



(86) Date de dépôt PCT/PCT Filing Date: 1999/01/28
(87) Date publication PCT/PCT Publication Date: 1999/08/05
(45) Date de délivrance/Issue Date: 2009/12/08
(85) Entrée phase nationale/National Entry: 2000/06/13
(86) N° demande PCT/PCT Application No.: US 1999/001824
(87) N° publication PCT/PCT Publication No.: 1999/038868
(30) Priorités/Priorities: 1998/01/28 (US09/015,001);
1998/01/28 (US09/014,734); 1998/01/28 (US09/015,002)

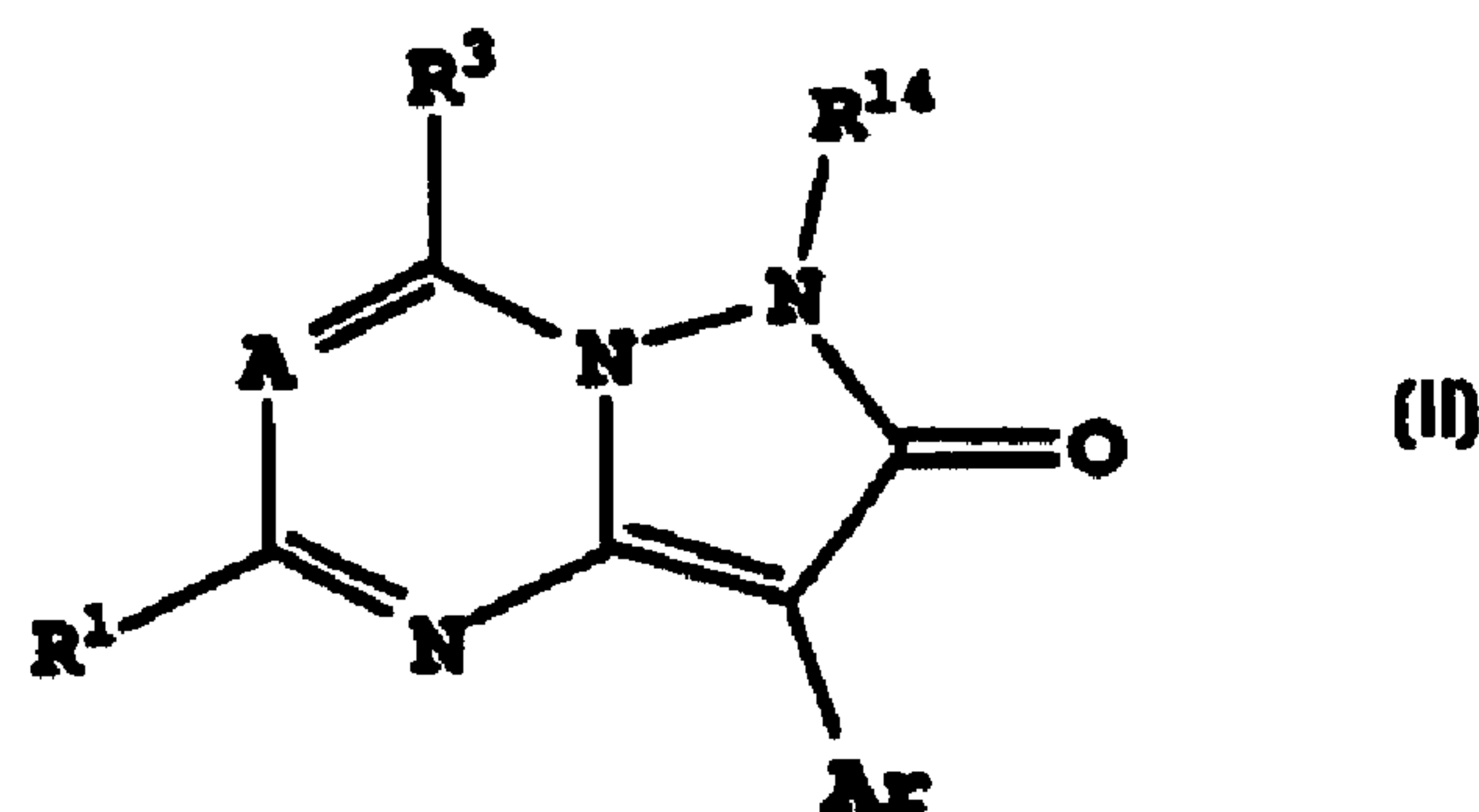
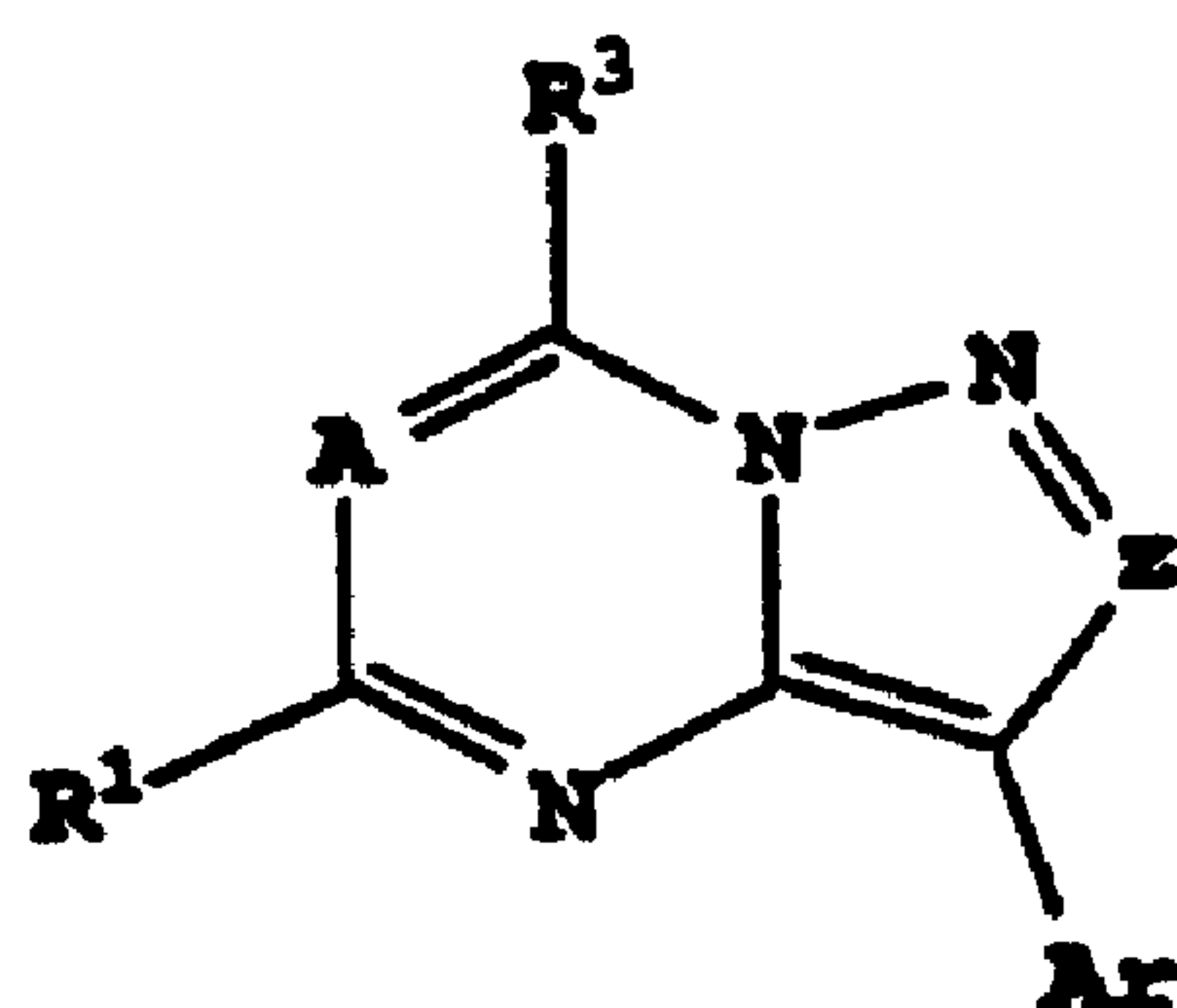
(51) Cl.Int./Int.Cl. *C07D 487/04* (2006.01),
A61K 31/495 (2006.01), *C07D 231/00* (2006.01),
C07D 239/00 (2006.01), *C07D 251/00* (2006.01)

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(54) Titre : AZOLO TRIAZINES ET PYRIMIDINES
(54) Title: AZOLO TRIAZINES AND PYRIMIDINES



(57) Abrégé/Abstract:

Corticotropin releasing factor (CRF) antagonists of formula (I) or (II) and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.



**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 487/04, A61K 31/495 // (C07D 487/04, 251:00, 231:00) (C07D 487/04, 239:00, 231:00)	A1	(11) International Publication Number: WO 99/38868 (43) International Publication Date: 5 August 1999 (05.08.99)
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(21) International Application Number: PCT/US99/01824

(22) International Filing Date: 28 January 1999 (28.01.99)

(30) Priority Data:

09/015,002	28 January 1998 (28.01.98)	US
09/014,734	28 January 1998 (28.01.98)	US
09/015,001	28 January 1998 (28.01.98)	US

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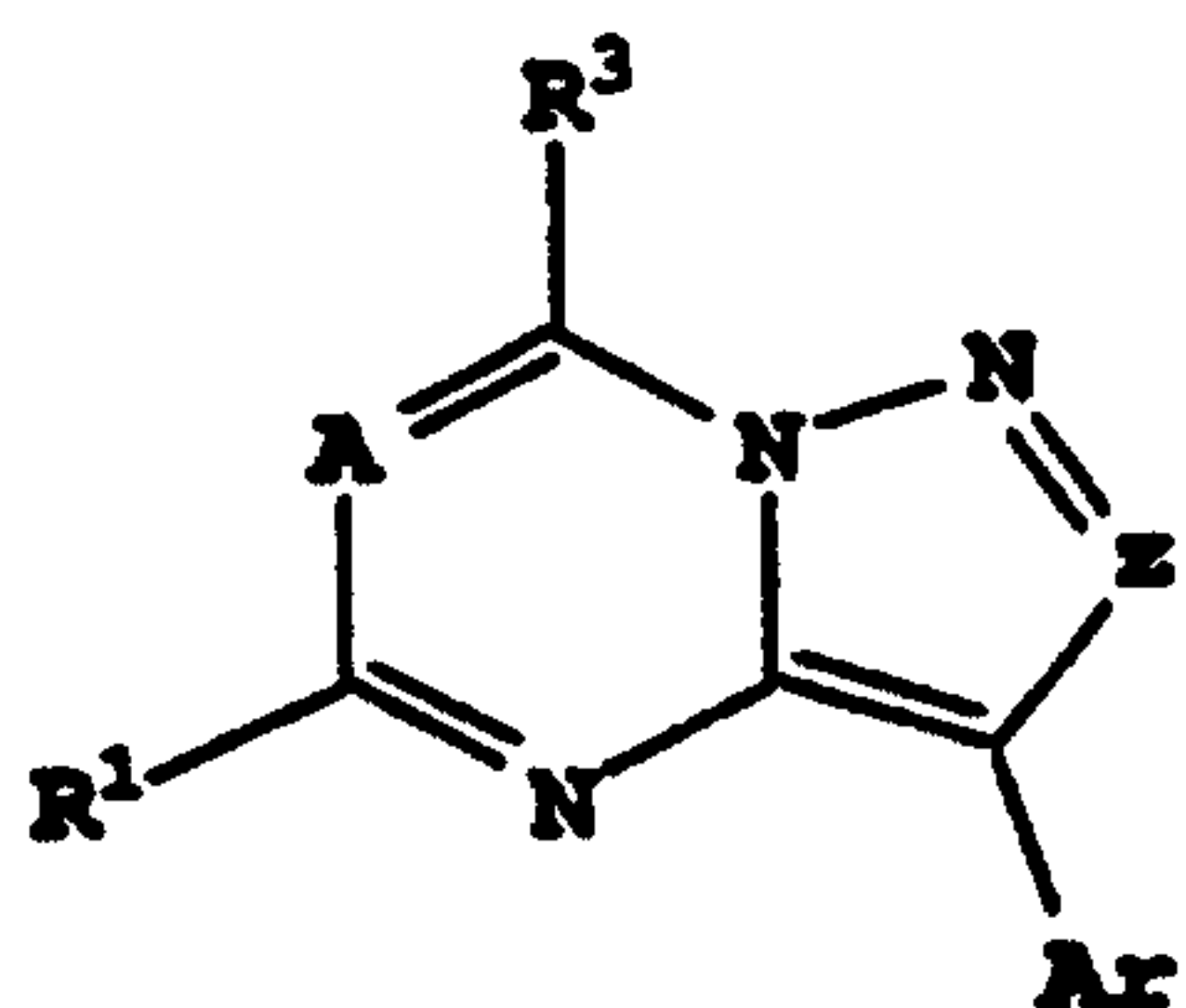
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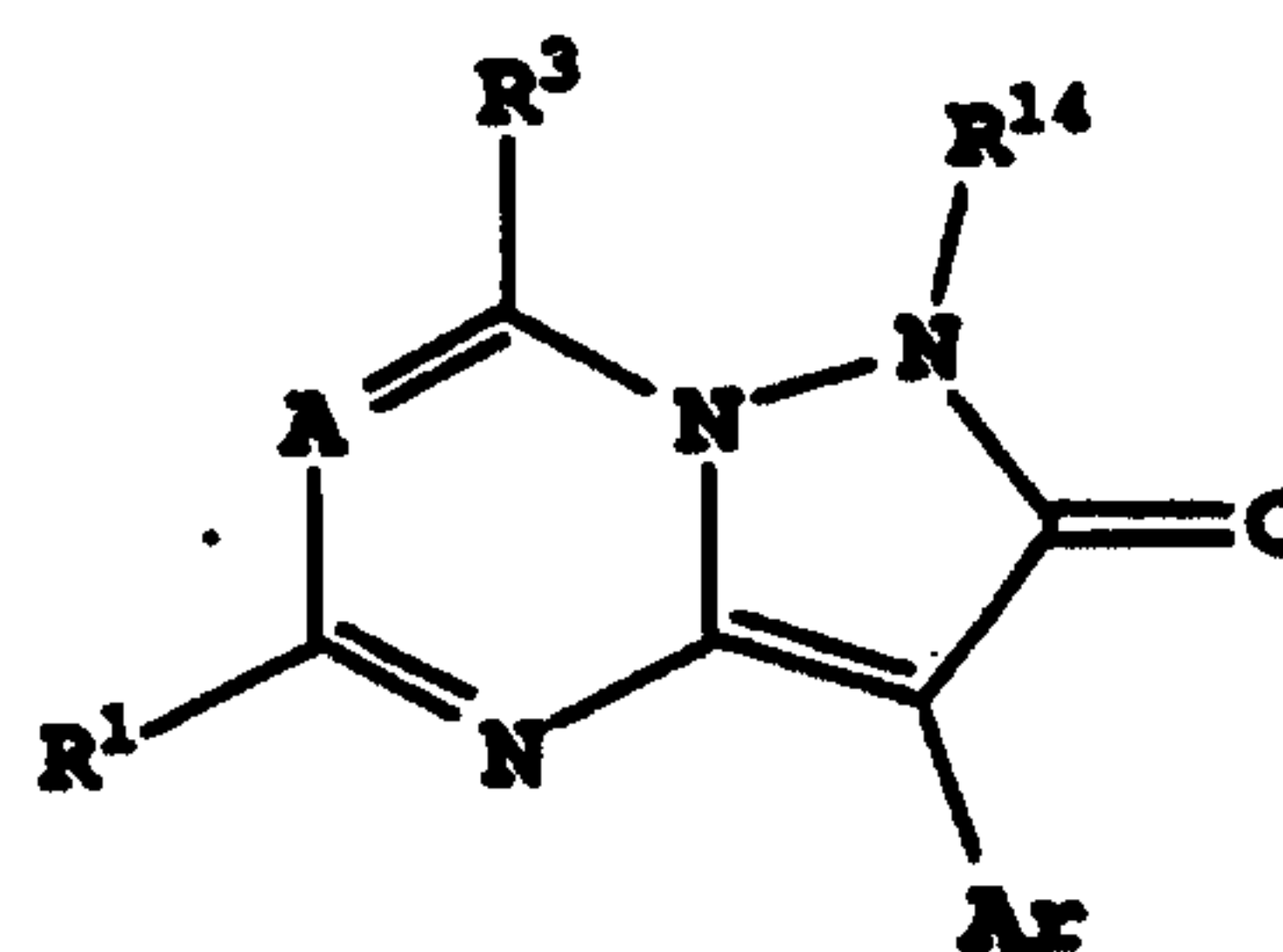
(81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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

(54) Title: AZOLO TRIAZINES AND PYRIMIDINES



(I)



(II)

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I) or (II) and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

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TITLE

AZOLO TRIAZINES AND PYRIMIDINES

5

FIELD OF THE INVENTION

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

20

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)].

