl-2-Me-Ph	CH(Et)CH_2OMe	amorph.
338	4-I-2,6-Me_2-Ph	CH(Et)CH_2OMe	148.5-150
339	4-NMe_2-2,6-$(Me)_2$-Ph	CH(Et)CH_2OMe	144-146
340	2-Cl-4-Me-Ph	CH(Et)CH_2OMe	88-89
341	2-Br-4-OMe-Ph	CH(Et)CH_2OMe	118-120
342	2-Me-4-CH_2OMe-Ph	CH(Et)CH_2OMe	oil
343	2,4,6-Me_3-Ph	CH(Et)CH_2OEt	127-130
344	2-Cl-4,6-Me_2-Ph	CH(Et)CH_2OEt	61-62
345	4-Br-2,6-Me_2-Ph	CH(Et)CH_2OEt	104-107
346	2,4-Me_2-Ph	CH(Et)CH_2OEt	oil
347	2-Br-4-Me-Ph	CH(Et)CH_2OEt	100-102
348	2,4,6-Me_3-Ph	CH(Et)CH_2OEt	94-96.5
349	2,4,6-Me_3-Ph	CH(C_3H_7)CH_2OMe	136-138
350	2-Cl-4,6-Me_2-Ph	CH(C_3H_7)CH_2OMe	amorph.
351	4-Br-2,6-Me_2-Ph	CH(C_3H_7)CH_2OMe	139-140.5
352	2,4-Me_2-Ph	CH(C_3H_7)CH_2OMe	oil
353	2-Br-4-Me-Ph	CH(C_3H_7)CH_2OMe	100.5-102
354	2,4,5-Me_3-Ph	CH(C_3H_7)CH_2OMe	122-124
355	2,4,6-Me_3-Ph	CH($CHMe_2$)CH_2OMe	94-96.5
356	2-Cl-4,6-Me_2-Ph	CH($CHMe_2$)CH_2OMe	155-156
357	4-Br-2,6-Me_2-Ph	CH($CHMe_2$)CH_2OMe	156-159
358	2,4-Me_2-Ph	CH($CHMe_2$)CH_2OMe	99-103

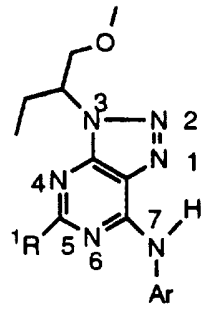
359	2-Br-4-Me-Ph	$CH(CHMe_2)CH_2OMe$	93-95
360	2,4,5-Me_3-Ph	$CH(CHMe_2)CH_2OMe$	130-131
361	2,4,6-Me_3-Ph	CH(sec-Bu)CH_2OMe	168-170.5
362	2-Cl-4,6-Me_2-Ph	CH(sec-Bu)CH_2OMe	136-139
363	4-Br-2,6-Me_2-Ph	CH(sec-Bu)CH_2OMe	139-142
364	2,4-Me_2-Ph	CH(sec-Bu)CH_2OMe	85-87
365	2-Br-4-Me-Ph	CH(sec-Bu)CH_2OMe	78.5-80
366	2,4,5-Me_3-Ph	CH(sec-Bu)CH_2OMe	150-153
367	2,4,6-Me_3-Ph	CH(isoBu)CH_2OMe	126.6-129
368	2-Cl-4,6-Me_2-Ph	CH(isoBu)CH_2OMe	103-10
369	4-Br-2,6-Me_2-Ph	CH(isoBu)CH_2OMe	127.5-130
370	2,4-Me_2-Ph	CH(isoBu)CH_2OMe	amorph.
371	2-Br-4-Me-Ph	CH(isoBu)CH_2OMe	99-100.5
372	2,4,5-Me_3-Ph	CH(isoBu)CH_2OMe	134-138
373	2-Cl-4,6-Me_2-Ph	$CH(CH_2OMe)_2$	98-99
374	4-Br-2,6-Me_2-Ph	$CH(CH_2OMe)_2$	115-116
375	4-OMe-2-Ph-Ph	$CH(CH_2OMe)_2$	55-57
376	3-Br-2,4,6-Me_3-Ph	$CH(CH_2OMe)_2$	151-152
377	4-Br-2,6-Et_2-Ph	$CH(CH_2OMe)_2$	154-155
378	2,4,6-$(Me)_3$-Ph	$CH(CH_2OMe)_2$	136-137
379	4-Br-2-Me-Ph	$CH(CH_2OMe)_2$	104-108
380	2-Br-4-Cl-Ph	$CH(CH_2OMe)_2$	123-125
381	2,4-Cl_2-Ph	$CH(CH_2OMe)_2$	87.5-90
382	4-NMe_2-2-Me-Ph	$CH(CH_2OMe)_2$	159-162
383	4-Cl-2-Me-Ph	$CH(CH_2OMe)_2$	100-102
384	4-I-2-Me-Ph	$CH(CH_2OMe)_2$	116-117.5
385	2,6-Me_2-4-I-Ph	$CH(CH_2OMe)_2$	amorph.
386	2-NMe_2-4-Me-Ph	$CH(CH_2OMe)_2$	100-102
387	2-Br-4-Me-Ph	$CH(CH_2OMe)_2$	106-108
388	2-Cl-4-Me-Ph	$CH(CH_2OMe)_2$	114-115
389	4-NMe_2-2,6-$(Me)_2$-Ph	$CH(CH_2OMe)_2$	71-73
390	2-Br-4-OMe-Ph	$CH(CH_2OMe)_2$	127-128
391	2-Br-4-NMe_2-Ph	$CH(CH_2OMe)_2$	139-141
392	2-Me-4-CH_2OMe-Ph	$CH(CH_2OMe)_2$	oil
393	2,4,6-Me_3-Ph	CH(Et)CH_2Ph	amorph.
394	2,4,6-Me_3-Ph	2-OMe-6-Me-Ph	202-205
395	2,4,6-Me_3-Ph	CH(Et)CH_2OH	amorph.

	396	2,4,6-Me_3-Ph	CH(Me)isoBu	126-127
	397	2,4,6-Me_3-Ph	CH(Me)isoPr	161-162
	398	2,4,6-Me_3-Ph	cyclopentyl	174-175
	399	2,4,6-Me_3-Ph	cyclohexyl	198-199
5	400	2,4,6-Me_3-Ph	4-methylcyclohexyl	178-180

Note: (+), (-), (R) or (S) denotes respective isomers

10 **Table 6**

3*H*-1,2,3-triazolo[4,5-d]pyrimidines:



Ex. No.	Ar	R^1	m.p. (°C)
401	2,4,6-Me_3-Ph	H	146-147
402	4-Br-2,6-Me_2-Ph	H	139-140
403	2,4,6-Me_3-Ph	CF_3	176-177
404	4-Br-2,6-Me_2-Ph	CF_3	183-184
405	2-Cl-4,6-Me_2-Ph	CF_3	174-175
406	2,4-Cl_2-6-Me-Ph	CF_3	160-161
407	2-Cl-4,6-Me_2-Ph	C_2H_5	111-112
408	2-Cl-4,6-Me_2-Ph	$MeOCH_2$	87-88

Example 409

6-[*N*-(2-chloro-4,6-dimethylphenyl)]-9-[(1-methoxymethyl)propyl]-2-methyl-9H-purin-6,8-diamine:

Part A: 2-methyl-4-chloro-6-(1-methoxymethyl) propylamino-5-aminopyridine (450 mg, 1.84 mmol) was

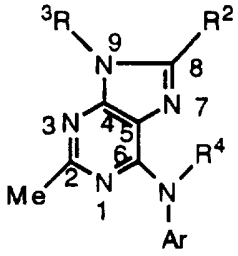
reacted with cyanogen bromide (234 mg, 2.2 mmol) in refluxing methanol for 24 h. The solvent was removed *in vacuo* and the resulting crude oil was taken up in ethyl acetate and washed 3 times with saturated aqueous $NaHCO_3$. The organic layer was dried then stripped *in vacuo* and the crude product was chromatographed on silica gel (20 g, ethyl acetate neat) providing 240 mg (48%) of 8-amino-6-chloro-9-[(1-methoxymethyl)propyl-2-methyl-9H-purine.