5 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)].

10 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
15 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
20 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
25 (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
30 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 α -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine

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

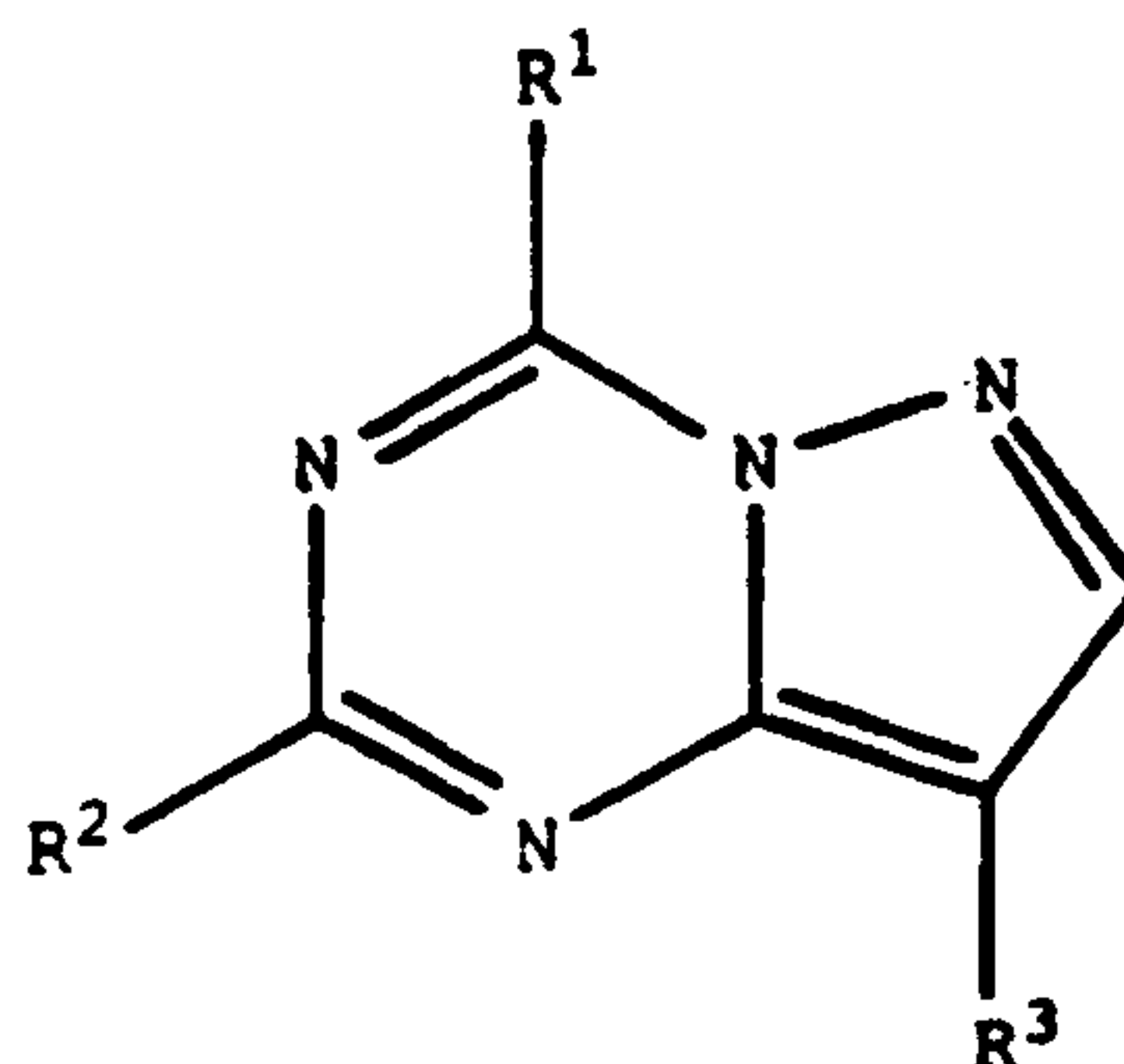
The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α -helical CRF₉₋₄₁) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

Several publications describe corticotropin releasing factor antagonist compounds

and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application WO 95/10506 , Pfizer WO 95/33750, Pfizer WO 95/34563, 5 Pfizer WO 95/33727 and Pfizer EP 0778 277 A1.

Insofar as is known, [1,5-a]-pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-1,3,5-triazines, [1,5-a]-pyrazolo-pyrimidines and [1,5-a]-1,2,3-triazolo-pyrimidines, have not been previously 10 reported as corticotropin releasing factor antagonist compounds useful in the treatment of psychiatric disorders and neurological diseases. However, there have been publications which teach some of these compounds for other uses.

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



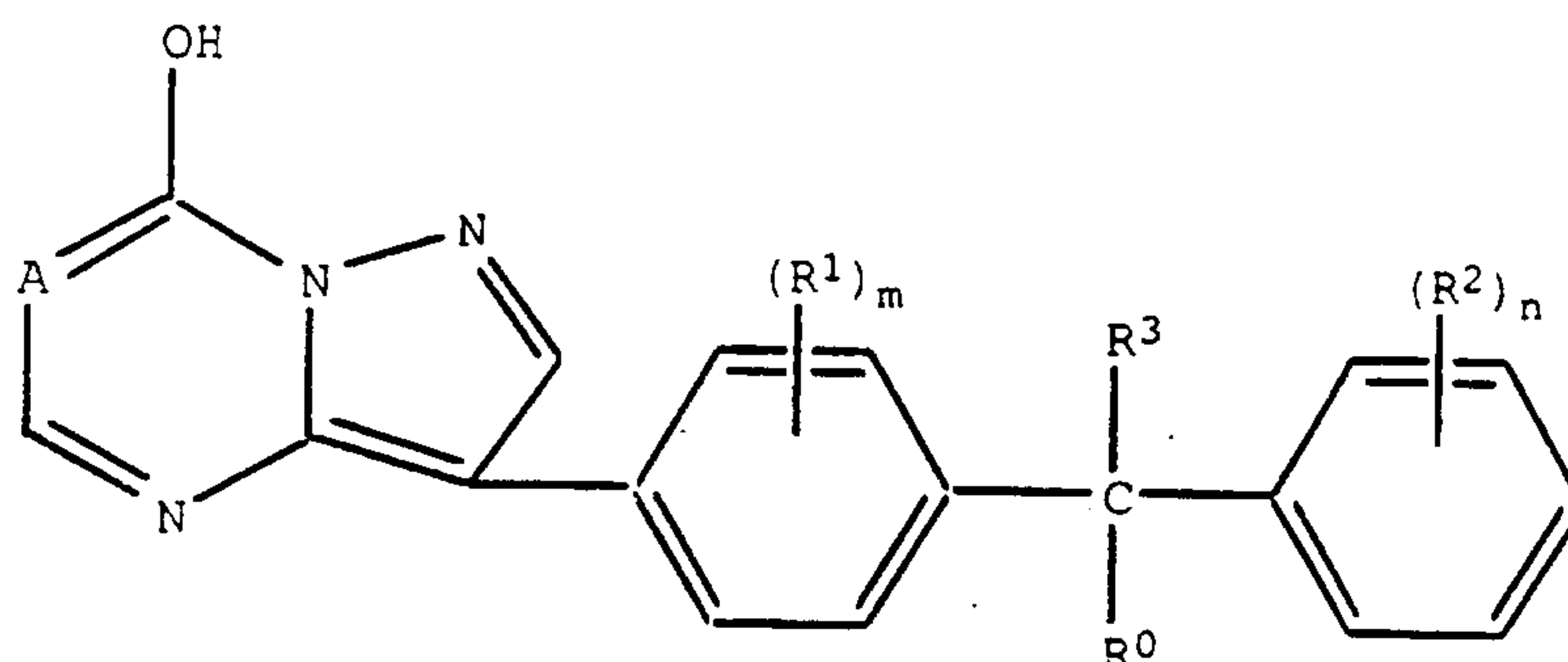
20 where R^1 is OH or alkanoyl, R^2 is H, OH, or SH, and R^3 is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

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

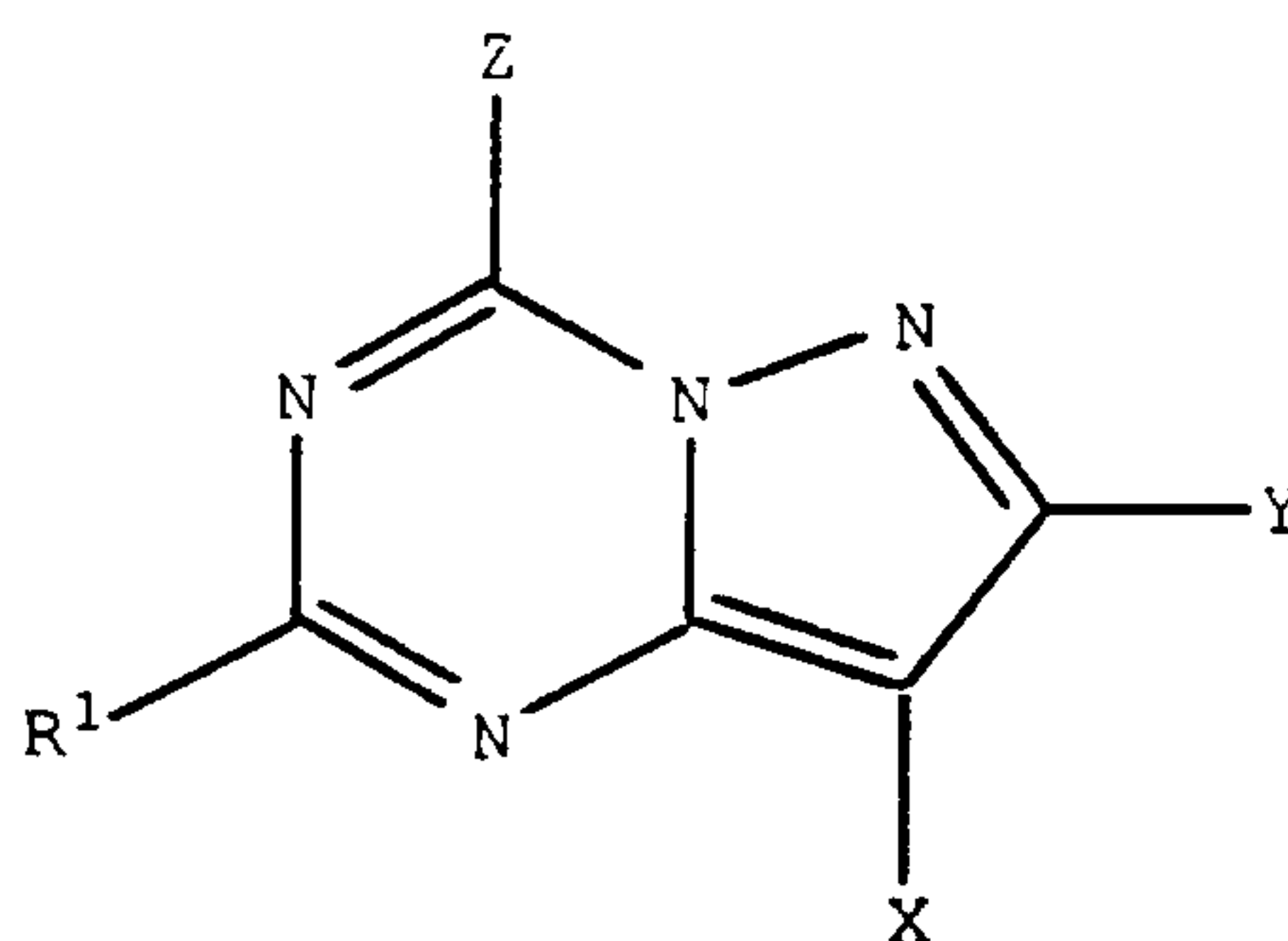
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where A is CH or N, R^0 and R^3 are H or alkyl, and R^1
 5 and R^2 are H, alkyl, alkoxyl, alkylthio, nitro, etc.,
 and states that the compounds inhibit androgen and are
 useful in treatment of benign prostatic hypertrophy and
 prostatic carcinoma.

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



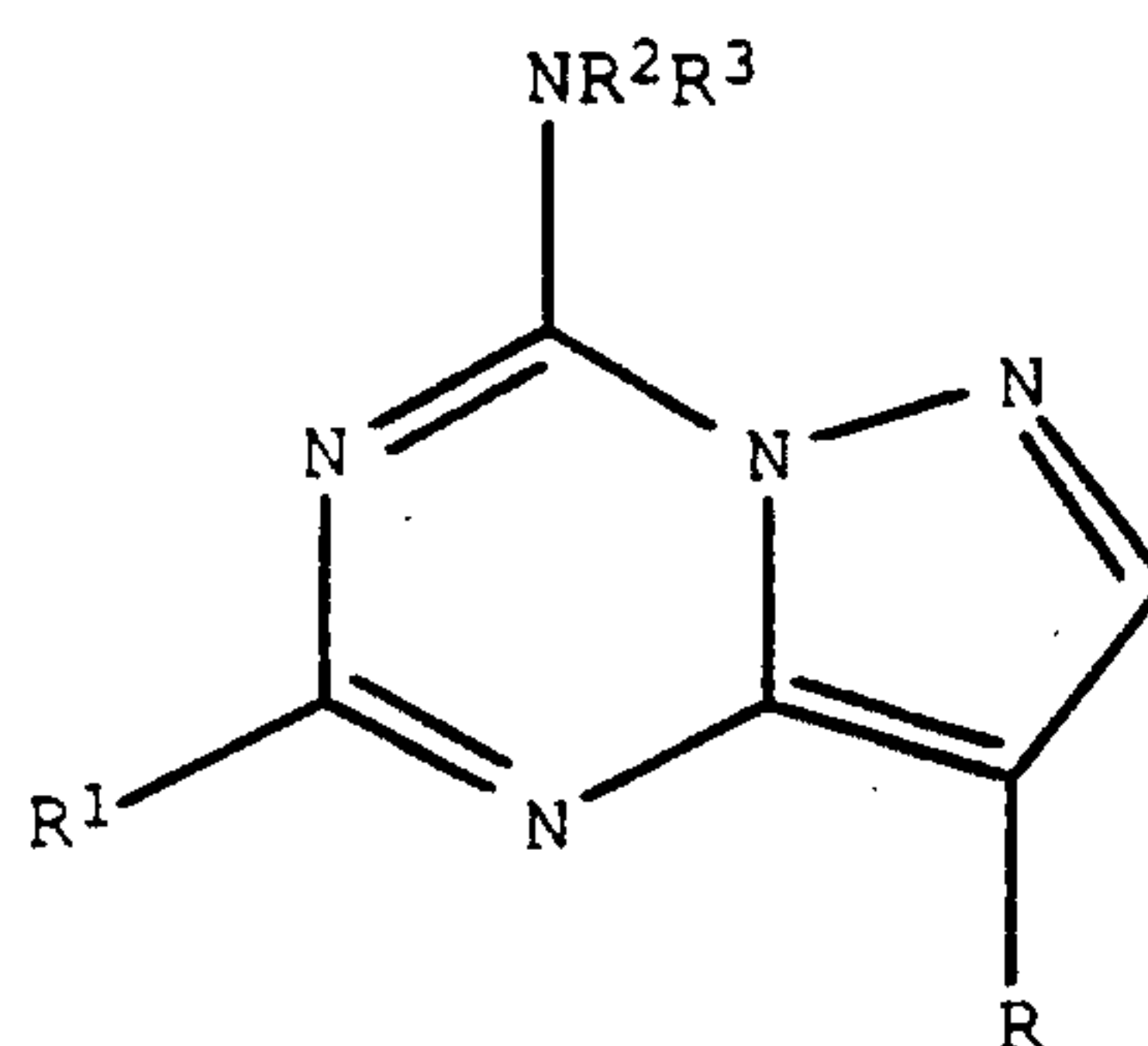
15 where R_1 is CH_3 , C_2H_5 or C_6H_5 , X is H, C_6H_5 , m- $CH_3C_6H_4$,
 CN, COOEt, Cl, I or Br, Y is H, C_6H_5 , o- $CH_3C_6H_4$, or p-
 $CH_3C_6H_4$, and Z is OH, H, CH_3 , C_2H_5 , C_6H_5 , n- C_3H_7 , i- C_3H_7 ,
 SH, SCH_3 , NHC_4H_9 , or $N(C_2H_5)_2$, and states that the
 compounds are c-AMP phosphodiesterase inhibitors useful
 20 as bronchodilators.

US 3,995,039 discloses pyrazolotriazines of

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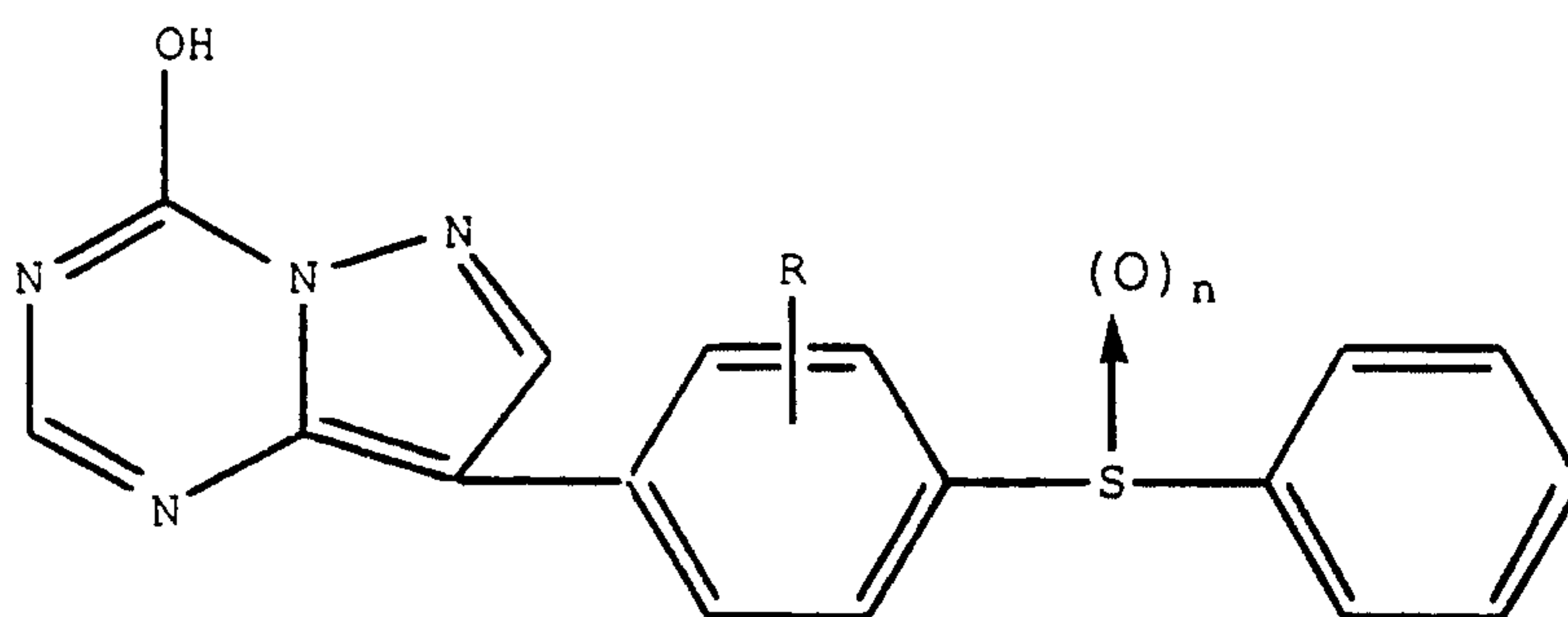
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the formula:



- 5 where R¹ is H or alkyl, R² is H or alkyl, R³ is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

- 10 US 5,137,887 discloses pyrazolotriazines of the formula

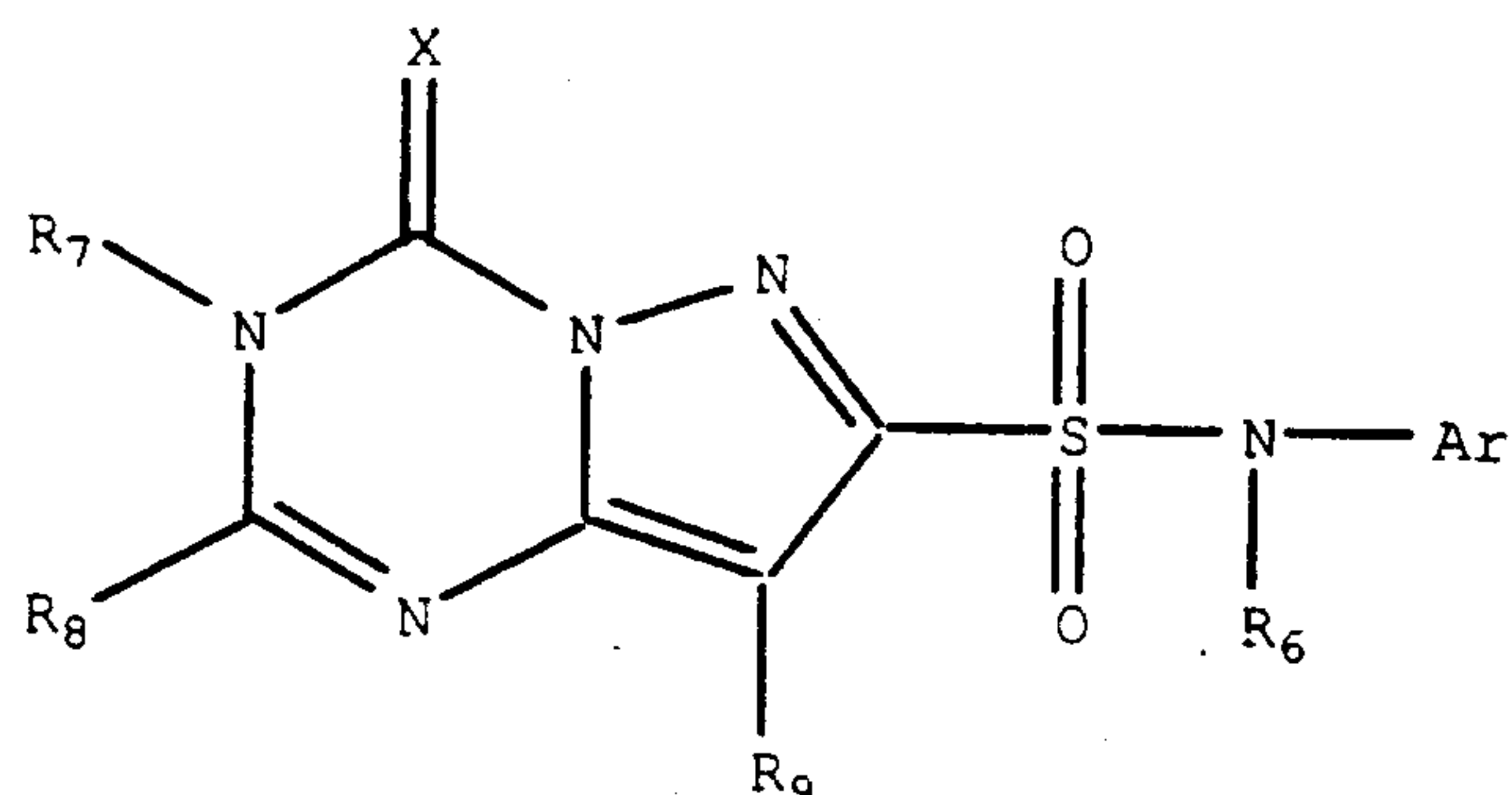


- 15 where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

- 20 US 4,892,576 discloses pyrazolotriazines of the formula

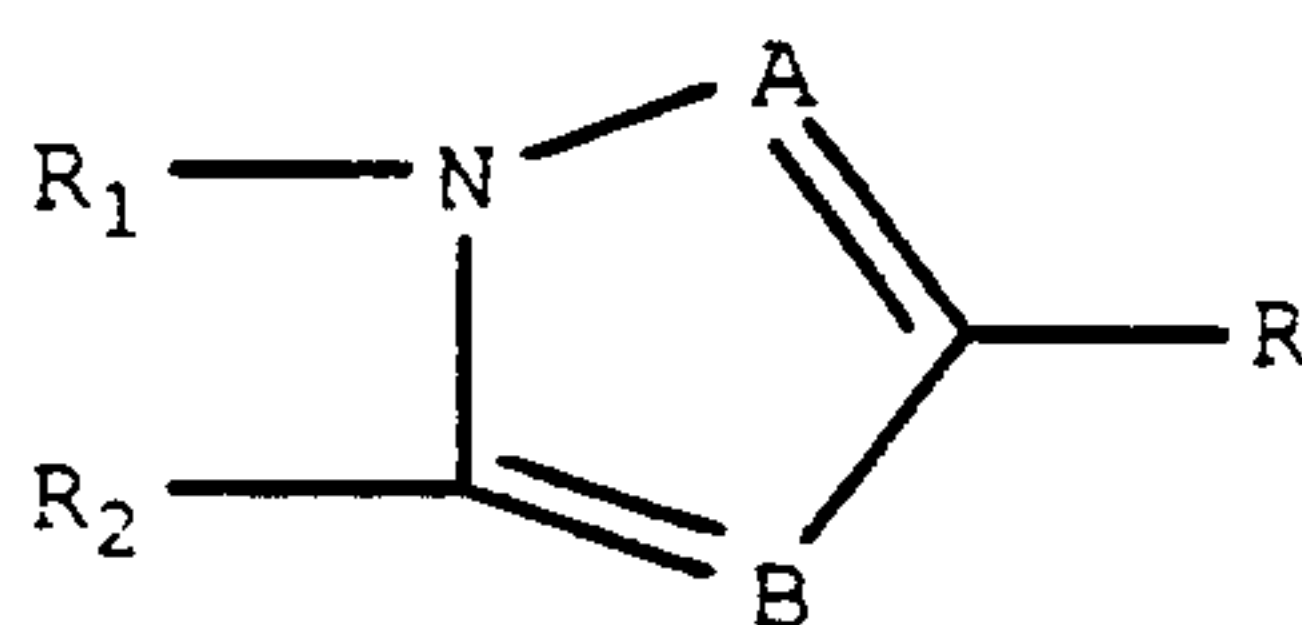
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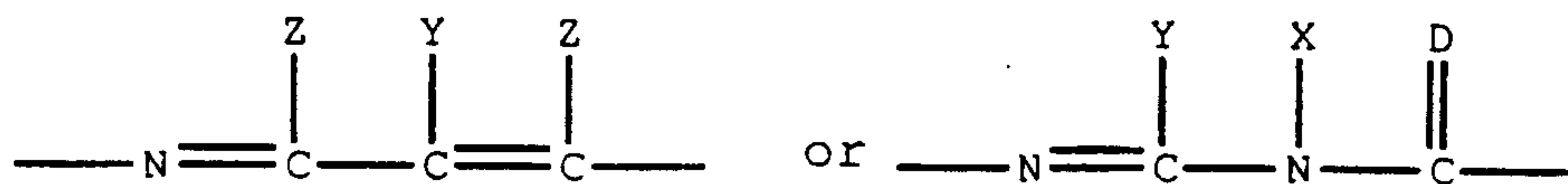


where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, R₆-R₈ are H, alkyl, etc., and R₉ is H, alkyl, phenyl, etc. The patent states that the compounds are useful as herbicides and plant growth regulants.

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



where A can be N, B can be CR₃, R₃ can be phenyl or substituted phenyl, etc., R is -N(R₄)SO₂R₅ or -SO₂N(R₆)R₇ and R₁ and R₂ can be taken together to form



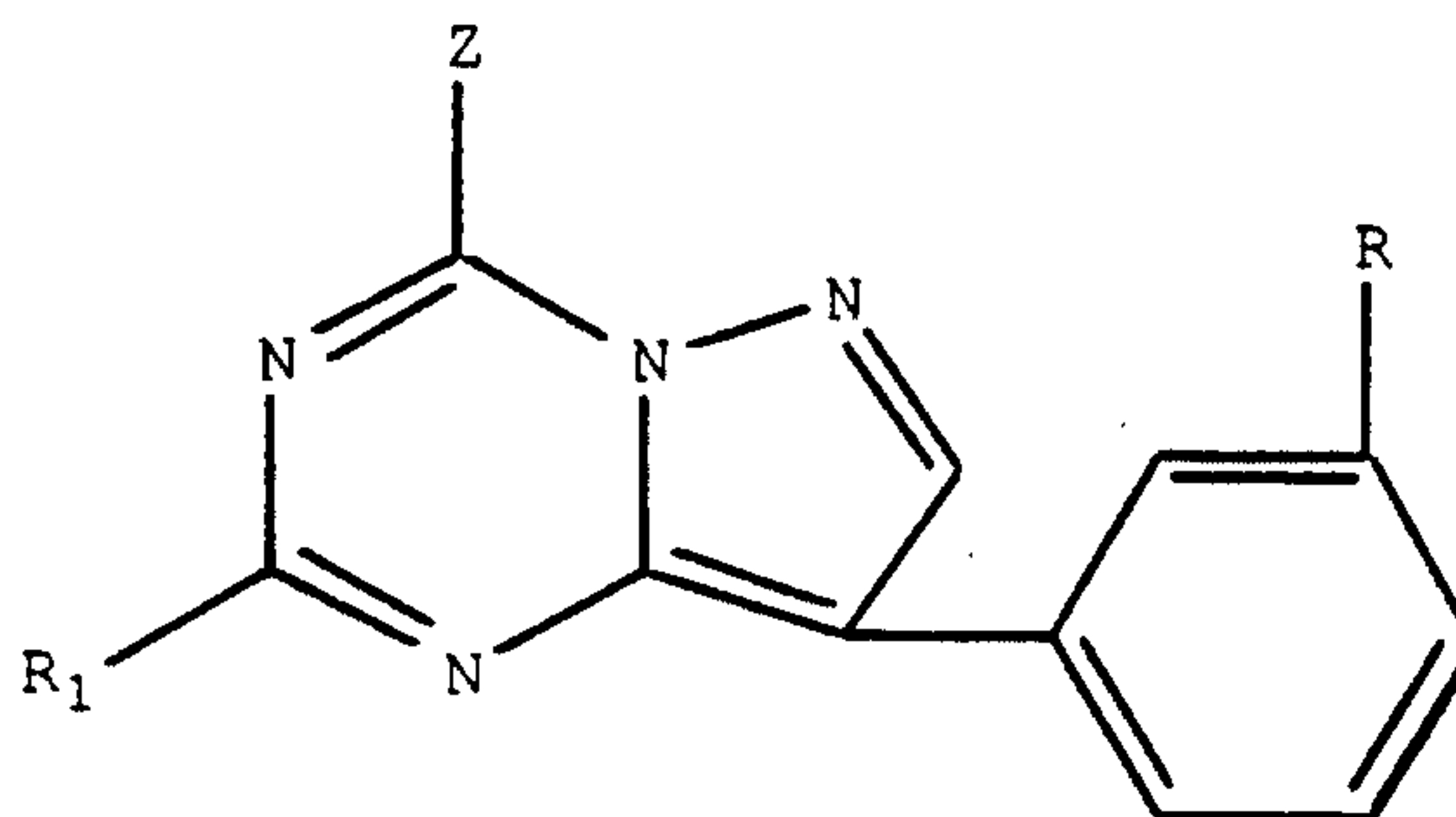
where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