Part B: The product from part B (50 mg, 0.20 mmol) was treated with 2-chloro-4,6-dimethylaniline (30 mg, 0.20 mmol) in refluxing 1.0 N HCl for 24 h. The reaction was cooled then poured into saturated aqueous $NaHCO_3$ and extracted (3 times 50 ml) with ethyl acetate. The organic fractions were combine, dried and stripped *in vacuo*. The resulting crude product was chromatographed on silica gel (20 g, ethyl acetate neat) providing 55 mg (71%) of the title compound. Anal. Calcd. for $C_{19}H_{25}N_6OCl$: C, 58.76; H, 6.44; N, 21.65. Found: C, 58.50; H, 6.32; N, 21.72.

The compounds of Table 7 can be made by the methods exemplified in Examples 209-211 and 409.

Table 7

9*H*-imidazo[4,5-d]pyrimidines:



Ex. No.	Ar	R^2	R^3	m.p. (°C)
410	2,4,6-(Me)3-Ph	H	$CH(Et)CH_2OCH_3$	212-213
411	2,4,6-(Me)3-Ph	NH_2	$CH(Et)CH_2OCH_3$	oil
412	2-Cl-4,6-(Me)2-Ph	NH_2	$CH(CH_2OCH_3)_2$	oil
413	2,4,6-(Me)3-Ph	NH_2	$CH(CH_2OCH_3)_2$	oil

Example414

(S)-(-)-*N*-(2-chloro-4,6-dimethylphenyl]-6-methyl-1-(1-methoxymethyl-3-methoxypropyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

Part A: L-Dimethyl aspartate hydrochloride (5 g, 25.3 mmol) and triphenylmethyl chloride (7.65 g, 27.5 mmol) were suspended in dry CH_3CN (50 mL) at 0 °C. To that Et_3N (4.5 mL, 32.3 mmol) was added dropwise, followed by N-methylmorpholine (2.5 mL, 27.5 mmol). The mixture was stirred at 0 °C for 1 h and at 25 °C for 30 min. Then it was partitioned between EtOAc (200 mL) and water (50 mL) and the organic extract was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and stripped in vacuo. The product, diethyl N-triphenylmethyl aspartate, was >90% clean by NMR analysis.

NMR($CDCl_3$)δ 7.16-7.51 (m, 15 H), 3.68 (s, 3H), 3.66-3.74 (m, 1H), 3.26 (s, 3H), 2.93 (d, 1H, J=9.9Hz), 2.63-2.69 (dd, 1H, J_1=14.6, J_2=5.1 Hz), 2.48-2.55 (dd, 1H, J_1=14.6 Hz, J_2=7 Hz).

Part B: (S)-Diethyl N-triphenylmethyl aspartate (~25 mmol) was dissolved in dry THF (150 mL) and cooled to 0 °C. To that a 1 M solution of of $LiAlH_4$ in THF (50 mL, 50 mmol) was added dropwise and the reaction was stirred for 2 h and allowed to warm to 25 °C. Then it was cooled and quenched with water (5 mL) and 1 N NaOH (4 mL), diluted with ether (200 mL) and the precipitated solids were filtered off. The filtrate was concentrated in vacuo to give the product, 2-N-triphenylamino-1,4-butane diol (>90% clean by NMR analysis).
NMR($CDCl_3$)δ 7.17-7.57 (m, 15H), 3.68-3.77 (m, 1H), 3.56-3.63 (m, 1H), 3.19 (d, 1H, J=8.8 Hz), 2.76-2.86 (m, 2H), 2.2-2.7 (br, 3H), 1.54-1.63 (m, 1H), 1.36-1.54 (m, 1H).

Part C: (S)-2-N-triphenylamino-1,4-butane diol (~25 mmol) dissolved in dry THF (50 mL) was added into a suspension of NaH 60% in oil (2.34 g, 58.5 mmol) in dry THF (50 mL) at 0 °C, and the mixture was stirred at 9 °C for 30 min and at 25 °C for 1 h. Then it was cooled in an ice bath and CH_3I (3.6 mL, 58.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 30 min and at 25 °C for 2 h, the excess NaH was quenched with water and the THF was stripped off. The residue was partitioned between EtOAc (200 mL) and water (50 mL) and the organic extract was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and stripped in vacuo. The product, 2-N-triphenylamino-1,4-dimethoxy butane was >90% clean by NMR analysis.
NMR($CDCl_3$)δ 7.15-7.59 (m, 15 H), 3.34-3.41 (m, 1H), 3.22 -3.30 (m, 1H), 3.24 (s, 3H), 3.03 (s, 3H), 2.86 (dd, 1H, J_1=9.5 Hz, J_2=3.3 Hz), 2.65-2.75 (m, 1H), 2.4-2.46 (br, 1H), 2.30-2.35 (m, 1H), 2.57-2.8 (m, 2H).

Part D: (S)-2-N-Triphenylamino-1,4-dimethoxy butane (~25 mmol) was dissolved in a mixture of CH_2Cl_2 (100 mL) and methanol (50 mL) and 1 M HCl in ether was added (50 mL). The reaction was stirred at 25 °C for 16 h, the solvent was stripped off and the residue was washed with 1:1 ether/hexane (3x50 mL). The remaining oil, 2-amino-1,4-dimethoxybutane hydrochloride, was dried under vacuum (3.87 g, 88%).
NMR($CDCl_3$)δ 8.2-8.5 (br, 3H), 3.5-3.7 (m, 5H), 3.41 (s, 3H), 3.36 (s, 3H), 2.05-2.2 (m, 1H), 1.90-2.01 (m, 1H).

Part E: (S)-6-Methyl-3-nitro-4-(1-methoxymethyl-3-methoxypropylamino) pyridone: 1-methoxymethyl-3-methoxypropylamine (4.19 g, 22.3 mmol), and 4-chloro-6-methyl-3-nitropyridone (3.87 g, 22.3 mmol) were mixed in CH_3CN (70 mL) and diisopropyl-ethylamine (9.4 mL, 53.6 mmol) was added. The reaction was stirred at 25 °C for 16 h and at reflux for 2.5 h. The solvent was stripped off and the residue was dissolved in CH_2Cl_2 (150 mL) and the CH_2Cl_2 was washed with water (80 mL). The water was extracted with CH_2Cl_2 (50 mL) and the combined organic extracts were dried ($MgSO_4$) and stripped in vacuo. The residue was crystallized from EtOAc and washed with 40% EtOAc/hexanes to give the product, (4.8 g, 75%).
NMR(DMSO)δ 9.13 (d, 1H, J=8.8 Hz), 5.9 (s, 1H), 3.92-4.02 (m, 1H), 3.20-3.25 (m, 2H), 3.28-3.4 (m, 2H), 3.25 (s, 3H), 3.18 (s, 3H), 2.09 (s, 3H), 1.65-1.90 (m, 2H).

Part F: (S)-2-Chloro-6-methyl-3-nitro-*N*-(1-methoxymethyl-3-methoxypropyl)pyridin-4-amine: 4-[3-(1,4-dimethoxybutyl)amino]-6-methyl-3-nitropyridone (4.8 g, 16.82 mmol) was dissolved in $POCl_3$ (50 mL) and stirred at 25 °C for 40 h. Then the reaction was poured into ice/water (500 mL), allowed to react, neutralized with solid $NaHCO_3$ after EtOAc was added (150 mL) and

extracted with EtOAc (2x300 mL). The EtOAc was dried ($MgSO_4$) and stripped in vacuo to give the product. NMR ($CDCl_3$)δ 7.08 (d, 1H, J=7.7 Hz), 6.65 (s, 1H), 3.85-3.95 (m, 1H), 3.30-3.50 (m, 4H), 3.38 (s, 3H), 3.33 (s, 3H), 2.43 (s, 3H), 1,80-2.02 (m, 2H).

Part G: (S)-3-amino-2-chloro-4-*N*-(1-methoxymethyl-3-methoxypropyl)-6-methyl-pyridin-4-amine: 2-Chloro-6-methyl-3-nitro-*N*-(1-methoxymethyl-3-methoxypropyl)pyridin-4-amine (~16.82 mmol) was heated at reflux with Fe powder (10 g) in methanol (120 mL) in the presence of glacial acetic acid (10 mL) for 2 h. Then the iron was filtered through celite, the celite was washed with methanol(80 mL) and the filtrate was stripped in vacuo. The residue was dissolved in 10% HCl (120 mL) and EtOAc was added (160 mL). The mixture was neutralized with solid $NaHCO_3$ and the aqueous layer was extracted with EtOAc (2x100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and stripped in vacuo (4.1 g).
NMR($CDCl_3$)d 6.4 (s, 1H), 5.2-5.35 (br s, 1H), 3.70-3.80 (m, 1H), 3.2-3.8 (m, 6H), 3.38 (s, 3H), 3.33 (s, 3H), 2.42 (s, 3H), 1.8-2.0 (m, 2H).