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

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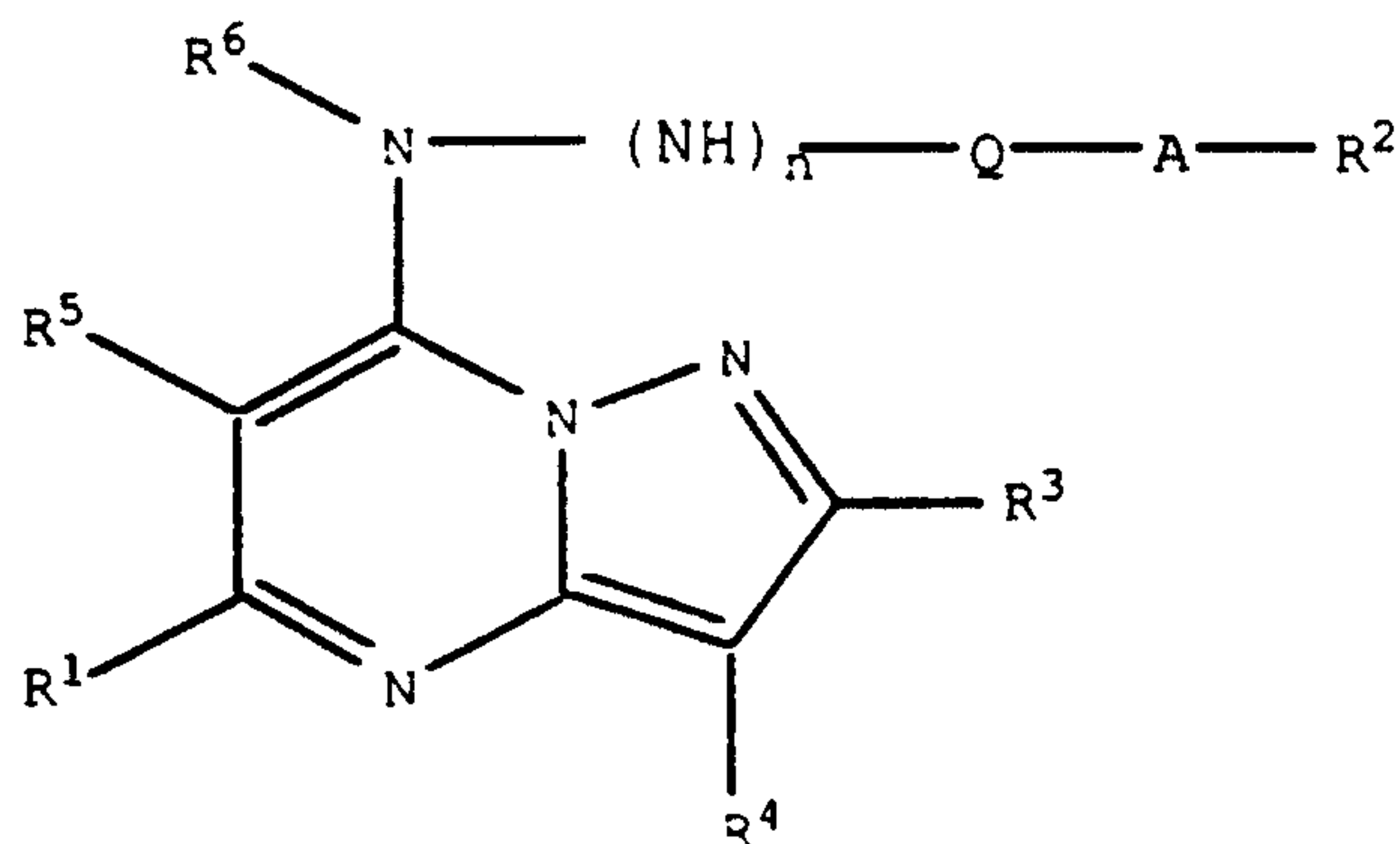
1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula



5

where Z is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇, iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, R is H or CH₃, and R₁ is CH₃ or C₂H₅. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

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



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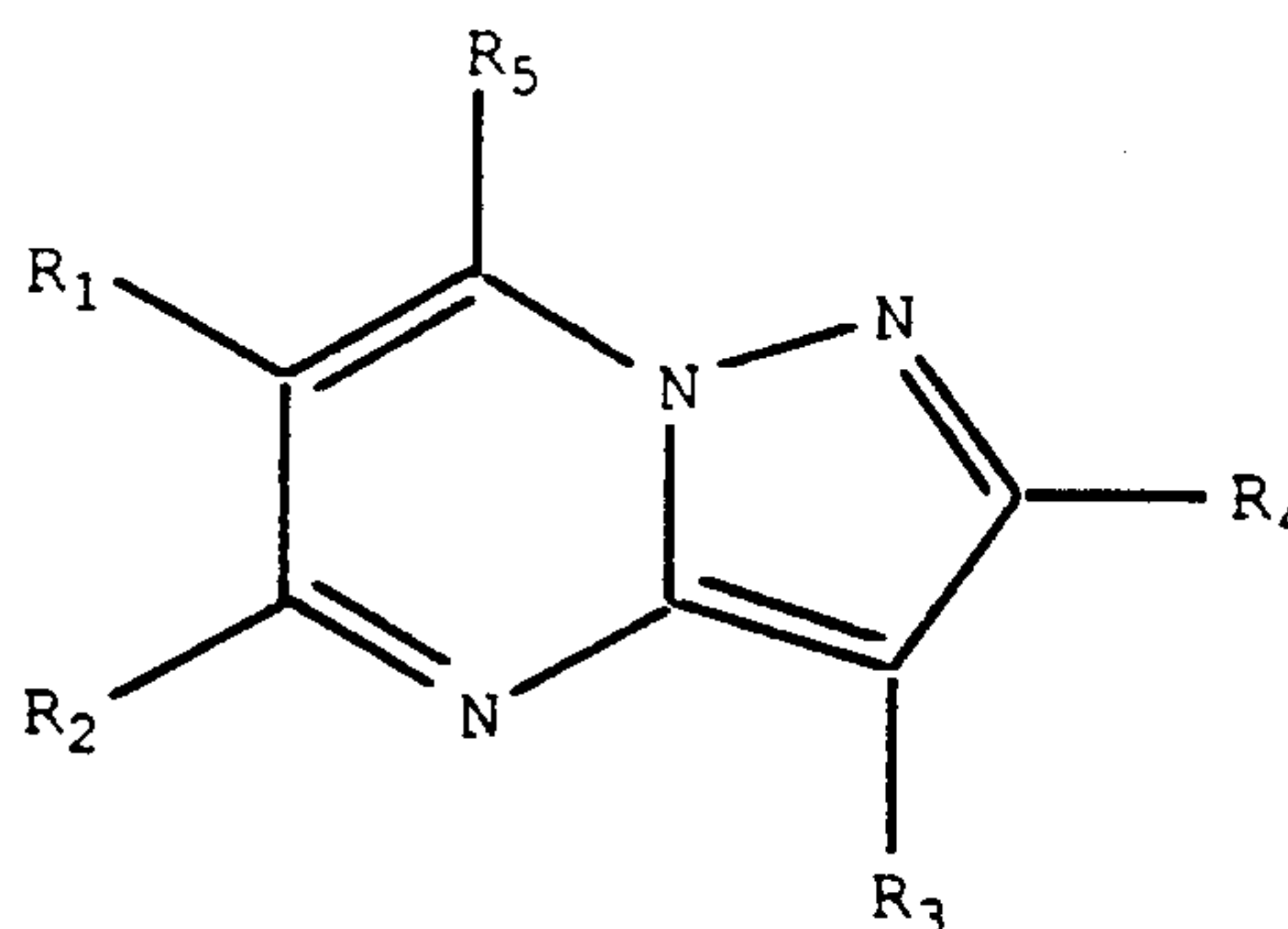
where Q is carbonyl or sulfonyl, n is 0 or 1, A is a

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single bond, alkylene or alkenylene, R¹ is H, alkyl, etc., R² is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R³ is H, alkyl or phenyl, R⁴ is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R⁵ and R⁶ are H or alkyl.

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

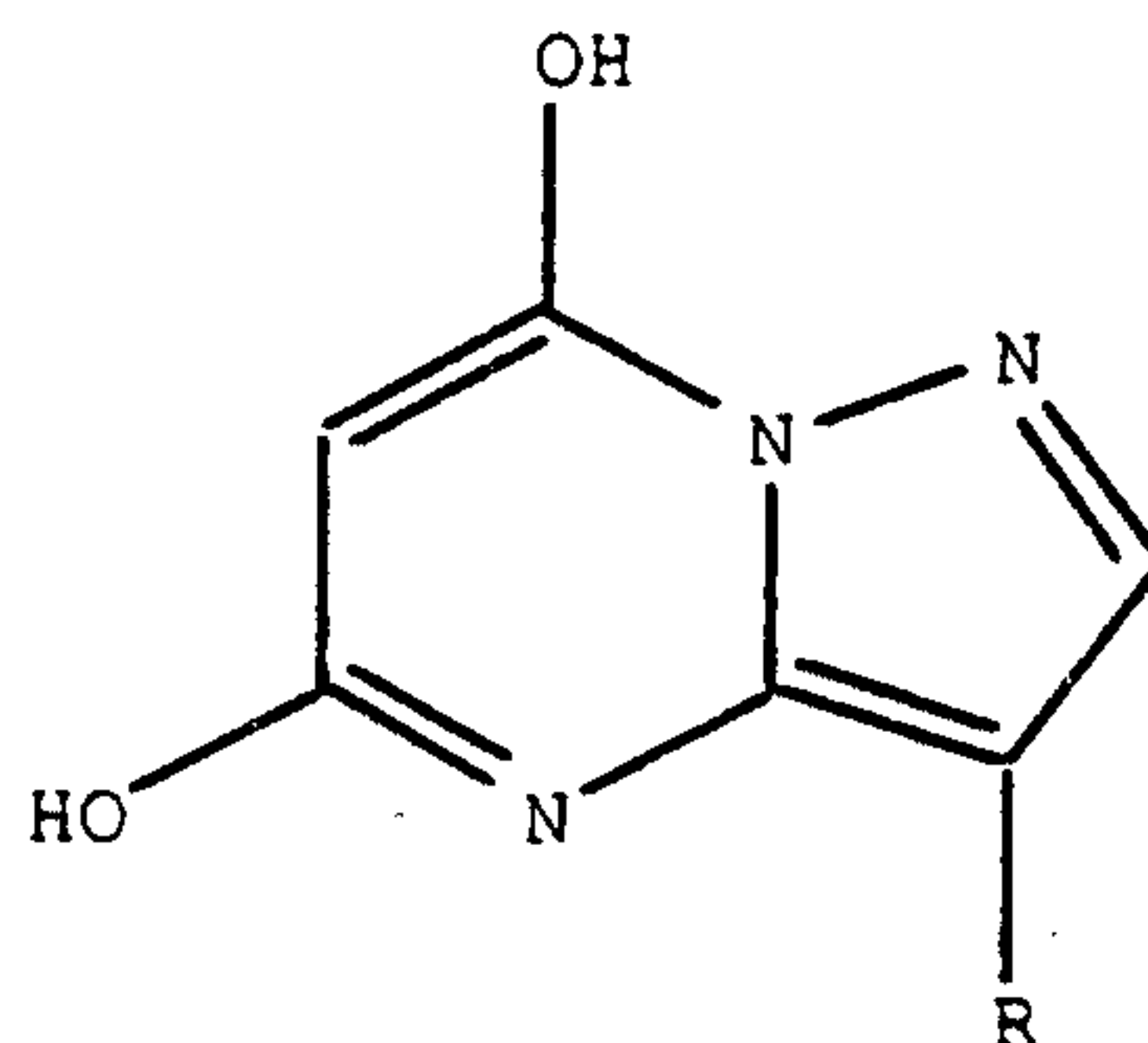


where R₁, R₂, R₃ and R₄ are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R₅ is SR₆ or NR₇R₈, R₆ is pyridyl or optionally substituted phenyl, and R₇ and R₈ are H or optionally substituted phenyl.

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

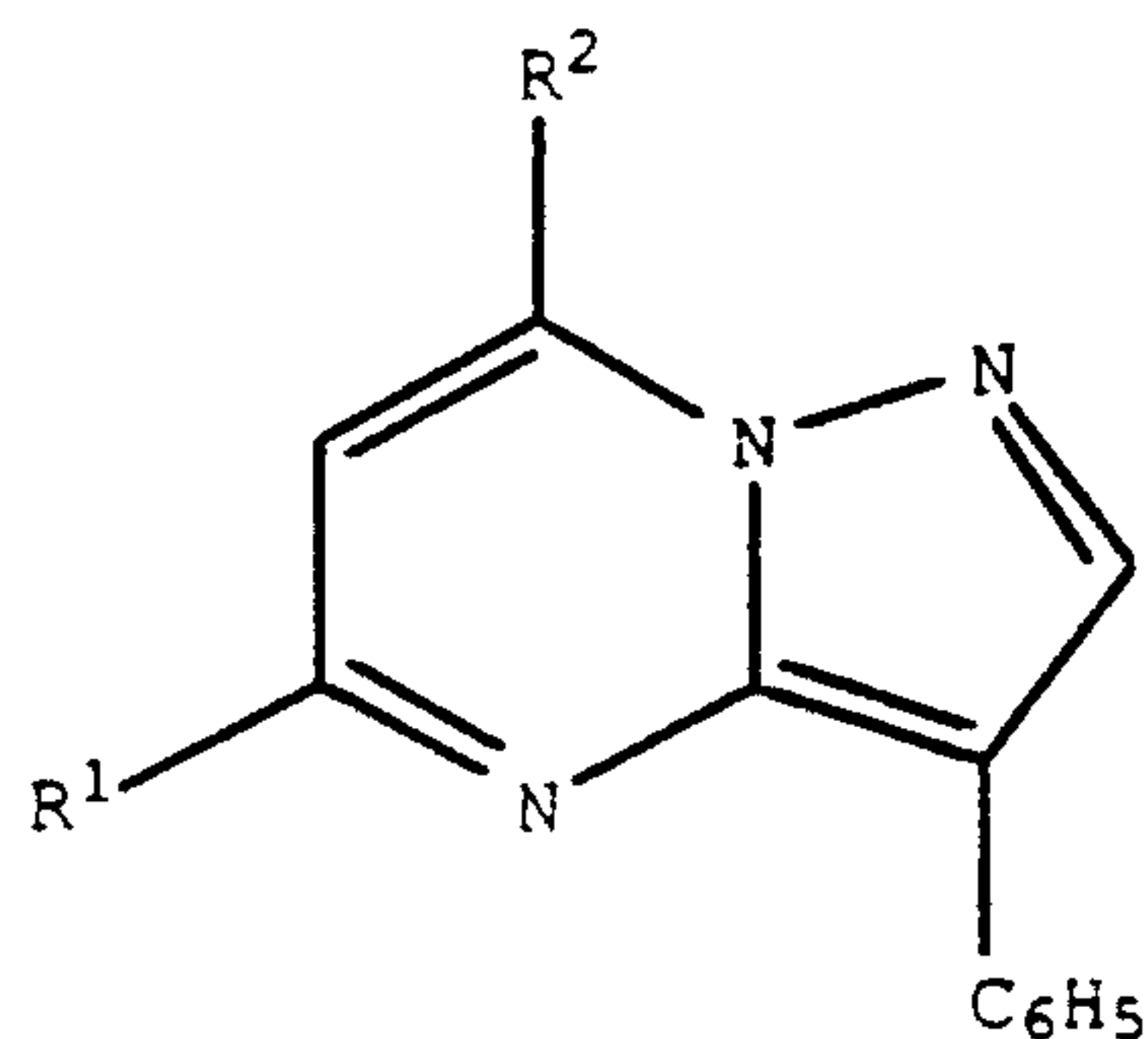
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where R can be phenyl, substituted phenyl or pyridyl,
and their use to treat gout, based on their ability to
5 inhibit xanthine oxidase.