Part H: (S)-4-chloro-1-(1-methoxymethyl-3-methoxypropyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridine: 3-amino-2-chloro-6-methyl-4-*N*-(1-methoxymethyl-3-methoxypropyl)pyridin-4-amine (4.1 g, 14.98 mmol) was dissolved in a mixture of CH_2Cl_2 (40 mL) and 50% acetic acid (40 mL) and cooled to 0 °C in an ice bath. To that a solution of $NaNO_2$ (1.84 g, 26.86 mmol) in water (10 mL) was added dropwise and the reaction was stirred at 0 °C for 30 min and at 25 °C for 1.5 h. Then the acetic acid was neutralized with solid $NaHCO_3$ and water (80 mL) was added. The mixture was extracted with EtOAc (2x100 mL) and the combined organic extracts were combined and washed with brine (50 mL), dried and

stripped in vacuo. The residue was chromatographed on silica gel (40% EtOAc/hexanes eluent) to give the product (4.05 g, 56% overall for the eight steps). NMR($CDCl_3$)δ 7.25 (s, 1H), 5.04-5.13 (m, 1H), 3.98 (dd, 1H, J_1=9.9 Hz, J_2=8.4 Hz), 3.84 (dd, 1H, J_1=10.2 Hz, J_2=4.4 Hz), 3.39 (dt, 1H, J_1=9.9 Hz, J_2=4.8 Hz), 3.25 (s, 3H), 3.17 (s, 3H), 2.91 (dt, 1H, J_1=9.5 Hz, J_2=4.0 Hz), 2.68 (s, 3H), 2.22-2.6 (m, 2H).

Part I: (S)-4-chloro-1-(1-methoxymethyl-3-methoxypropyl)-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridine (2.0 g, 7 mmol) and 2-chloro-4,6-dimethylaniline (1.094 g, 7 mmol) were dissolved in dry THF and cooled to 0 °C in an ice bath. To that a 1 M solution sodium hexamethyldisilazide (16 mL, 16 mmol) was added dropwise and the solution was stirred at 0 °C for 45 min. Then it was quenched with water (30 mL) and partitioned between EtOAc and water (20 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$) and stripped in vacuo. The residue was purified by silica gel chromatography (40% EtOAc/hexanes eluent) and crystallized from hexanes to give the product (2.42 g, 85%), mp 108-109 °C, [α]D25 -32.38 (c=0.200 g/dL, $CHCl_3$) 99.6% ee by chiral HPLC. This was converted to the methylsulfonate salt, mp 98-100 °C, after crystallization from ether/hexanes, [α]D25 -29.00 (c=0.200 g/dL, $CHCl_3$).

Example 414A

(R,S)-*N*-(2-chloro-4,6-dimethylphenyl]-6-methyl-1-(1-methoxymethyl-3-methoxypropyl)-1*H*-1,2,3-triazolo[4,5-c] pyridin-4-amine

Part A: (R,S)-2-Aminobutyrolactone hydrobromide (8.0 g, 44 mmol) and triphenylmethyl chloride (12.8 g, 46 mmol) were suspended in dry CH_3CN (80 mL) at 25 °C. To that Et_3N (13.6 mL, 100 mmol) was added dropwise, the

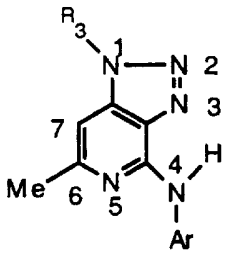
reaction mixture was stirred at 25 °C for 4 h and partitioned between EtOAc (120 mL) and water (50 mL). The organic layer was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and stripped in vacuo. The residue was recrystallized from EtOAc/hexanes to give 2-triphenylmethylamino-butyrolactone (10.5 g).

Part B: Lithium aluminum hydride (1.4 g, 36 mmol) was suspended in dry THF (50 mL) and cooled to 0 °C in an ice bath. To that a solution of 2-triphenylmethylamino-butyrolactone (11 g, 31.9 mmol) in dry THF (70 mL) was added dropwise over a period of 20 min. After the addition was over the reaction mixture was stirred at 0 °C for 1 h, at 25 °C for 3h and quenched by the sequential addition of water (2 mL) 1 N NaOH (2 mL) and water (3 mL), and diluted with ether (150 mL). The precipitated solids were filtered off and the filtrate was concentrated in vacuo to give (R,S)-2-N-triphenylamino-1,4-butanediol. This was used in the same synthetic scheme as previously described for the chiral material (Example 414, Parts C-I) to obtain the racemic material.

The compounds listed in Table 8 were prepared by the methods exemplified in Examples 221-232, 259, 414 and 414A.

Table 8

1*H*-1,2,3-triazolo[4,5-c]pyridines:



Ex. No.	R^3	Ar	m.p. (°C)
415	$CH(Et)_2$	4-Br-2,6-$(Me)_2$-Ph	191-192
416	$CH(Et)_2$	2,6-$(Me)_2$-4-SMe-Ph	172-173
417	$CH(Et)_2$	2-Cl-4,6-$(Me)_2$-Ph	171-172
418	$CH(Et)_2$	2,4-$(Cl)_2$-6-Me-Ph	164-165
419	$CH(Et)_2$	2,4-$(Me)_2$-Ph	90-91
420	$CH(Et)_2$	2-Me-4-OMe-Ph	104-105
421	$CH(Et)_2$	2-Br-4,6-$(Me)_2$-Ph	178-179
422	$CH(Et)_2$	4-CN-2,6-$(Cl)_2$-Ph	189-190
423	$CH(Et)_2$	3-Br-2,4,6-$(Me)_3$-Ph	156-157
424	$CH(Et)_2$	4-Br-2-SMe-Ph	112-114
425	$CH(Et)_2$	2-CN-4,6-Me_2-Ph	181-183
426	$CH(Et)_2$	2-Br-5-F-4-Me-Ph	132-134
427	$CH(Et)_2$	4-Br-5-F-2-Me-Ph	115-116
428	$CH(Et)_2$	2,4-Br_2-Ph	164-166
429	$CH(Et)_2$	4-Ac-2-SMe-Ph	142-144
430	$CH(Et)_2$	4-Br-2-Cl-Ph	152-153
431	$CH(Et)_2$	2,4-Cl_2-Ph	134-135
432	$CH(Et)_2$	2,4-Me2-6-SMe-Ph	135-136
433	CH(Et)n-Pr	2,4,6-$(Me)_3$-Ph	117-118
434	$CH(Et)CH_2OMe$	4-Br-2,6-$(Me)_2$-Ph	165-166
435	$CH(Et)CH_2OMe$	2-Cl-4,6-$(Me)_2$-Ph	126-127
436	$CH(Et)CH_2OMe$	3-Br-2,4,6-$(Me)_3$-Ph	117-118
437	$CH(Et)CH_2OMe$	2,4-$(Cl)_2$-6-Me-Ph	131-134
438	$CH(Et)CH_2OMe$	2-Br-4,6-$(Me)_2$-Ph	127-128
439	$CH(Et)CH_2OMe$	4-Br-2-Cl-6-Me-Ph	136-137
440	$CH(Et)CH_2OMe$	4-Br-2,6-$(Cl)_2$-Ph	119-120

441	CH(Et)CH_2OMe	2,4-$(Me)_2$-Ph	76-77
442	CH(Et)CH_2OMe	4-MeO-2-Me-Ph	76-77
443	CH(Et)CH_2OMe	2,4,5-$(Me)_3$-Ph	94-95
444	CH(Et)CH_2OMe	2-Cl-4,6-$(OMe)_2$-Ph	167-168
445	CH(Et)CH_2OMe	2,4,5-$(Cl)_3$-Ph	151-152
446	CH(Et)CH_2OMe	2,5-$(Cl)_2$-4-NO_2-Ph	157-158
447	CH(Et)CH_2OMe	2-CN-4,5-$(OMe)_2$-Ph	162-163
448	CH(Et)CH_2OMe	2-Me-4,5-$(OMe)_2$-Ph	118-119
449	CH(Et)CH_2OMe	2,6-Cl_2-4-OMe-Ph	136-137
450	CH(Et)CH_2OCH_3	4-Br-2-OMe-6-Me-Ph	159-162
451	CH(Et)CH_2OCH_3	4-Br-5-F-2-Me-Ph	111-113
452	CH(Et)CH_2OCH_3	2-CN-4,6-Me_2-Ph	154-156
453	CH(Et)CH_2OCH_3	2-OMe-4,6-Me_2-Ph	115-116
454	CH(Et)CH_2OCH_3	2-Ac-4-Cl-6-Me-Ph	127-129
455	CH(Et)CH_2OCH_3	2-Br-4,6-F_2-Ph	138-140
456	CH(Et)CH_2OCH_3	2,4,6-Me_3-Ph	119-121
457	CH(Et)CH_2OCH_3	4-Br-2-SMe-Ph	70-73
458	CH(Et)CH_2OCH_3	2,4-Br_2-Ph	119-120
459	CH(Et)CH_2OCH_3	2,4,6-Me_3-Ph	113-115
460	CH(Et)CH_2OCH_3	2,4,6-Me_3-Ph	113-115
461	CH(Et)CH_2OCH_3	2,4-Me_2-6-SMe-Ph	104-106
462	CH(Et)CH_2OCH_3	4-Br-2-Me-Ph	amorph.
463	CH(Et)CH_2OCH_3	4-I-2-Me-Ph	103-105
464	CH(Et)CH_2OCH_3	3-F-2,4,6-Me_3-Ph	amorph.
465	CH(Et)CH_2OCH_3	4-Cl-2-Me-Ph	104-105
466	CH(Et)CH_2OCH_3	4-Br-2,6-F_2-Ph	138-140
467	CH(Et)CH_2OCH_3	4-Cl-2-CN-6-Me-Ph	177-180
468	$CH(CH_2OMe)_2$	2,4,6-$(Me)_3$-Ph	115-116
469	$CH(CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph	145-146
470	$CH(CH_2OMe)_2$	2,4-$(Cl)_2$-6-Me-Ph	111-112
471	$CH(CH_2OMe)_2$	3-Br-2,4,6-$(Me)_3$-Ph	105-106
472	$CH(CH_2OMe)_2$	2,4,5-$(Me)_3$-Ph	110-111
473	$CH(CH_2OMe)_2$	2-Br-4-CH$(Me)_2$-Ph	107-108
474	$CH(CH_2OMe)_2$	2-Br-4,6-$(Me)_2$-Ph	83-84
475	$CH(CH_2OMe)_2$	2,4-$(Me)_2$-Ph	72-73
476	$CH(CH_2OMe)_2$	4-MeO-2-Me-Ph	65-67
477	$CH(CH_2OMe)_2$	4-CH$(Me)_2$-Ph	oil

478	$CH(CH_2OMe)_2$	2,5-Cl_2-4-$N(Me)_2$-Ph	110-111
479	$CH(CH_2OMe)_2$	2-Me-4,5-$(OMe)_2$-Ph	111-112
480	$CH(CH_2OMe)_2$	4-Cl-2,5-$(OMe)_2$-Ph	167-168
481	$CH(CH_2OMe)_2$	2-Cl-4,5-$(Me)_2$-Ph	169-170
482	$CH(CH_2OMe)_2$	2,6-$(Cl)_2$-4-OMe-Ph	145-146
483	$CH(CH_2OMe)_2$	4-t-Bu-2,6-$(Me)_2$-Ph	134-135
484	$CH(CH_2OMe)_2$	4-Cl-2-Me-5-NO_2-Ph	163-164
485	$CH(CH_2OMe)_2$	4-Br-2-Cl-5-Me-Ph	159-160
486	$CH(CH_2OMe)_2$	2-Cl-4-OMe-6-Me-Ph	117-118
487	$CH(CH_2OMe)_2$	4-Cl-2,5-Me_2-Ph	115-116
488	$CH(CH_2OMe)_2$	2-Cl-4-CN-6-Me-Ph	127-128
489	$CH(CH_2OMe)_2$	4-Br-2,6-$(Et)_2$-Ph	168-169
490	$CH(CH_2OMe)_2$	4-Br-2-Cl-6-Me-Ph	104-105
491	$CH(CH_2OMe)_2$	2-Cl-4,6-$(OMe)_2$-Ph	139-140
492	$CH(CH_2OMe)_2$	2-Br-4,6-$(OMe)_2$-Ph	155-156
493	$CH(CH_2OMe)_2$	5-Cl-4-NMe_2-2-OMe-Ph	110-111
494	$CH(CH_2OMe)_2$	2,4-$(Cl)_2$-5-CF_3-Ph	162-163
495	$CH(CH_2OMe)_2$	4-Cl-2-OMe-5-CF_3-Ph	161-162
496	$CH(CH_2OMe)C_2H_4OMe$	4-Cl-2-Et-6-Me-Ph	101-103
497	$CH(CH_2OMe)C_2H_4OMe$	2-F-4,6-Me_2-Ph	172-174
498	$CH(CH_2OMe)C_2H_4OMe$	2,4-Me_2-6-SMe-Ph	147-148
499	$CH(CH_2OMe)C_2H_4OMe$	2-Br-4,6-Me_2-Ph	144-147
500	$CH(CH_2OMe)C_2H_4OMe$	4-Cl-2,6-Me_2-Ph	97-100
501	$CH(CH_2OMe)C_2H_4OMe$	4-Br-2-Et-6-Me-Ph	111-113
502	$CH(CH_2OMe)C_2H_4OMe$	2,4,6-Me_3-Ph	115-116
503	$CH(CH_2OMe)C_2H_4OMe$	4-Br-2,6-Me_2-Ph	amorph.
504	$CH(CH_2OMe)C_2H_4OMe$	4-Br-2-OMe-6-Me-Ph	131-133
505	$CH(CH_2OMe)C_2H_4OMe$	2-Cl-4,6-Me_2-Ph	127-129
506	$CH(CH_2OMe)C_2H_4OMe$	2-I-4,6-Me_2-Ph	150-152
507	$CH(CH_2OMe)C_2H_4OMe$	2-Cl-4-I-6-Me-Ph	119-120
508	$CH(CH_2OMe)C_2H_4OMe$	3-F-2,4,6-Me_3-Ph	amorph.
509	$CH(CH_2OMe)C_2H_4OMe$	2-Cl-4,6-Me_2-Ph	127-129
510	$CH(CH_2OMe)C_2H_4OMe$	2-Cl-4,6-Me_2-Ph	108-109
511	$CH(CH_2OMe)C_2H_4OMe$	2-Br-6-F-4-Me-Ph	150-152
512	$CH(CH_2OMe)C_2H_4OMe$	2-Cl-5-F-4,6-Me_2-Ph	107-108
513	$CH(CH_2OMe)C_2H_4OMe$	3-F-2,4,6-Me_3-Ph	117-119
514	$CH(CH_2OMe)C_2H_4OMe$	3-F-2,4,6-Me_3-Ph	117-119

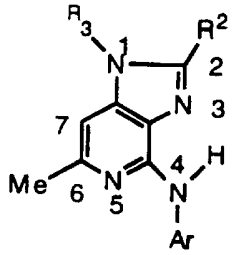
515	$CH(CH_2OMe)C_2H_4OMe$	2-Cl-5-F-4,6-Me_2-Ph	107-109
516	$CH(CH_2OMe)C_2H_4OMe$	4-Br-2,6-Me_2-Ph	-
517	$CH(CH_2OMe)C_2H_4OMe$	4-Br-2,6-Me_2-Ph	amorph.
518	$CH(CH_2OMe)C_2H_4OMe$	2,4,5-Me_3-Ph	oil
519	$CH(CH_2OMe)C_2H_4OMe$	2,4,5-Me_3-Ph	oil
520	$CH(CH_2OMe)C_3H_6OMe$	2,4,6-Me_3-Ph	128-130
521	$CH(CH_2OMe)C_3H_6OMe$	4-Cl-2,6-Me_2-Ph	114-115
522	CH(Bz)CH_2OMe	2,4,6-$(Me)_3$-Ph	55-57
523	CH(Bz)CH_2OMe	2,4-$(Cl)_2$-6-Me-Ph	64-65

Note: (+), (-), (R) or (S) denotes respective isomers.

The compounds listed in table 9 were prepared by the methods exemplified in Examples 209-211 using the intermediate from example 259, part G.

Table 9

1*H*-imidazo[4,5-c]pyridines:



Ex. No.	Ar	R^2	R^3	m.p. (°C)
524	2-Cl-4,6-$(Me)_2$-Ph	H	$CH(CH_2OCH_3)_2$	129-130
525	2-Cl-4,6-$(Me)_2$-Ph	Me	$CH(CH_2OCH_3)_2$	156-157

Example 526

This example illustrates an alternative method for making the compound of Example 32.