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



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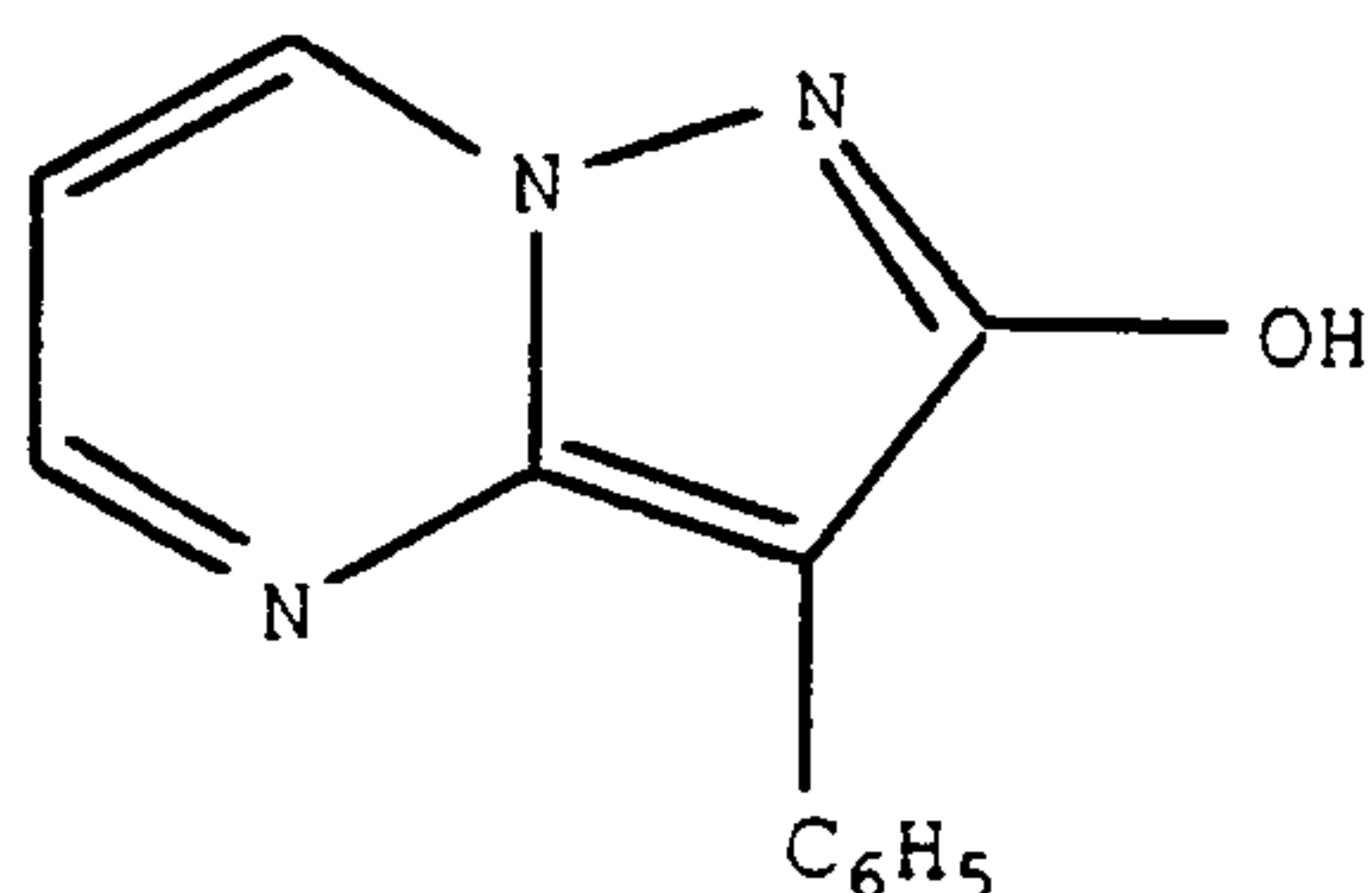
where R¹ is CF₃, C₂F₅, or C₆H₄F, and R² is CH₃, C₂H₅,
CF₃, or C₆H₄F.

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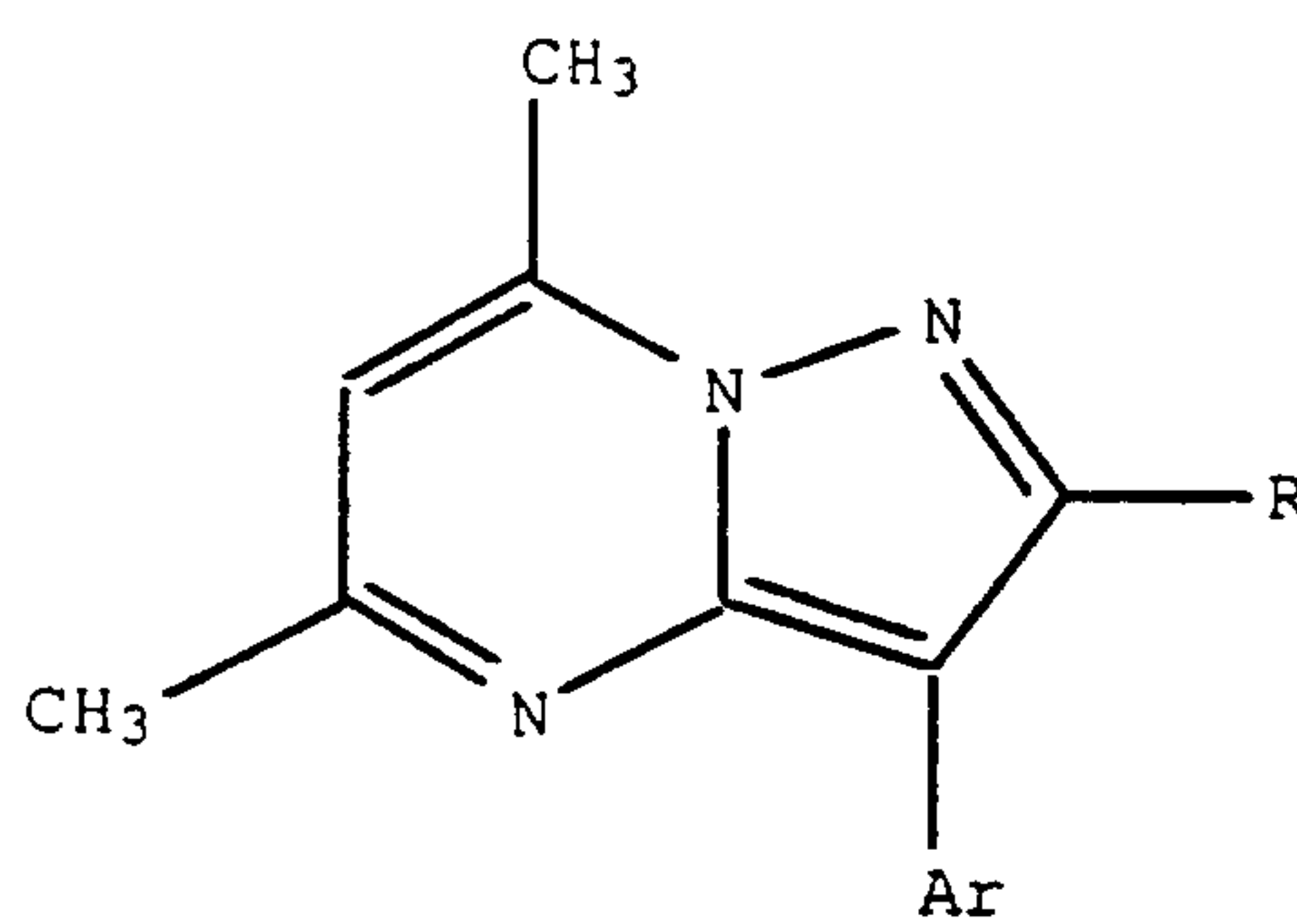
Maquestiau et al., Bull. Soc. Belg., vol.101,
no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-
a]pyrimidine of the formula

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



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

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

SUMMARY OF THE INVENTION

In accordance with one aspect, the present

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

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

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

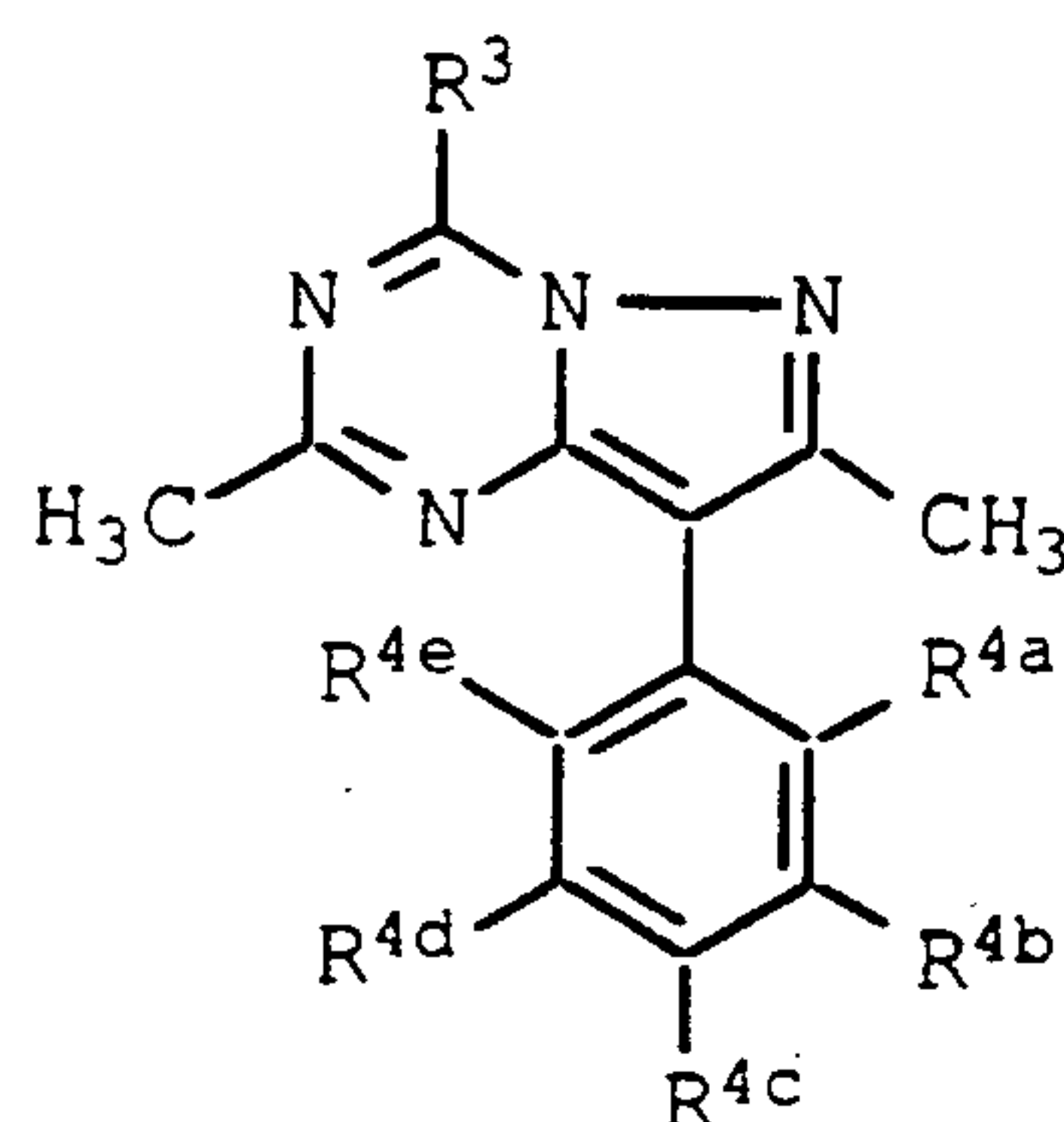
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According to another aspect, the present invention provides novel compounds described below which are useful as antagonists of the corticotropin releasing factor. The compounds of the present
5 invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of Formulae (1) and (2), and methods of
10 using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect of the
15 invention, the 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.
20

DETAILED DESCRIPTION OF INVENTION

[1] The present invention provides compounds of
25 Formula (50)



FORMULA (50)

- 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof, selected from the group:
- 10 a compound of Formula (50) wherein R³ is -NHCH(CH₂CH₂OMe)(CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 15 a compound of Formula (50) wherein R³ is -NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R³ is 2-ethylpiperid-1-yl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R³ is cyclobutyl-amino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R³ is N(Me)CH₂CH=CH₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R³ is N(Et)CH₂CH=CH₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

- 5 a compound of Formula (50) wherein R^3 is $N(Me)CH_2cPr$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is H;
- a compound of Formula (50) wherein R^3 is $N(Et)CH_2cPr$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is H;
- 10 a compound of Formula (50) wherein R^3 is $N(Pr)CH_2cPr$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is H;
- 15 a compound of Formula (50) wherein R^3 is $N(Me)Pr$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 20 a compound of Formula (50) wherein R^3 is $N(Me)Et$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 25 a compound of Formula (50) wherein R^3 is $N(Me)Bu$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 30 a compound of Formula (50) wherein R^3 is
 $N(Me)propargyl$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH(CH_3)CH_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-$
 $CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is
 H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Me$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,

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

5 a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Et$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Pr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-$
 CH_2cPr , R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH_2CH_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

20 a compound of Formula (50) wherein R^3 is $NHCH(cPr)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is H;

25 a compound of Formula (50) wherein R^3 is 2-
ethylpiperid-1-yl, R^{4a} is Me, R^{4b} is H, R^{4c} is
OMe, R^{4d} is Me and R^{4e} is H;

30 a compound of Formula (50) wherein R^3 is cyclobutyl-
amino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me
and R^{4e} is H;

a compound of Formula (50) wherein R^3 is
 $N(Me)CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;

35 a compound of Formula (50) wherein R^3 is
 $N(Et)CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;

40 a compound of Formula (50) wherein R^3 is $N(Me)CH_2cPr$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
is H;

- a compound of Formula (50) wherein R^3 is $N(Et)CH_2cPr$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
 is H;
- 5 a compound of Formula (50) wherein R^3 is $N(Pr)CH_2cPr$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
 is H;
- 10 a compound of Formula (50) wherein R^3 is $N(Me)Pr$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is
 H;
- 15 a compound of Formula (50) wherein R^3 is $N(Me)Et$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is
 H;
- 20 a compound of Formula (50) wherein R^3 is $N(Me)Bu$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is
 H;
- 25 a compound of Formula (50) wherein R^3 is
 $N(Me)propargyl$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH(CH_3)CH_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is Me and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe) -$
 $CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is
 Me and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Me$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Et$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,

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

5 a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Pr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-$
 CH_2cPr , R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me
and R^{4e} is H;

a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH_2CH_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
is H;

20 a compound of Formula (50) wherein R^3 is $NHCH(cPr)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
is H;

25 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$,
 R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is H;

30 a compound of Formula (50) wherein R^3 is 2-
ethylpiperid-1-yl, R^{4a} is OMe, R^{4b} is H, R^{4c} is
OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is cyclobutyl-
amino, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;

35 a compound of Formula (50) wherein R^3 is
 $N(Me)CH_2CH=CH_2$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

40 a compound of Formula (50) wherein R^3 is
 $N(Et)CH_2CH=CH_2$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $N(Me)CH_2cPr$,
 R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is H;
- 5 a compound of Formula (50) wherein R^3 is $N(Et)CH_2cPr$,
 R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is H;
- 10 a compound of Formula (50) wherein R^3 is $N(Pr)CH_2cPr$,
 R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is H;
- 15 a compound of Formula (50) wherein R^3 is $N(Me)Pr$, R^{4a}
 is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 20 a compound of Formula (50) wherein R^3 is $N(Me)Et$, R^{4a}
 is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- a compound of Formula (50) wherein R^3 is $N(Me)Bu$, R^{4a}
 is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 25 a compound of Formula (50) wherein R^3 is
 $N(Me)propargyl$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is
 $N(Et)propargyl$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH(CH_3)CH_3$, R^{4a} is OMe, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe) -$
 $CH_2CH=CH_2$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d}
 is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Me$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe,

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

5 a compound of Formula (50) wherein R^3 is
N(CH₂CH₂OMe)Et, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is
N(CH₂CH₂OMe)Pr, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-
CH₂cPr, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is
NHCH(CH₃)CH₂CH₃, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

20 a compound of Formula (50) wherein R^3 is NHCH(cPr)₂,
 R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is H;

25 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)₂,
 R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is H;

30 a compound of Formula (50) wherein R^3 is NHCH(Et)₂, R^{4a}
is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is
H;

a compound of Formula (50) wherein R^3 is N(Et)₂, R^{4a} is
OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

35 a compound of Formula (50) wherein R^3 is 2-
ethylpiperid-1-yl, R^{4a} is OMe, R^{4b} is H, R^{4c} is
OMe, R^{4d} is Me and R^{4e} is H;

40 a compound of Formula (50) wherein R^3 is cyclobutyl-
amino, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me
and R^{4e} is H;

a compound of Formula (50) wherein R^3 is

$\text{N}(\text{Me})\text{CH}_2\text{CH}=\text{CH}_2$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

5 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})\text{CH}_2\text{CH}=\text{CH}_2$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{CH}_2\text{cPr}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})\text{CH}_2\text{cPr}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $\text{N}(\text{Pr})\text{CH}_2\text{cPr}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

20 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{Pr}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

25 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{Et}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

30 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{Bu}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

35 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{propargyl}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})\text{propargyl}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