Part A. (±)-1-Methoxy-2-butanol Methanesulfonate (1). A solution of 1-methoxy-2-butanol (52.08 g, 57.23 mL, 0.5 mol) and Et_3N (108.2 mL, 0.75 mol, 1.5 equiv) in CH_2Cl_2 (500 mL) was treated dropwise with methanesulfonyl chloride (68.73 g, 46.44 mL, 0.6 mol, 1.2 equiv) at 0 °C under N_2. The reaction mixture was warmed to 25 °C and stirred at 25 °C for an additional 4 h before being quenched with H_2O (300 mL). The two layers were separated, and the aqueuos was extracted with CH_2Cl_2 (3 x 100 mL). The combined CH_2Cl_2 extracts were washed with H_2O (2 x 200 mL) and saturated aqueuos NaCl (200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dried enough in vacuo to afforded the desired mesylate **1** (85-90.0 g, 91 g theoretical, 93-98%) as a pale-yellow oil, which was pure enough and directly used in the next reaction without further purification.

The analytically pure sample of **1** was obtained by silicon-gel column chromatography purification and **1** was obtained as a colorless oil.

Part B. (±)-1-Methoxy-2-butyl Azide (2). A solution of crude mesylate **1** (90.0 g, 0.495 mol) in DMF (500 mL) was treated with NaN_3 (48.22g, 0.74 mol, 1.5 equiv) at 25 °C under N_2. The resulting reaction mixture was warmed to 55-60 °C for 6-8 h with stirring before being quenched with H_2O (500 mL). The pale-yellow solution was then extracted with EtOAc or Et_2O (4 x 200 mL). The combined EtOAc (or Et_2O) extracts were washed with H_2O (3 x 500 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual solution was found to contain desired azide **2** (60.3 g, 64.5 g theoretical,

94%), which was found to be pure enough and directly used in the following reaction without further purification.

The analytically pure sample of **2** was obtained by SiO_2 column chromatography purification as a colorless, low boiling-point liquid.

Part C. (±)-4-Amino-5-carbamoyl-1-(1-methoxy-2-)butyl-1*H*-1,2,3-triazole (3). A suspension of cyanoacetamide (46.5 g, 0.553 mol, 1.2 equiv) in absolute EtOH (200 mL) was treated with EtONa (62.73 g, 0.922 mol, 2.0 equiv) at 25 °C under N_2, and the resulting mixture was warmed to reflux for 15 min under N_2. The cooled mixture was then treated with a solution of 1-methoxy-2-butyl azide **2** (59.5 g, 0.467 mol) in Et_2O and the mixture was diluted with additional EtOH (260 mL) at 25 °C. The resulting reaction mixture was warmed to reflux and stirred for 6-8 h at reflux before being cooled to room tempearture. The solvent was removed in vacuo, and the residue was treated with H_2O (300 mL) and EtOAc (300 mL). The two layers were separated, and the aqueous was extracted with EtOAc (5 x 100 mL). The combined EtOAc extracts were washed with saturated aqueous NaCl (50 mL), dried in vacuo, and concentrated in vacuo. The residual yellow solid was directly recrystalized from MeOH (100-150 mL) to afford the desired 1,2,3-triazole **3** (70.7 g, 98.2 g theoretical, 72%) as white crystals.

Part D. (±)-9-(1-Methoxy-2-)butyl-2-methyl-8-azaadenine (4). Method A: A solution of **3** (10.65 g, 0.05 mol) in absolute EtOH (50 mL) was treated with EtONa (6.8 g, 0.1 mol, 2.1 equiv) and EtOAc (8.8 g, 10.0 mL, 0.5 mol, 10 equiv) at 25 °C under N_2, and the resulting reaction mixture was warmed to reflux with stirring for 6-8 h before being quenched with H_2O (50 mL). The solution was then concentrated in vacuo to

remove most of EtOH. The residue was treated with H_2O (50 mL), acidified with concentrated HCl (pH 6-7), and extracted with EtOAc (5 x 50 mL). The combined EtOAc extracts were washed with saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual pale-yellow solid was directly recrystalized from 80% EtOAc-Hexane or EtOH to afford 8-azaadenine **4** (8.4 g, 11.85 theoretical, 71%) as white crystals.

Method B: A suspension of cyanoacetamide (47.1 g, 0.561 mol, 1.2 equiv) in absolute EtOH (200 mL) was treated with EtONa (95.3 g, 1.4 mol, 3.0 equiv) at 25°C under N_2, and the resulting mixture was warmed to reflux for 15 min. under N_2. The cooled mixture was then treated with a solution of 1-methoxy-2-butyl azide **2** (60.3 g, 0.467 mol) in EtOAc (or Et_2O) in absolute EtOH (170 mL) at 25 °C, and the resulting reaction mixture was warmed to reflux and stirred 4-6 h at reflux before being cooled to RT. EtOAc (120 mL) was added to the reaction mixture, and the resulting mixture was warmed to reflux for an additional 6-10 h. The cooled reaction mixture was treated with H_2O (200 mL), and the solution was concentrated in vacuo to remove most of EtOH. The residue was treated with H_2O (100 mL) and acidified with concentrated HCl (pH 6-7), and extracted with EtOAc (6 x 150 mL). The combined EtOAc extracts were washed with saturated aqueous NaCl (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual pale-yellow solid was recrystalized from 80% EtOAc-Hexane (or EtOH) to afford 8-azaadenine **4** (70.8 g, 110.7 g theoretical, 64% for two steps) as white crystals.

Part E. (±)-4-Chloro-1-(1-methoxy-2-)butyl-2-methyl-8-azaadenine (5). Method A: A solution of **4** (6.78 g, 0.017 mol) in $POCl_3$ (30 mL) was warmed to reflux for 3 h. The excess $POCl_3$ was removed in vacuo, and the residue was treated with H_2O (50 mL) and EtOAc (50 mL). The two layers were separated, and the aqueous

was extracted with EtOAc (3 x 50 mL). The combined EtOAc extracts were washed with H_2O (2 x 50 mL) and saturated aqueous NaCl (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 10-20% EtOAc-Hexane gradient elution) afforded **5** (6.65 g, 7.30 g theoretical, 91%) as a colorless oil, which solidified upon standing in vacuo.

Method B: A solution of **4** (170 mg, 0.72 mmol) was treated with $POCl_3$ (2 mL) and *N,N*-diethylaniline (0.5 mL) at 25 °C under N_2, and the resulting mixture was warmed to reflux for 4-6 h. The excess $POCl_3$ was removed in vacuo, and the residue was directly purified by flash chromatography (SiO_2, 10-20% EtOAc-Hexane gradient elution) to afford **5** (159 mg, 184 mg theoretical, 86%) as a colorless oil, which solidified in vacuo. The product obtained by Method B was identical in all comparable respects with that obtained from Method A.

Part F. (±)-1-(1-Methoxy-2-)butyl-2-methyl-4-[(2,4,6-trimethyl)phenyl]amino-8-azaadenine (6).

A solution of **5** (7.0 g, 0.0274 mol) in toluene (50 mL) was treated with 2,4,6-trimethylphenyl amine (8.1 g, mL, 0.06 mol, 2.2 equiv) at 25 °C under N_2. The resulting reaction mixture was warmed to reflux for 6-8 h under N_2. The white solid (2,4,6-trimethylaniline HCl salt) was filtered and the solid was washed with toluene (10-20 mL). The filtrate was concentrated in vacuo. The residual pale-yellow solid was recrystalized from 30% EtOAc-Hexane to afford the title compound **6** (7.9 g, 9.7 g theoretical, 81%) as white crystals.

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 was performed as described by G. Battaglia et al. *Synapse* **1**:572 (**1987**). Briefly, assays were carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6}m) and 0.8

mg original wet weight tissue (approximately 40-60 mg protein). Reactions were 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) was added to each tube prior to separation. The separation of [32P]cAMP from [32P]ATP was performed by sequential elution over Dowex and alumina columns. Recovery was consistently greater than 80%.

Some compounds of this invention were tested in this assay and found to be active.

In vivo Biological Assay

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

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

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

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be

administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

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

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

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

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but

not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

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

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

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

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

Capsules

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

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

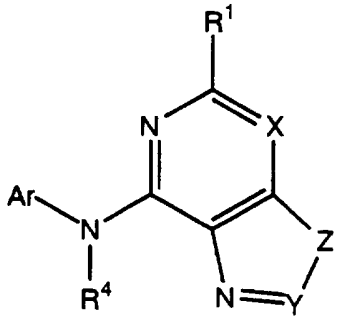
Tablets

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

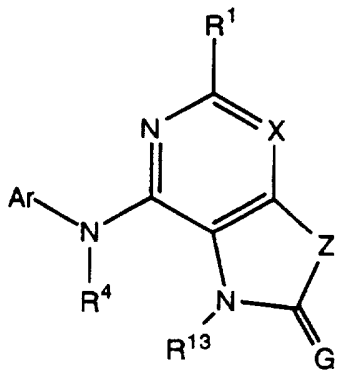
The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Claims:

1. A CRF antagonist compound of formula I or formula II:



I



II

or a pharmaceutically acceptable salt or pro-drug form thereof, wherein:

X is N or CR^1;

Y is N or CR^2;

Z is NR^3, O, or $S(O)_n$;

G is O or S;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each optionally substituted with 1 to 5 R^5 groups;

R^1 is independently at each occurrence H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, NR^9COR^{10}, $-OR^{11}$, SH or $-S(O)_nR^{12}$;

R^2 is H, C_1-C_4 alkyl, C_1-C_6 cycloalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl or C_4-C_{12} cycloalkylalkyl each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-CONR^6R^7$, aryl, heteroaryl and heterocyclyl, where the aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

R^4 is H, C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl, allyl, or propargyl is optionally substituted with C_3-C_6 cycloalkyl and where C_1-C_4 alkyl is optionally substituted with, $-OR^7$, $-S(O)_nR^{12}$ or $-CO_2R^7$;

R^5 is independently at each occurrence C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NO_2$, halo, -CN, C_1-C_4 haloalkyl, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, $-CO(NOR^9)R^7$, CO_2R^7, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted

with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, CO_2R^7, $-CO(NOR^9)R^7$, or $-S(O)_nR^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

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

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

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

provided that R^4 in formula I is not H:

(a) when X is N, Y is N, Z is NR^3, R^1 is H, R^3 is H or benzyl, and Ar is p-methylphenyl;

(b) when X is N, Y is N, Z is NR^3, R^1 is butyl, R^3 is benzyl, and Ar is phenyl;

(c) when X is N, Y is CH, Z is NR^3, R^3 is methyl, R^1 is H, and Ar is phenyl or 2-fluorophenyl;

(d) when X is N, Y is CH, Z is NR^3, R^3 is methyl, R^1 is Cl and Ar is phenyl;

(e) when X is N, Y is CH, Z is NR^3, R^1 is Cl, R^3 is benzyl, and Ar is phenyl or substituted phenyl;

(f) when X is N, Y is CH, Z is NR^3, R^3 is p-methylbenzyl, and Ar is phenyl;

(g) when X is N, Y is CR^2, Z is NR^3, R^2 is CH_3, R^3 is H, and Ar is phenyl or phenyl substituted with methyl, ethyl, isopropyl, fluoro or chloro;

(h) when X is N, Y is N, Z is NR^3, R3 is cyclopropylmethyl, R1 is H, and Ar is 2-bromo-4-isopropylphenyl, or

(i) when X is N, Y is N, Z is S, R^1 is H, and Ar is 2-bromo-4-isopropylphenyl.

2. A CRF antagonist compound of claim 1 or a pharmaceutically acceptable salt or pro-drug form thereof, wherein:

X is N or CR^1;

Y is N or CR^2;

Z is NR^3, O, or $S(O)_n$;

G is O or S;

Ar is phenyl, pyridyl, each optionally substituted with 1 to 3 R^5 groups;

R^1 is independently at each occurrence H, C_1-C_4 alkyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, $-OR^{11}$ or $-S(O)_nR^{12}$;

R^2 is H, C_1-C_4 alkyl, C_1-C_6 cycloalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, C_1-C_4 haloalkyl, $-OR^7$ or $-S(O)_nR^{12}$;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl or C_4-C_{12} cycloalkylalkyl each optionally substituted with 1 to 3 substituents

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

R^4 is H, C_1-C_4 alkyl, allyl, or propargyl;

R^5 is independently at each occurrence C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_8 cycloalkylalkyl, $-NO_2$, halo, $-CN$ C_1-C_4 haloalkyl, $-NR^6R^7$, COR^7 $-OR^7$, $-CONR^6R^7$, $-CO(NOR^9)R^7$, CO_2R^7, or $-S(O)_nR^7$, where C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, $-CN$, $-NR^6R^7$, COR^7, $-OR^7$, $-CONR^6R^7$, CO_2R^7, $-CO(NOR^9)R^7$, or $-S(O)_nR^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

aryl is phenyl or naphthyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, cyano, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^8$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{12}$, and $-NR^6R^7$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, halo, cyano, $-OR^7$, $-S(O)_nR^{12}$, $-CO_2R^8$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{12}$, and $-NR^6R^7$;

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

3. A CRF antagonist compound of claim 1 selected from the group consisting of:

N-[2-bromo-4-(1-methylethyl)phenyl]-5-methyl-3-propyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1methylethyl)phenyl]-N-ethyl-5-methyl-3-propyl-3H - 1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-{2-bromo-4-(1-methylethyl)phenyl]-3-butyl-N-ethyl-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-3-(cyclopropylmethyl)-N-ethyl-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methyl)ethylphenyl]-5-methyl-3-[(1-methoxymethyl)-2-methoxyethyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-3-(2-methoxyethyl)-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-2-bromo-4-(1-methylethyl)phenyl]-N-ethyl-3-(2-methoxyethyl)-5-methyl-3H-1,2,3-triazoloi[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-N-ethyl-3-(3-methoxypropyl)-5-methyl-3H-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

(+/-)-N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-(1-methoxymethyl)propyl]-5-methyl-3H-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

(+/-)-N-[2-bromo-4-(1-methylethyl)phenyl]-N-ethyl-3-[1-(1-methoxymethyl)propyl]-5-methyl-3H-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

(S)-N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-(1-methoxymethyl)-2-phenylethyl]-5-methyl-3H-1,2,3-triazolo[4,5-d] pyrimidin-7-amine

(S)-methyl 7 - [2-bromo-4-(1-methylethyl)phenyl]-5-methyl-a-2-(methylthio)ethyl]3H-1,2,3-triazolo[4,5-d]pyrimidine-3-acetate

(+/-)-N-[2-bromo-4-(1-methylethyl)phenyl]3-1-ethylpentyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-[2-bromo-4-(1-methylethyl)phenyl]-N-ethyl-3-[1-ethylpentyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-propylbutyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-butylpentyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-ethylbutyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-7-[2-bromo-4-(1-methylethyl)phenyl]-5-methyl-a-propyl-3H-1,2,3-triazolo[4,5-d]pyrimidine-3-ethanol

N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-ethylpropyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-N-ethyl-3-[1-ethylpropyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-(2-bromo-4,6-dimethylphenyl)-5-methyl-3-[1-propylbutyl]-3H-1,2,3-triazolo[4,5-pyrimidin-7-amine

5-methyl-N-[4-(1-methylethyl-2-(methylthio)phenyl]-3-[1-propylbutyl]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(trifluoromethyl)phenyl)]-5-methyl-3-[1-propylbutyl]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4,6-(dimethoxy)phenyl)]-5-methyl-3-[1-propylbutyl]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2,6-dimethyl-4-(methylthio)phenyl)]-5-methyl-3-[1-propylbutyl]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-(4-acetyl-2-bromophenyl)-3-[1-ethylpropyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-(4acetyl-2-bromophenyl)-3-[1-(1-methoxymethyl)propyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-(4-bromo-2,6-dimethylphenyl)-3-[1-(1-methoxymethyl)propyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-[2,6-dimethyl-4-(methylthio)phenyl]-3-[1-(1-methoxymethyl)propyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-(2-bromo-4,6-dimethoxyphenyl)-3-[1-(1-methoxymethyl)propyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-(2-chloro-4,6-dimethoxyphenyl)-3-[1-(1-methoxymethylpropyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-3-[1-(1-methoxymethyl) propyl]-5-methyl-N-(2,4,6-trmethylphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-ethyl-3-[1-(1-methoxy-methyl)propyl]-5-methyl-N-(2,4,6-trimethylphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