40 a compound of Formula (50) wherein R^3 is $\text{NHCH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_3$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-CH_2CH=CH_2$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
5
- a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)Me$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)Et$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is
15 $N(CH_2CH_2OMe)Pr$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-CH_2cPr$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is
20 Me and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $NHCH(CH_3)CH_2CH_3$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
25
- a compound of Formula (50) wherein R^3 is $NHCH(cPr)_2$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a} is
35 OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $N(Et)_2$, R^{4a} is
40 OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is 2-ethylpiperid-1-yl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- 5 a compound of Formula (50) wherein R^3 is cyclobutyl-amino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- 10 a compound of Formula (50) wherein R^3 is $N(Me)CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- 15 a compound of Formula (50) wherein R^3 is $N(Et)CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- 20 a compound of Formula (50) wherein R^3 is $N(Me)CH_2cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $N(Et)CH_2cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- 25 a compound of Formula (50) wherein R^3 is $N(Pr)CH_2cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- 30 a compound of Formula (50) wherein R^3 is $N(Me)Pr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- 35 a compound of Formula (50) wherein R^3 is $N(Me)Et$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- 40 a compound of Formula (50) wherein R^3 is $N(Me)Bu$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $N(Me)propargyl$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is Me;

- 5 a compound of Formula (50) wherein R^3 is
 $N(Et)propargyl$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH(CH_3)CH_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is H and R^{4e} is Me;
- 10 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-$
 $CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is
 H and R^{4e} is Me;
- 15 a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Me$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Et$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 20 R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Pr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is Me;
- 25 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-$
 CH_2cPr , R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
 and R^{4e} is Me;
- 30 a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH_2CH_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is Me;
- 35 a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 Me;
- a compound of Formula (50) wherein R^3 is $NHCH(cPr)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 40 is Me;

- a compound of Formula (50) wherein R^3 is $\text{NHCH}(\text{Et})_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 5 a compound of Formula (50) wherein R^3 is 2-ethylpiperid-1-yl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 10 a compound of Formula (50) wherein R^3 is cyclobutyl-amino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 15 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{CH}_2\text{CH}=\text{CH}_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 20 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})\text{CH}_2\text{CH}=\text{CH}_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{CH}_2\text{cPr}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 25 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})\text{CH}_2\text{cPr}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 30 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Pr})\text{CH}_2\text{cPr}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 35 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{Pr}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 40 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{Et}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{Bu}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

- 5 a compound of Formula (50) wherein R^3 is
 $N(Me)propargyl$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is OMe;
- a compound of Formula (50) wherein R^3 is
 $N(Et)propargyl$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is OMe;
- 10 a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH(CH_3)CH_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is H and R^{4e} is OMe;
- 15 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-$
 $CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is
 H and R^{4e} is OMe;
- 20 a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Me$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is OMe;
- 25 a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Et$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is OMe;
- a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Pr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is OMe;
- 30 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-$
 CH_2cPr , R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
 and R^{4e} is OMe;
- 35 a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH_2CH_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is OMe;
- 40 a compound of Formula (50) wherein R^3 is $NHCH(cPr)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is OMe;
- a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$,

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

5 a compound of Formula (50) wherein R^3 is $\text{NHCH}(\text{Et})_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

10 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

a compound of Formula (50) wherein R^3 is $\text{NHCH}(\text{Et})_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

15 a compound of Formula (50) wherein R^3 is 2-ethylpiperid-1-yl, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

20 a compound of Formula (50) wherein R^3 is cyclobutyl-amino, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

25 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{CH}_2\text{CH}=\text{CH}_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

30 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})\text{CH}_2\text{CH}=\text{CH}_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

a compound of Formula (50) wherein R^3 is $\text{N}(\text{Me})\text{CH}_2\text{cPr}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

35 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})\text{CH}_2\text{cPr}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

40 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Pr})\text{CH}_2\text{cPr}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

- a compound of Formula (50) wherein R^3 is N(Me)Pr, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 5 a compound of Formula (50) wherein R^3 is N(Me)Et, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 10 a compound of Formula (50) wherein R^3 is N(Me)Bu, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 15 a compound of Formula (50) wherein R^3 is N(Me)propargyl, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 20 a compound of Formula (50) wherein R^3 is N(Et)propargyl, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- a compound of Formula (50) wherein R^3 is NHCH(CH₃)CH(CH₃)CH₃, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 25 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-CH₂CH=CH₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 30 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Me, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 35 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Et, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 40 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Pr, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-CH₂cPr, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

and R^{4e} is OMe;

5 a compound of Formula (50) wherein R³ is
NHCH(CH₃)CH₂CH₃, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is OMe;

10 a compound of Formula (50) wherein R³ is NHCH(cPr)₂,
R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is OMe;

a compound of Formula (50) wherein R³ is N(CH₂CH₂OMe)₂,
R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is OMe;

15 a compound of Formula (50) wherein R³ is NHCH(Et)₂, R^{4a}
is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
OMe;

20 a compound of Formula (50) wherein R³ is N(Et)₂, R^{4a} is
Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;

a compound of Formula (50) wherein R³ is NHCH(Et)₂, R^{4a}
is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
H;
25

a compound of Formula (50) wherein R³ is 2-
ethylpiperid-1-yl, R^{4a} is Cl, R^{4b} is H, R^{4c} is
OMe, R^{4d} is H and R^{4e} is H;

30 a compound of Formula (50) wherein R³ is cyclobutyl-
amino, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;

35 a compound of Formula (50) wherein R³ is
N(Me)CH₂CH=CH₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R³ is
N(Et)CH₂CH=CH₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
40 R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R³ is N(Me)CH₂cPr,

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

5 a compound of Formula (50) wherein R^3 is N(Et)CH₂cPr,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is N(Pr)CH₂cPr,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is N(Me)Pr, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is N(Me)Et, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

20 a compound of Formula (50) wherein R^3 is N(Me)Bu, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

25 a compound of Formula (50) wherein R^3 is N(Me)propargyl, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

30 a compound of Formula (50) wherein R^3 is N(Et)propargyl, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

35 a compound of Formula (50) wherein R^3 is NHCH(CH₃)CH(CH₃)CH₃, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-CH₂CH=CH₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

40 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Me, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Et$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is
 $N(CH_2CH_2OMe)Pr$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-$
 CH_2cPr , R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is
 $NHCH(CH_3)CH_2CH_3$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $NHCH(cPr)_2$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is H;
- a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is H;
- 25 a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a}
is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
H;
- 30 a compound of Formula (50) wherein R^3 is $N(Et)_2$, R^{4a}
is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.
- 35 a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a}
is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is
H;
- a compound of Formula (50) wherein R^3 is 2-
ethylpiperid-1-yl, R^{4a} is Cl, R^{4b} is H, R^{4c} is
OMe, R^{4d} is F and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is cyclobutyl-
amino, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F

and R^{4e} is H;

5 a compound of Formula (50) wherein R³ is
N(Me)CH₂CH=CH₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
R^{4d} is F and R^{4e} is H;

10 a compound of Formula (50) wherein R³ is
N(Et)CH₂CH=CH₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
R^{4d} is F and R^{4e} is H;

a compound of Formula (50) wherein R³ is N(Me)CH₂cPr,
R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e}
is H;

15 a compound of Formula (50) wherein R³ is N(Et)CH₂cPr,
R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e}
is H;

20 a compound of Formula (50) wherein R³ is N(Pr)CH₂cPr,
R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e}
is H;

25 a compound of Formula (50) wherein R³ is N(Me)Pr, R^{4a}
is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is
H;

a compound of Formula (50) wherein R³ is N(Me)Et, R^{4a}
is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is
30 H;

a compound of Formula (50) wherein R³ is N(Me)Bu, R^{4a}
is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is
H;

35 a compound of Formula (50) wherein R³ is
N(Me)propargyl, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
R^{4d} is F and R^{4e} is H;

40 a compound of Formula (50) wherein R³ is
NH(CH(CH₃)CH(CH₃)CH₃), R^{4a} is Cl, R^{4b} is H, R^{4c} is
OMe, R^{4d} is F and R^{4e} is H;

a compound of Formula (50) wherein R³ is N(CH₂CH₂OMe) -

$\text{CH}_2\text{CH}=\text{CH}_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;

5 a compound of Formula (50) wherein R^3 is
 $\text{N}(\text{CH}_2\text{CH}_2\text{OMe})\text{Me}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is F and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is
 $\text{N}(\text{CH}_2\text{CH}_2\text{OMe})\text{Et}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is F and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is
 $\text{N}(\text{CH}_2\text{CH}_2\text{OMe})\text{Pr}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is F and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $\text{N}(\text{CH}_2\text{CH}_2\text{OMe})\text{-CH}_2\text{cPr}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;

20 a compound of Formula (50) wherein R^3 is
 $\text{NH}(\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3)$, R^{4a} is Cl, R^{4b} is F, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

25 a compound of Formula (50) wherein R^3 is $\text{NHCH}(\text{cPr})_2$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e}
 is H;

30 a compound of Formula (50) wherein R^3 is $\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e}
 is H;

35 a compound of Formula (50) wherein R^3 is $\text{NHCH}(\text{Et})_2$, R^{4a}
 is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is
 H;

a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})_2$, R^{4a}
 is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H.

40 a compound of Formula (50) wherein R^3 is $\text{NHCH}(\text{Et})_2$, R^{4a}
 is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is
 H;

- 5 a compound of Formula (50) wherein R^3 is 2-ethylnpiperid-1-yl, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is cyclobutyl-amino, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $N(Me)CH_2CH=CH_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $N(Et)CH_2CH=CH_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $N(Me)CH_2cPr$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $N(Et)CH_2cPr$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $N(Pr)CH_2cPr$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $N(Me)Pr$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $N(Me)Et$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $N(Me)Bu$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is

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

5 a compound of Formula (50) wherein R^3 is
 NH(CH(CH₃))CH(CH₃)CH₃, R^{4a} is Cl, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is OMe and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-
 CH₂CH=CH₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is
 F and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is
 N(CH₂CH₂OMe)Me, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is OMe and R^{4e} is H;

a compound of Formula (50) wherein R^3 is
 N(CH₂CH₂OMe)Et, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is OMe and R^{4e} is H;

20 a compound of Formula (50) wherein R^3 is
 N(CH₂CH₂OMe)Pr, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is OMe and R^{4e} is H;

25 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-
 CH₂cPr, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is
 OMe and R^{4e} is H;

30 a compound of Formula (50) wherein R^3 is
 NHCH(CH₃)CH₂CH₃, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is OMe and R^{4e} is H;

35 a compound of Formula (50) wherein R^3 is NHCH(cPr)₂,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and
 R^{4e} is H;

a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)₂,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and
 R^{4e} is H;

40 a compound of Formula (50) wherein R^3 is NHCH(Et)₂, R^{4a}
 is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is

H;

5 a compound of Formula (50) wherein R^3 is $N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (50) wherein R^3 is 2-ethylpiperid-1-yl, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is cyclobutyl-amino, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

20 a compound of Formula (50) wherein R^3 is $N(Me)CH_2CH=CH_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

25 a compound of Formula (50) wherein R^3 is $N(Et)CH_2CH=CH_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

30 a compound of Formula (50) wherein R^3 is $N(Me)CH_2cPr$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $N(Et)CH_2cPr$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

35 a compound of Formula (50) wherein R^3 is $N(Pr)CH_2cPr$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

40 a compound of Formula (50) wherein R^3 is $N(Me)Pr$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

- 5 a compound of Formula (50) wherein R^3 is N(Me)Et, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is N(Me)Bu, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is N(Me)propargyl, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is NH(CH(CH₃)CH(CH₃)CH₃), R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-CH₂CH=CH₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Me, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Et, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Pr, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-CH₂cPr, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is NH(CH(CH₃)CH₂CH₃), R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is NHCH(cPr)₂,

- R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$,
 R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and
 R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a}
is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is
H;
- 15 a compound of Formula (50) wherein R^3 is $N(Et)_2$, R^{4a}
is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e}
is H;
- 20 a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a}
is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is
H;
- 25 a compound of Formula (50) wherein R^3 is 2-
ethylpiperid-1-yl, R^{4a} is Me, R^{4b} is H, R^{4c} is
OMe, R^{4d} is OMe and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is cyclobutyl-
amino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe
and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is
 $N(Me)CH_2CH=CH_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is OMe and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $N(Et)CH_2cPr$,

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

5 a compound of Formula (50) wherein R^3 is N(Pr)CH₂cPr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

10 a compound of Formula (50) wherein R^3 is N(Me)Pr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

15 a compound of Formula (50) wherein R^3 is N(Me)Et, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (50) wherein R^3 is N(Me)Bu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

20 a compound of Formula (50) wherein R^3 is N(Me)propargyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

25 a compound of Formula (50) wherein R^3 is NH(CH(CH₃)CH(CH₃)CH₃), R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

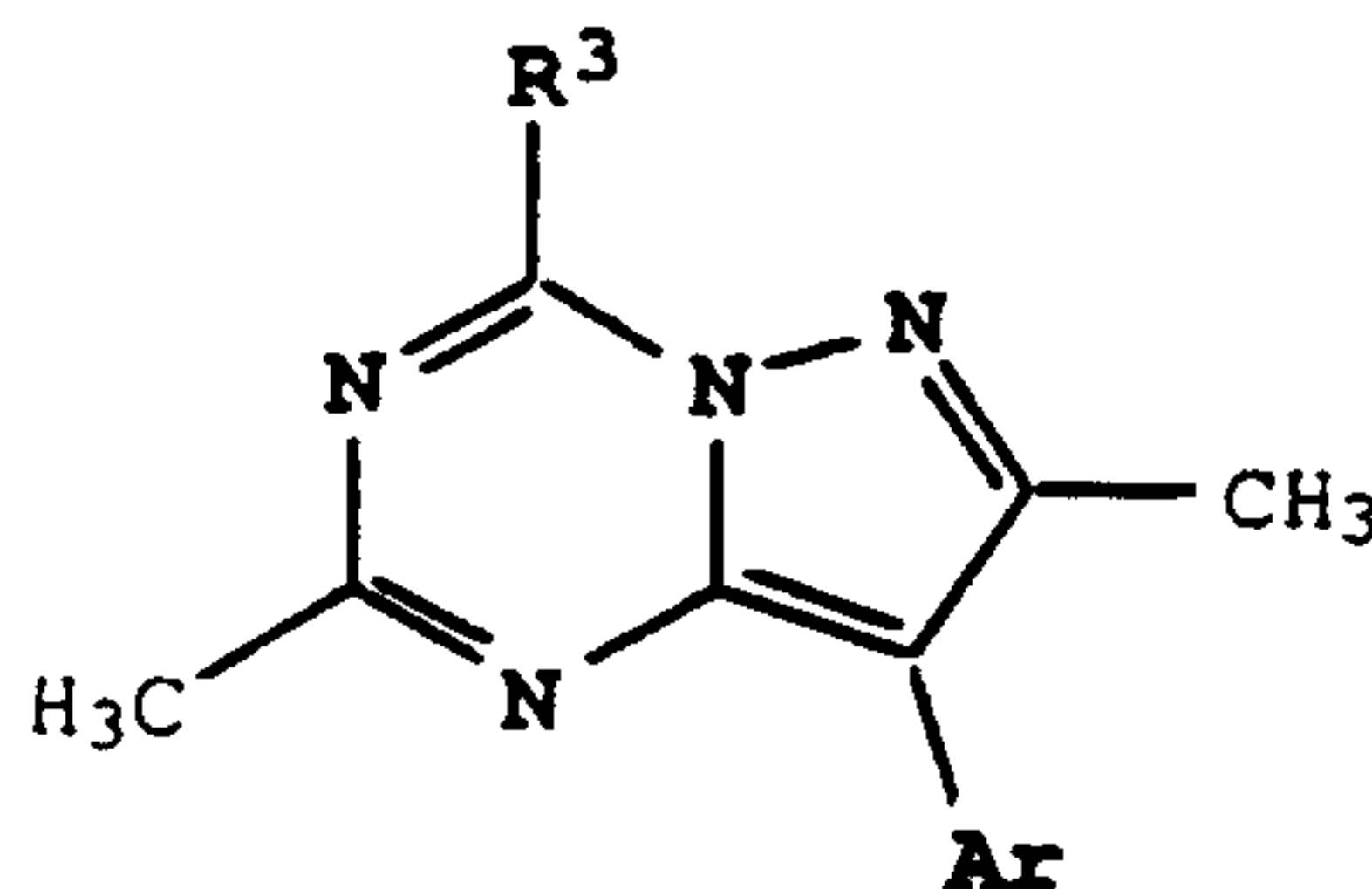
30 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-CH₂CH=CH₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;