3-[1-(1-ethyl)propyl]-5-methyl-N-(2,4,6-trimethylphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-3-[1,(1-ethyl)butyl]-5-methyl-N-(2,4,6-trimethylphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-3-[1-(1-ethyl)pentyl]-5-methyl-N-(2,4,6-trimethylphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidine-7-amine

5-methyl-3-[1-(1-propylbutyl]-N-(2,4,6-trimethylphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

3-(2-methoxyethyl)-5-methyl-N-(2,4,6-trimethylphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-ethyl-3-(2-methoxyethyl)-5-methyl-N-(2,4,6-trimethylphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-(2-Methyl-4-bromophenyl)-3-[1-(1-propyl)butyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-3-[1-(1-ethyl)butyl]-5-methyl-N-(2-methyll-4-bromophenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-(4-bromo-2-methylphenyl)-3-[1-(1-methoxymethyl)propyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-3-[1-(1-ethyl)pentyl]-5-methyl-N-[2,4,6-trimethyl)-3-pyridyl-]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-ethyl-3-[1-(1-ethyl) pentyl]-5-methyl-N-[2,4,6-trimethyl)-3-pyridyl-]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-3-[1-(1-ethyl)butyl]-5-methyl-N-[(2,4,6-trimethyl)3-pyridyl-]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-ethyl-3-[1-(1-ethyl)butyl]-5-methyl-N-[2,4,6-trimethyl)-3-pyridyl-]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amin

3-[1-(1-propyl)butyl]-5-methyl-N-[(2,4,6-trimethyl)-3-pyridyl-]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-ethyl-3-[1-(1-propyl) butyl]-5-methyl-N-[2,4,6-trimethyl)-3-pyridyl-]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-3-[1-(1-methoxymethyl) propyl]-5-methyl-N-[2,4,6-trimethyl)-3-pyridyl-]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

(+/-)-N-ethyl-3-[1-(1-methoxy methyl) propyl)-5-methyl-N-[(2,4,6-trimethyl-3-pyridyl-]-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-2,4-dibromophenyl)-5-methyl-3-(1-propyl)butyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[4-acetyl-2-bromphenyl]-5-methyl-3-(1-propyl)butyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-3-[1-(N,N-dimethylamino-methyl)butyl]-5-methyl-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-2-methyl-9-(1-propylbutyl)-9H-purin-6-amine

(+/-)-N-[2-bromo-4-(1-methylethyl)phenyl]-9-(1-ethylpentyl)-2-methyl-9H-purin-6-amine

(+/-)-N-[2-bromo-4-(trifluoromethyl)phenyl]-9-1-(methoxymethyl)propyl]-2-methyl-9H-purin-6-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-N-ethyl-5-methyl-[1,2,3]thiadiazolo[5,4-d]pyrimidin-7-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-1-(1-ethylpropyl)-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

N-(2-bromo-4,6-dimethoxyphenyl)-1-(1-ethylpropyl)-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

N-(2-chloro-4,6-dimethoxyphenyl)-1-(1-ethylpropyl)-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

N-(2-bromo-4,6-dimethoxyphenyl)-6-methyl-1-(1-propylbutyl)-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

N-(2-chloro-4,6-dimethoxyphenyl)-6-methyl-1-(1-propylbutyl)-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

(+/-)-N-[2-bromo-4-(1-methylethyl)phenyl]-1-(1-ethylpentyl)-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

(+/-)-N-(2-bromo-4,6-dimethoxyphenyl)-1-(1ethylpentyl)-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

(+/-)-N-(2-chloro-4,6-dimethoxyphenyl)-1-(1-ethylpentyl)-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

N-[2-bromo-4-(1-methylethyl)phenyl]-6-methyl-1-(1-propylbutyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

N-[4-1-methylethyl)-2-sulfonylmethylphenyl]-6-methyl-1-(1-propylbutyl)-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

N-[4-(4-acetyl-2-bromophenyl]-6-methyl-1-(1-propyl-butyl)-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine

N-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-methoxyethyl]-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

Mesylate salt of N-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-methoxyethyl]-6-methyl-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

6-[*N*-(2-chloro-4,6-dimethylphenyl)]-9-[(1-methoxymethyl)propyl]-2-methyl-9H-purin-6,8-diamine

(S)-(-)-*N*-(2-chloro-4,6-dimethylphenyl]-6-methyl-1-(1-methoxymethyl-3-methoxypropyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine

(R,S)-*N*-(2-chloro-4,6-dimethylphenyl]-6-methyl-1-(1-methoxymethyl-3-methoxypropyl)-1*H*-1,2,3-triazolo[4,5-c]pyridin-4-amine.

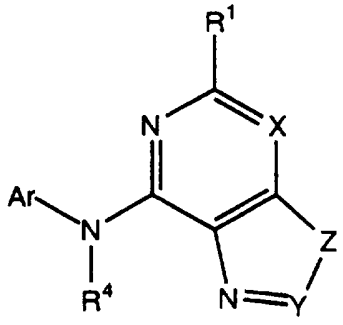
4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a

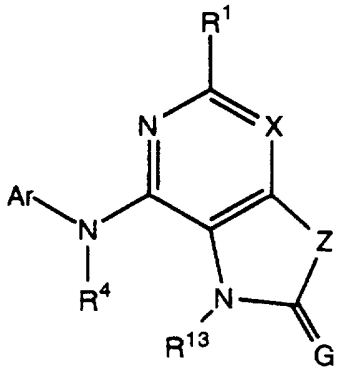
therapeutically effective amount of a compound of claim 2.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 3.

7. A method of treating 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, or fertility problem in a mammal comprising administering to the mammal a therapeutically effective amount of a CRF antagonist compound of formula I or II:



I



II

or a pharmaceutically acceptable salt or pro-drug form thereof, wherein:

X is N or CR^1;

Y is N or CR^2;

Z is NR^3, O, or $S(O)_n$;

G is O or S;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each optionally substituted with 1 to 5 R^5 groups;

R^1 is independently at each occurrence H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, NR^9COR^{10}, $-OR^{11}$, SH or $-S(O)_nR^{12}$;

R^2 is H, C_1-C_4 alkyl, C_1-C_6 cycloalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl or C_4-C_{12} cycloalkylalkyl each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-CONR^6R^7$, aryl, heteroaryl and heterocyclyl, where the aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

R^4 is H, C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl, allyl, or propargyl is optionally substituted with C_3-C_6 cycloalkyl and where C_1-C_4 alkyl is optionally substituted with, $-OR^7$, $-S(O)_nR^{12}$ or $-CO_2R^7$;

R^5 is independently at each occurrence C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NO_2$, halo, $-CN$, C_1-C_4 haloalkyl, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, $-CO(NOR^9)R^7$, CO_2R^7, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, $-CN$, $-NR^6R^7$, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, CO_2R^7, $-CO(NOR^9)R^7$, or $-S(O)_nR^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

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

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

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

provided that R^4 in formula I is not H:

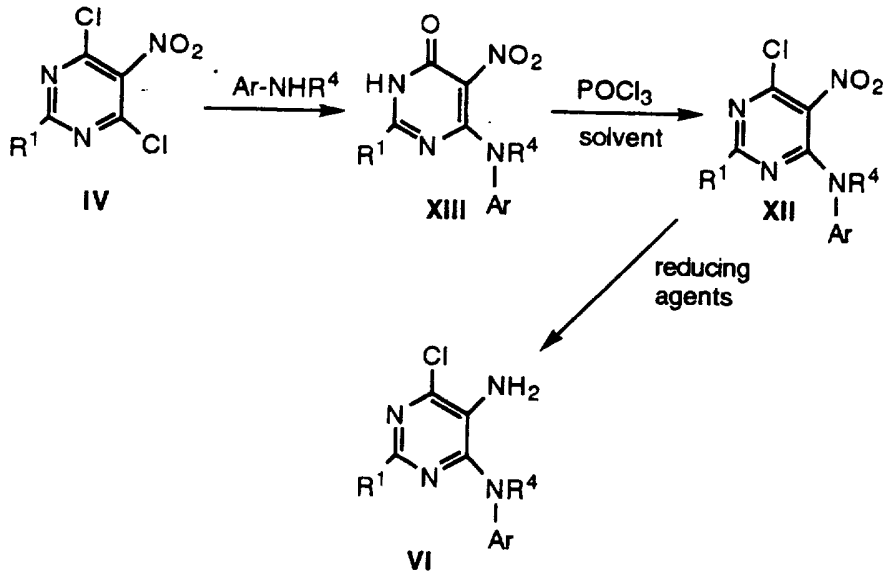
(a) when X is N, Y is N, Z is NR^3, R3 is cyclopropylmethyl, R1 is H, and Ar is 2-bromo-4-isopropylphenyl, or

(b) when X is N, Y is N, Z is S, R^1 is H, and Ar is 2-bromo-4-isopropylphenyl.

8. A method of treating an affective disorder, anxiety, or depression in a mammal comprising administering to the mammal a therapeutically effective amount of a CRF antagonist compound of claim 2.

9. A method of treating an affective disorder, anxiety, or depression in a mammal comprising administering to the mammal a therapeutically effective amount of a CRF antagonist compound of claim 3.

10. A process for making a 5-amino-4-chloro-6-arylamino-2-substituted pyrimidine of formula VI which comprises reacting a 4,6-dichloro-5-nitro-2-substituted pyrimidine of formula IV whith an arylamine of formula $ArNHR^4$ in the presence of a solvent selected from dialkylsulfoxides, dialkylformamides and alkyl alcohols to produce a pyrimidone of formula XIII, reacting the pyrimidone with phosporous oxychloride to produce a 4-chloro-6-arylamino-5-nitro-2-substituted pyrmidine of formula XII, then treating the pyrmidine of formula XII with a reducing agent, as shown in the following scheme:



wherein

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each optionally substituted with 1 to 5 R^5 groups;

R^1 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, NR^9COR^{10}, $-OR^{11}$, SH or $-S(O)_nR^{12}$;

R^4 is H, C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl, allyl, or propargyl is optionally substituted with C_3-C_6 cycloalkyl and where C_1-C_4 alkyl is optionally substituted with, $-OR^7$, $-S(O)_nR^{12}$ or $-CO_2R^7$;

R^5 is independently at each occurrence C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NO_2$, halo, -CN, C_1-C_4 haloalkyl, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, $-CO(NOR^9)R^7$, CO_2R^7, or

$-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, $-CN$, $-NR^6R^7$, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, CO_2R^7, $-CO(NOR^9)R^7$, or $-S(O)_nR^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

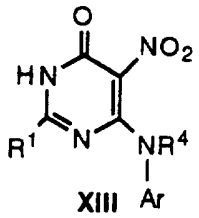
aryl is phenyl or naphthyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-

C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

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

11. A pyrimidone of formula XIII



XIII

wherein

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each optionally substituted with 1 to 5 R^5 groups;

R^1 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, NR^9COR^{10}, $-OR^{11}$, SH or $-S(O)_nR^{12}$;

R^4 is H, C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl, allyl, or propargyl is optionally substituted with C_3-C_6 cycloalkyl and where C_1-C_4 alkyl is optionally substituted with, $-OR^7$, $-S(O)_nR^{12}$ or $-CO_2R^7$;

R^5 is independently at each occurrence C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NO_2$, halo, -CN, C_1-C_4 haloalkyl, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, $-CO(NOR^9)R^7$, CO_2R^7, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, $-NO_2$, halo, -CN, $-NR^6R^7$, $-NR^6R^7$, NR^8COR^7, $NR^8CO_2R^7$, $-COR^7$ $-OR^7$, $-CONR^6R^7$, CO_2R^7, $-CO(NOR^9)R^7$, or $-S(O)_nR^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

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

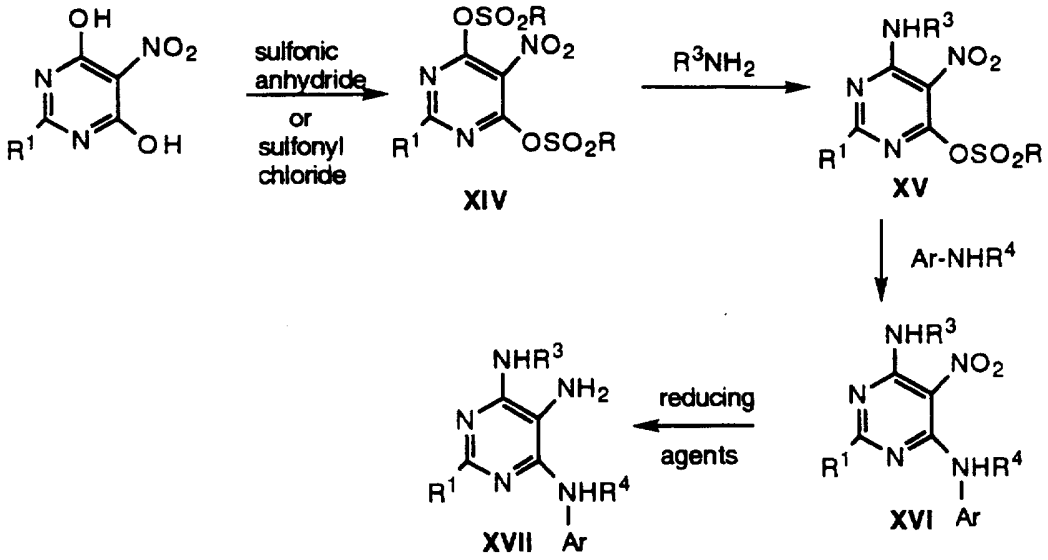
heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

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

provided that: when Ar is phenyl substituted with 2 or 3 substituents selected from C_1-C_4 alkyl, chloro and bromo, or pyridyl substituted with 2 or 3

substituents selected from C_1-C_4 alkyl, chloro and bromo; and R1 is methyl or ethyl; then R4 is not H or methyl.

12. A method of making a compound of formula XVII by reacting a 4,6-dihydroxy-5-nitropyrimidine with an aryl sulfonic anhydride, aryl sulfonyl chloride, alkyl sulfonic anhydride or alkyl sulfonyl chloride to produce a compound of formula XIV, reacting the latter compound with an amine of the formula R^3NH_2 to produce a compound of formula XV, reacting the latter compound with an arylamine of the formula $ArNHR^4$ to produce a compound of formula XVI, then treating the latter compound with a reducing agent, as shown in the following scheme:



wherein

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl,

benzthiazolyl, isoxazolyl or pyrazolyl, each optionally substituted with 1 to 5 R^5 groups;

R is the hydrocarbon residue of the aryl or alkyl sulfonic anhydride or sulfonyl chloride;

R^1 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, NR^9COR^{10}, $-OR^{11}$, SH or $-S(O)_nR^{12}$;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl or C_4-C_{12} cycloalkylalkyl each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-CONR^6R^7$, aryl, heteroaryl and heterocyclyl, where the aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

R^4 is H, C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl, allyl, or propargyl is optionally substituted with C_3-C_6 cycloalkyl and where C_1-C_4 alkyl is optionally substituted with, $-OR^7$, $-S(O)_nR^{12}$ or $-CO_2R^7$;

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

-CN, C_1-C_4 haloalkyl, -NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, -COR^7 -OR^7; -$CONR^6R^7$, -$CO(NOR^9)R^7$, CO_2R^7, or -$S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, -NO_2, halo, -CN, -NR^6R^7, -NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, -COR^7 -OR^7, -$CONR^6R^7$, CO_2R^7, -$CO(NOR^9)R^7$, or -$S(O)_nR^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

alkyl in alkyl sulfonic anhydrides and alkyl sulfonyl chorides is C_1-C_4 branched or straight chain

alkyl optionally substituted with 1 to 3 fluorines;.

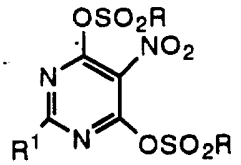
aryl is phenyl or naphthyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$,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

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

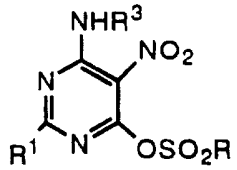
heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

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

13. A compound of formula XIV or XV:



XIV



XV

wherein:

R is aryl as defined below or is C_1-C_4 branched or straight chain alkyl optionally substituted with 1 to 3 fluorines;

R^1 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, $-NR^9R^{10}$, NR^9COR^{10}, $-OR^{11}$, SH or $-S(O)_nR^{12}$;

R^3 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl or C_4-C_{12} cycloalkylalkyl each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-CONR^6R^7$, aryl, heteroaryl and heterocyclyl, where the aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

R^6 and R7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl,

aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-; or NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine;

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

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

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

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

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

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

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, or indazolyl, each optionally substituted with 1 to 3 substituents

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

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, $-OR^7$, SH, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-OC(O)R^{13}$, $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, and $-CONR^6R^7$;

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