35 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Me, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Et, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

40 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Pr, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

- 5 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-CH_2cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $NH(CH(CH_3)CH_2CH_3)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $NHCH(cPr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H; and
- 25 a compound of Formula (50) wherein R^3 is $N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H.
- [2] The present invention also provides compounds of Formula (60)



FORMULA (60)

and isomers thereof, stereoisomeric forms thereof, or

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

5 a compound of Formula (60) wherein R^3 is $\text{NHCH}(\text{Et})_2$, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is 2-ethylpiperid-1-yl, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
10

a compound of Formula (60) wherein R^3 is cyclobutyl-amino, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

15 a compound of Formula (60) wherein R^3 is $\text{N}(\text{Me})\text{CH}_2\text{CH}=\text{CH}_2$, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is $\text{N}(\text{Et})\text{CH}_2\text{cPr}$,
20 Ar is 6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is $\text{N}(\text{Pr})\text{CH}_2\text{cPr}$,
Ar is 6-dimethylamino-4-methylpyrid-3-yl;

25 a compound of Formula (60) wherein R^3 is $\text{N}(\text{Me})\text{Pr}$, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is $\text{N}(\text{Me})\text{Et}$, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
30

a compound of Formula (60) wherein R^3 is $\text{N}(\text{Me})\text{Bu}$, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

- a compound of Formula (60) wherein R^3 is
N(Me)propargyl, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
- 5 a compound of Formula (60) wherein R^3 is
N(Et)propargyl, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
10 NH(CH(CH₃)CH(CH₃)CH₃), Ar is 6-dimethylamino-4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is N(CH₂CH₂OMe)-
CH₂CH=CH₂, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
15
- a compound of Formula (60) wherein R^3 is
N(CH₂CH₂OMe)Me, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
20
- a compound of Formula (60) wherein R^3 is
N(CH₂CH₂OMe)Et, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
- 25 a compound of Formula (60) wherein R^3 is
N(CH₂CH₂OMe)Pr, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is N(CH₂CH₂OMe)-
30 CH₂cPr, Ar is 6-dimethylamino-4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
NH(CH(CH₃)CH₂CH₃), Ar is 6-dimethylamino-4-

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methypyrid-3-yl;

- 5 a compound of Formula (60) wherein R^3 is $NHCH(cPr)_2$ Ar is 6-dimethylamino-4-methypyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)_2$, Ar is 6-dimethylamino-4-methypyrid-3-yl;
- 10 a compound of Formula (60) wherein R^3 is $NHCH(Et)_2$ Ar is 6-dimethylamino-4-methypyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(Et)_2$, Ar is 6-dimethylamino-4-methypyrid-3-yl;
- 15 a compound of Formula (60) wherein R^3 is 2-ethylpiperid-1-yl, Ar is 6-dimethylamino-4-methypyrid-3-yl;
- a compound of Formula (60) wherein R^3 is cyclobutyl-amino, Ar is 6-dimethylamino-4-methypyrid-3-yl;
- 20 a compound of Formula (60) wherein R^3 is $N(Me)CH_2CH=CH_2$, Ar is 6-dimethylamino-4-methypyrid-3-yl;
- 25 a compound of Formula (60) wherein R^3 is $N(Et)CH_2cPr$, Ar is 6-dimethylamino-4-methypyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(Pr)CH_2cPr$, Ar is 6-dimethylamino-4-methypyrid-3-yl;
- 30 a compound of Formula (60) wherein R^3 is $N(Me)Pr$, Ar is

6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is N(Me)Et, Ar is
6-dimethylamino-4-methylpyrid-3-yl;

5

a compound of Formula (60) wherein R^3 is N(Me)Bu, Ar is
6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is
10 N(Me)propargyl, Ar is 6-dimethylamino-4-
methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is
NH(CH(CH₃)CH(CH₃)CH₃), Ar is 6-dimethylamino-4-
15 methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is N(CH₂CH₂OMe)-
CH₂CH=CH₂, Ar is 6-dimethylamino-4-methylpyrid-3-
yl;

20

a compound of Formula (60) wherein R^3 is
N(CH₂CH₂OMe)Me, Ar is 6-dimethylamino-4-
methylpyrid-3-yl;

25 a compound of Formula (60) wherein R^3 is
N(CH₂CH₂OMe)Et, Ar is 6-dimethylamino-4-
methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is
30 N(CH₂CH₂OMe)Pr, Ar is 6-dimethylamino-4-
methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is N(CH₂CH₂OMe)-

CH₂cPr, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R³ is
NH(CH(CH₃)CH₂CH₃), Ar is 6-dimethylamino-4-
5 methylpyrid-3-yl;

a compound of Formula (60) wherein R³ is NHCH(cPr)₂, Ar
is 6-dimethylamino-4-methylpyrid-3-yl;

10 a compound of Formula (60) wherein R³ is N(CH₂CH₂OMe)₂,
Ar is 6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R³ is NHCH(Et)₂, Ar
is 6-dimethylamino-4-methylpyrid-3-yl;

15

a compound of Formula (60) wherein R³ is N(Et)₂, Ar is
6-dimethylamino-4-methylpyrid-3-yl.

a compound of Formula (60) wherein R³ is 2-
20 ethylpiperid-1-yl, Ar is 6-methoxy-4-
methylpyrid-3-yl;

a compound of Formula (60) wherein R³ is cyclobutyl-
amino, Ar is 6-methoxy-4-methylpyrid-3-yl;

25

a compound of Formula (60) wherein R³ is
N(Me)CH₂CH=CH₂, Ar is 6-methoxy-4-methylpyrid-3-
yl;

30 a compound of Formula (60) wherein R³ is N(Et)CH₂cPr,
Ar is 6-methoxy-4-methylpyrid-3-yl;

- a compound of Formula (60) wherein R^3 is $N(Pr)CH_2cPr$,
Ar is 6-methoxy -4-methylpyrid-3-yl;
- 5 a compound of Formula (60) wherein R^3 is $N(Me)Pr$, Ar is
6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(Me)Et$, Ar is
6-methoxy -4-methylpyrid-3-yl;
- 10 a compound of Formula (60) wherein R^3 is $N(Me)Bu$, Ar is
6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
15 $N(Me)propargyl$, Ar is 6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
20 $N(Et)propargyl$, Ar is 6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
 $NHCH(CH_3)CH(CH_3)CH_3$, Ar is 6-methoxy -4-methylpyrid-3-yl;
- 25 a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)-CH_2CH=CH_2$, Ar is 6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
30 $N(CH_2CH_2OMe)Me$, Ar is 6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is

N(CH₂CH₂OMe)Et, Ar is 6-methoxy-4-methylpyrid-3-yl;

5 a compound of Formula (60) wherein R³ is
N(CH₂CH₂OMe)Pr, Ar is 6-methoxy-4-methylpyrid-3-yl;

10 a compound of Formula (60) wherein R³ is N(CH₂CH₂OMe)-
CH₂cPr, Ar is 6-methoxy-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R³ is
NHCH(CH₃)CH₂CH₃, Ar is 6-methoxy-4-methylpyrid-3-yl;

15 a compound of Formula (60) wherein R³ is NHCH(cPr)₂ Ar
is 6-methoxy-4-methylpyrid-3-yl;

20 a compound of Formula (60) wherein R³ is N(CH₂CH₂OMe)₂,
Ar is 6-methoxy-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R³ is NHCH(Et)₂ Ar
is 6-methoxy-4-methylpyrid-3-yl;

25 a compound of Formula (60) wherein R³ is N(Et)₂, Ar is
6-methoxy-4-methylpyrid-3-yl;

30 a compound of Formula (60) wherein R³ is 2-
ethylpiperid-1-yl, Ar is 4-methoxy-6-methylpyrid-3-yl;

a compound of Formula (60) wherein R³ is cyclobutyl-
amino, Ar is 4-methoxy-6-methylpyrid-3-yl;

- a compound of Formula (60) wherein R^3 is
 $N(Me)CH_2CH=CH_2$, Ar is 4-methoxy-6-methylpyrid-3-yl;
- 5 a compound of Formula (60) wherein R^3 is $N(Et)CH_2cPr$,
Ar is 4-methoxy-6-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(Pr)CH_2cPr$,
Ar is 4-methoxy-6-methylpyrid-3-yl;
- 10 a compound of Formula (60) wherein R^3 is $N(Me)Pr$, Ar is
4-methoxy-6-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(Me)Et$, Ar is
15 4-methoxy-6-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(Me)Bu$, Ar is
4-methoxy-6-methylpyrid-3-yl;
- 20 a compound of Formula (60) wherein R^3 is
 $N(Me)propargyl$, Ar is 4-methoxy-6-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
25 $NHCH(CH_3)CH(CH_3)CH_3$, Ar is 4-methoxy-6-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)-CH_2CH=CH_2$, Ar is 4-methoxy-6-methylpyrid-3-yl;
- 30 a compound of Formula (60) wherein R^3 is
 $N(CH_2CH_2OMe)Me$, Ar is 4-methoxy-6-methylpyrid-3-

yl;

5 a compound of Formula (60) wherein R^3 is
N(CH₂CH₂OMe)Et, Ar is 4-methoxy-6-methylpyrid-3-
yl;

10 a compound of Formula (60) wherein R^3 is
N(CH₂CH₂OMe)Pr, Ar is 4-methoxy-6-methylpyrid-3-
yl;

a compound of Formula (60) wherein R^3 is N(CH₂CH₂OMe)-
CH₂cPr, Ar is 4-methoxy-6-methylpyrid-3-yl;

15 a compound of Formula (60) wherein R^3 is
NH(CH(CH₃)CH₂CH₃), Ar is 4-methoxy-6-methylpyrid-3-
yl;

20 a compound of Formula (60) wherein R^3 is NHCH(cPr)₂, Ar
is 4-methoxy-6-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is N(CH₂CH₂OMe)₂,
Ar is 4-methoxy-6-methylpyrid-3-yl;

25 a compound of Formula (60) wherein R^3 is NHCH(Et)₂, Ar
is 6-methoxy-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is N(Et)₂, Ar is
4-methoxy-6-methylpyrid-3-yl;

30 a compound of Formula (60) wherein R^3 is 2-
ethylpiperid-1-yl, Ar is 4,6-dimethylpyrid-3-yl;

- a compound of Formula (60) wherein R^3 is cyclobutyl-amino, Ar is 4,6-dimethylpyrid-3-yl;
- 5 a compound of Formula (60) wherein R^3 is
N(Me)CH₂CH=CH₂, Ar is 4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is N(Et)CH₂cPr,
Ar is 4,6-dimethylpyrid-3-yl;
- 10 a compound of Formula (60) wherein R^3 is N(Pr)CH₂cPr,
Ar is 4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is N(Me)Pr, Ar is
4,6-dimethylpyrid-3-yl;
- 15 a compound of Formula (60) wherein R^3 is N(Me)Et Ar is
4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is N(Me)Bu, Ar is
20 4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
N(Me)propargyl, Ar is 4,6-dimethylpyrid-3-yl;
- 25 a compound of Formula (60) wherein R^3 is
N(Et)propargyl, Ar is 4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
NHCH(CH₃)CH(CH₃)CH₃, Ar is 4,6-dimethylpyrid-3-yl;
- 30 a compound of Formula (60) wherein R^3 is N(CH₂CH₂OMe) -
CH₂CH=CH₂, Ar is 4,6-dimethylpyrid-3-yl;

- a compound of Formula (60) wherein R^3 is
 $N(CH_2CH_2OMe)Me$, Ar is 4,6-dimethylpyrid-3-yl;
- 5 a compound of Formula (60) wherein R^3 is
 $N(CH_2CH_2OMe)Et$, Ar is 4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
 $N(CH_2CH_2OMe)Pr$, Ar is 4,6-dimethylpyrid-3-yl;
- 10 a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)-$
 CH_2cPr , Ar is 4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
15 $NHCH(CH_3)CH_2CH_3$, Ar is 4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $NHCH(cPr)_2$, Ar
is 4,6-dimethylpyrid-3-yl;
- 20 a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)_2$,
Ar is 4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $NHCH(Et)_2$ Ar
is 4,6-dimethylpyrid-3-yl;
- 25 a compound of Formula (60) wherein R^3 is $N(Et)_2$, Ar is
4,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is 2-
30 ethylpiperid-1-yl, Ar is 2,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is cyclobutyl-

amino, Ar is 2,6-dimethylpyrid-3-yl;

a compound of Formula (60) wherein R³ is
N(Me)CH₂CH=CH₂, Ar is 2,6-dimethylpyrid-3-yl;

5

a compound of Formula (60) wherein R³ is N(Et)CH₂cPr,
Ar is Ar is 2,6-dimethylpyrid-3-yl;

a compound of Formula (60) wherein R³ is N(Pr)CH₂cPr,
10 Ar is Ar is 2,6-dimethylpyrid-3-yl;

a compound of Formula (60) wherein R³ is N(Me)Pr, Ar is
2,6-dimethylpyrid-3-yl;

15 a compound of Formula (60) wherein R³ is N(Me)Et, Ar is
2,6-dimethylpyrid-3-yl;

a compound of Formula (60) wherein R³ is N(Me)Bu, Ar is
2,6-dimethylpyrid-3-yl;

20

a compound of Formula (60) wherein R³ is
N(Me)propargyl, Ar is 2,6-dimethylpyrid-3-yl;

a compound of Formula (60) wherein R³ is
25 NH(CH(CH₃)CH(CH₃)CH₃), Ar is 2,6-dimethylpyrid-3-
yl;

a compound of Formula (60) wherein R³ is N(CH₂CH₂OMe)-
CH₂CH=CH₂, Ar is 2,6-dimethylpyrid-3-yl;

30

a compound of Formula (60) wherein R³ is
N(CH₂CH₂OMe)Me, Ar is 2,6-dimethylpyrid-3-yl;

- a compound of Formula (60) wherein R^3 is
 $N(CH_2CH_2OMe)Et$, Ar is 2,6-dimethylpyrid-3-yl;
- 5 a compound of Formula (60) wherein R^3 is
 $N(CH_2CH_2OMe)Pr$, Ar is 2,6-dimethylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)-$
 CH_2cPr , Ar is 2,6-dimethylpyrid-3-yl;
- 10 a compound of Formula (60) wherein R^3 is
 $NH(CH(CH_3)CH_2CH_3)$, Ar is 2,6-dimethyl pyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $NHCH(cPr)_2$, Ar
 15 is 2,6-dimethyl pyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)_2$,
 Ar is 2,6-dimethylpyrid-3-yl;
- 20 a compound of Formula (60) wherein R^3 is $NHCH(Et)_2$, Ar
 is 2,6-dimethyl-pyrid-3-yl; and
- a compound of Formula (60) wherein R^3 is $N(Et)_2$, Ar is
 2,6-dimethyl-pyrid-3-yl.
- 25 [3] Specifically preferred compounds of the present
 invention include compounds and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 30 acceptable salt forms thereof, wherein said compound
 is selected from the group:

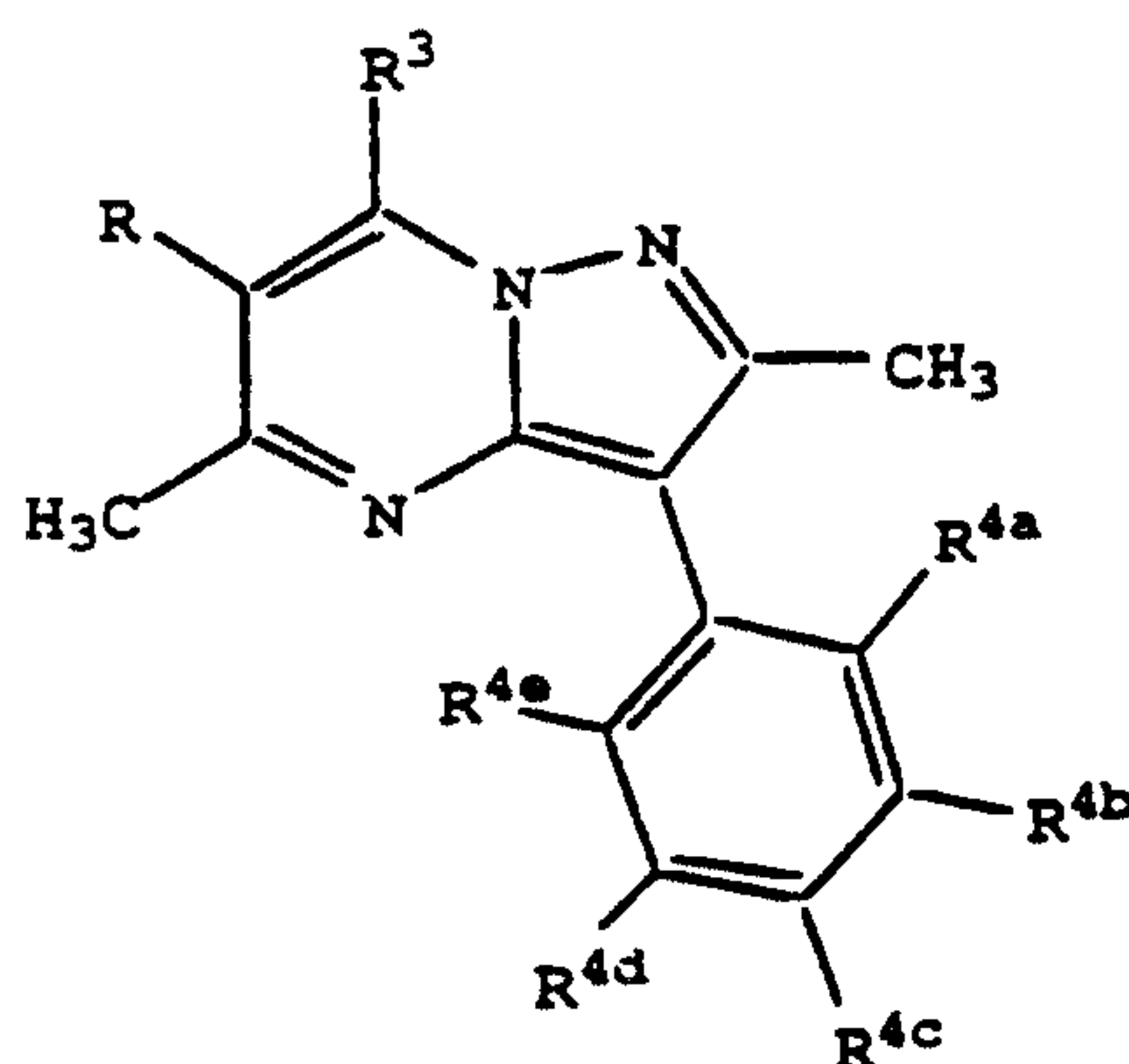
4-((2-butyl)amino)-2,7-dimethyl-8-(2-methyl-4-

- methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 4 - ((2-butyl) amino) -2,7-dimethyl-8-(2,5-di methyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 5 4 - ((3-pentyl) amino) -2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 10 4 - ((3-pentyl) amino) -2,7-dimethyl-8-(2-methyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 15 4 - (N-cyclopropylmethyl-N-propylamino) -2,7-dimethyl-8-(2-methyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 20 4 - (N-allyl-N-(2-methoxyethyl) amino) -2,7-dimethyl-8-(2-methyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 25 4 - (N-allyl-N-(2-methoxyethyl) amino) -2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 30 4 - (diallylamino) -2,7-dimethyl-8-(2-methyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 35 4 - (diallylamino) -2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-triazine;
- 4 - (N-ethyl-N-(2-methoxyethyl) amino) -2,7-dimethyl-8-(2-methyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-1,3,5-

triazine; and

4 - (N-ethyl-N- (2-methoxyethyl) amino) -2,7-dimethyl-8-
 (2,5-dimethyl-4-methoxyphenyl) - [1,5-a] -pyrazolo-
 5 1,3,5-triazine.

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



10

FORMULA (70)

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

20 a compound of Formula (70) wherein R is Cl, R³ is -
 NHCH(n-Pr)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
 is H and R^{4e} is H;

25 a compound of Formula (70) wherein R is Cl, R³ is -
 NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
 is H and R^{4e} is H;

30 a compound of Formula (70) wherein R is Cl, R³ is -
 N(CH₂CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
 is H and R^{4e} is H;

- a compound of Formula (70) wherein R is Cl, R³ is -N(c-Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (70) wherein R is Cl, R³ is -N(CH₂CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is Cl, R³ is -NHCH(CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is Cl, R³ is -NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (70) wherein R is Cl, R³ is -N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (70) wherein R is Cl, R³ is -N(n-Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (70) wherein R is Cl, R³ is -N(n-Bu)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is Cl, R³ is -NHCH(n-Pr)(CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (70) wherein R is Cl, R³ is -NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Cl, R³ is -NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (70) wherein R is Cl, R³ is (S) -

NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

5 a compound of Formula (70) wherein R is Cl, R³ is - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

10 a compound of Formula (70) wherein R is Cl, R³ is - N(CH₂CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

15 a compound of Formula (70) wherein R is Cl, R³ is - NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R³ is - NHCH(n-Pr)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

20 a compound of Formula (70) wherein R is Cl, R³ is - NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

25 a compound of Formula (70) wherein R is Cl, R³ is (S) - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

30 a compound of Formula (70) wherein R is Cl, R³ is - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

35 a compound of Formula (70) wherein R is Cl, R³ is -N(n-Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R³ is - N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

40 a compound of Formula (70) wherein R is Cl, R³ is (S) - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is

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

5 a compound of Formula (70) wherein R is Cl, R³ is -
NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is
Me, R^{4d} is H and R^{4e} is H;

10 a compound of Formula (70) wherein R is Cl, R³ is -
N(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H
and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R³ is -N(c-
Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;

15 a compound of Formula (70) wherein R is Cl, R³ is -N(c-
Pr)(CH₂CH₂CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;

20 a compound of Formula (70) wherein R is Cl, R³ is -NHCH
(n-Pr)(CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;

25 a compound of Formula (70) wherein R is Cl, R³ is -NHCH
(n-Pr)(CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me,
R^{4d} is H and R^{4e} is H;

30 a compound of Formula (70) wherein R is Cl, R³ is -
NHCH(Et)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is
OMe and R^{4e} is H;

a compound of Formula (70) wherein R is Cl, R³ is -
NHCH(Et)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is
H and R^{4e} is H;

35 a compound of Formula (70) wherein R is Cl, R³ is -
N(CH₂CH₂OMe)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;

40 a compound of Formula (70) wherein R is Cl, R³ is -
NHCH(CH₂OMe)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;

- a compound of Formula (70) wherein R is Cl, R³ is -
N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H
and R^{4e} is H;
- 5 a compound of Formula (70) wherein R is Cl, R³ is -
N(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is
OMe and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is Cl, R³ is -
NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is
OMe and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is Cl, R³ is -
N(CH₂CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}
is H and R^{4e} is H;
- 20 a compound of Formula (70) wherein R is Cl, R³ is -
NHCH(CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}
is H and R^{4e} is H;
- 25 a compound of Formula (70) wherein R is Cl, R³ is -
N(Pr)(CH₂CH₂CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is Cl, R³ is -
NHCH(Et)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (70) wherein R is Cl, R³ is -
NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is
H and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Cl, R³ is -
NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is
H and R^{4e} is H;
- a compound of Formula (70) wherein R is Cl, R³ is -

NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

5 a compound of Formula (70) wherein R is Cl, R³ is - NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

10 a compound of Formula (70) wherein R is Cl, R³ is - NEt₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

15 a compound of Formula (70) wherein R is Cl, R³ is - N(Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R³ is - NHCH(n-Pr)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

20 a compound of Formula (70) wherein R is Me, R³ is - NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

25 a compound of Formula (70) wherein R is Me, R³ is - N(CH₂CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

30 a compound of Formula (70) wherein R is Me, R³ is -N(c-Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

35 a compound of Formula (70) wherein R is Me, R³ is - N(CH₂CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R³ is - NHCH(CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

40 a compound of Formula (70) wherein R is Me, R³ is - NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is

H and R^{4e} is H;

5 a compound of Formula (70) wherein R is Me, R³ is -
N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H
and R^{4e} is H;

10 a compound of Formula (70) wherein R is Me, R³ is -N(n-
Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R³ is -N(n-
Bu)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;

15 a compound of Formula (70) wherein R is Me, R³ is -
NHCH(n-Pr)(CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is
Me, R^{4d} is H and R^{4e} is H;

20 a compound of Formula (70) wherein R is Me, R³ is -
NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is
H and R^{4e} is H;

25 a compound of Formula (70) wherein R is Me, R³ is -
NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;

30 a compound of Formula (70) wherein R is Me, R³ is (S) -
NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is
Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R³ is -
NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is
Me, R^{4d} is H and R^{4e} is H;

35 a compound of Formula (70) wherein R is Me, R³ is -
N(CH₂CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d}
is H and R^{4e} is H;

40 a compound of Formula (70) wherein R is Me, R³ is -
NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H
and R^{4e} is H;

- a compound of Formula (70) wherein R is Me, R³ is - NHCH(n-Pr)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (70) wherein R is Me, R³ is - NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is Me, R³ is (S) - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is Me, R³ is - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (70) wherein R is Me, R³ is -N(n-Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (70) wherein R is Me, R³ is - N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (70) wherein R is Me, R³ is (S) - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is Me, R³ is - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (70) wherein R is Me, R³ is - N(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (70) wherein R is Me, R³ is -N(c-Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Me, R³ is -N(c-

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- Pr) (CH₂CH₂CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (70) wherein R is Me, R³ is -NHCH (n-Pr) (CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is Me, R³ is -NHCH (n-Pr) (CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is Me, R³ is -NHCH(Et)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 20 a compound of Formula (70) wherein R is Me, R³ is -NHCH(Et)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (70) wherein R is Me, R³ is -NHCH(CH₂OMe)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is Me, R³ is -N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (70) wherein R is Me, R³ is -N(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Me, R³ is -N(CH₂CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}

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

5 a compound of Formula (70) wherein R is Me, R³ is -
NHCH(CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}
is H and R^{4e} is H;

10 a compound of Formula (70) wherein R is Me, R³ is -
N(Pr)(CH₂CH₂CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R³ is -
N(Bu)(Et), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is
H and R^{4e} is H;

15 a compound of Formula (70) wherein R is Me, R³ is -
NHCH(Et)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
R^{4d} is H and R^{4e} is H;

20 a compound of Formula (70) wherein R is Me, R³ is -
NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is
H and R^{4e} is H;

25 a compound of Formula (70) wherein R is Me, R³ is -
NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is
H and R^{4e} is H;

30 a compound of Formula (70) wherein R is Me, R³ is -
NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is
H and R^{4e} is H;

a compound of Formula (70) wherein R is Me, R³ is -
NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is
H and R^{4e} is H;

35 a compound of Formula (70) wherein R is Me, R³ is -
NEt₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H; and

40 a compound of Formula (70) wherein R is Me, R³ is -
N(Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;

- a compound of Formula (70) wherein R is F, R³ is -
NHCH(n-Pr)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;
- 5 a compound of Formula (70) wherein R is F, R³ is -
NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is F, R³ is -
N(CH₂CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is F, R³ is -N(c-
Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -
N(CH₂CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d}
20 is H and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -
NHCH(CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;
- 25 a compound of Formula (70) wherein R is F, R³ is -
NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is
H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is F, R³ is -
N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H
and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -N(n-
35 Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
is H and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -N(n-
Bu)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d}
40 is H and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -

NHCH(n-Pr)(CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- 5 a compound of Formula (70) wherein R is F, R³ is - NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is F, R³ is - NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is F, R³ is (S) - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (70) wherein R is F, R³ is - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (70) wherein R is F, R³ is - N(CH₂CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is F, R³ is - NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (70) wherein R is F, R³ is - NHCH(n-Pr)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is F, R³ is - NHCH(CH₂OMe)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is F, R³ is (S) - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is F, R³ is - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is

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

5 a compound of Formula (70) wherein R is F, R³ is -N(n-Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

10 a compound of Formula (70) wherein R is F, R³ is -N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R³ is (S) - NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

15 a compound of Formula (70) wherein R is F, R³ is -NH(CH₂CH₂OMe)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

20 a compound of Formula (70) wherein R is F, R³ is -N(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

25 a compound of Formula (70) wherein R is F, R³ is -N(c-Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

30 a compound of Formula (70) wherein R is F, R³ is -N(c-Pr)(CH₂CH₂CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R³ is -NHCH(n-Pr)(CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

35 a compound of Formula (70) wherein R is F, R³ is -NHCH(n-Pr)(CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

40 a compound of Formula (70) wherein R is F, R³ is -NHCH(Et)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

- a compound of Formula (70) wherein R is F, R³ is -
NHCH(Et)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is
H and R^{4e} is H;
5
- a compound of Formula (70) wherein R is F, R³ is -
N(CH₂CH₂OMe)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is F, R³ is -
NHCH(CH₂OMe)₂, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -
15 N(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H
and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -
N(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is
20 OMe and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -
NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is
25 OMe and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -
N(CH₂CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}
is H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is F, R³ is -
NHCH(CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}
is H and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -
35 N(Pr)(CH₂CH₂CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
R^{4d} is H and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -
N(Bu)(Et), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is
40 H and R^{4e} is H;

- a compound of Formula (70) wherein R is F, R³ is -
NHCH(Et)CH₂OMe, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (70) wherein R is F, R³ is -
NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is
H and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is F, R³ is -
NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is
H and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is F, R³ is -
NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is
H and R^{4e} is H;
- 20 a compound of Formula (70) wherein R is F, R³ is -
NHCH(Et)₂, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is
H and R^{4e} is H;
- a compound of Formula (70) wherein R is F, R³ is -NEt₂,
R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is H; and
- 25 a compound of Formula (70) wherein R is F, R³ is -
N(Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is Cl, R³ is -
N(Pr)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (70) wherein R is Cl, R³ is -
N(Et)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Cl, R³ is -
N(Me)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
- a compound of Formula (70) wherein R is Cl, R³ is -
NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

and R^{4e} is H;

- 5 a compound of Formula (70) wherein R is Cl, R³ is -
NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is Cl, R³ is -
NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is Cl, R³ is -NH-
2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;
- 20 a compound of Formula (70) wherein R is Cl, R³ is
cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (70) wherein R is Cl, R³ is -
N(Pr)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is Me and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is Cl, R³ is -
N(Et)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is Me and R^{4e} is H;
- 35 a compound of Formula (70) wherein R is Cl, R³ is -
N(Me)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is Me and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Cl, R³ is -
NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me
and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Cl, R³ is -
NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me
and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Cl, R³ is -
NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me

and R^{4e} is H;

5 a compound of Formula (70) wherein R is Cl, R³ is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

10 a compound of Formula (70) wherein R is Cl, R³ is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is ME and R^{4e} is H;

a compound of Formula (70) wherein R is F, R³ is -N(Pr)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

15 a compound of Formula (70) wherein R is F, R³ is -N(Et)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

20 a compound of Formula (70) wherein R is F, R³ is -N(Me)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

25 a compound of Formula (70) wherein R is F, R³ is -NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

30 a compound of Formula (70) wherein R is F, R³ is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (70) wherein R is F, R³ is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

35 a compound of Formula (70) wherein R is F, R³ is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

40 a compound of Formula (70) wherein R is F, R³ is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,

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

5 a compound of Formula (70) wherein R is F, R^3 is -
N(Pr)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;

10 a compound of Formula (70) wherein R is F, R^3 is -
N(Et)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;

a compound of Formula (70) wherein R is F, R^3 is -
N(Me)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is Me and R^{4e} is H;

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

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

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

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

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

35 a compound of Formula (70) wherein R is Me, R^3 is -
N(Pr)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

40 a compound of Formula (70) wherein R is Me, R^3 is -
N(Et)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;

- a compound of Formula (70) wherein R is Me, R³ is -
N(Me)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
5
- a compound of Formula (70) wherein R is Me, R³ is -
NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is Me, R³ is -
NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;
- 15 a compound of Formula (70) wherein R is Me, R³ is -
NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;
- 20 a compound of Formula (70) wherein R is Me, R³ is -NH-
2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H
and R^{4e} is H;
- 25 a compound of Formula (70) wherein R is Me, R³ is
cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (70) wherein R is Me, R³ is -
N(Pr)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is Me and R^{4e} is H;
- a compound of Formula (70) wherein R is Me, R³ is -
N(Et)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is Me and R^{4e} is H;
- 35 a compound of Formula (70) wherein R is Me, R³ is -
N(Me)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is Me and R^{4e} is H;
- 40 a compound of Formula (70) wherein R is Me, R³ is -
NMeEt, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me
and R^{4e} is H;

- a compound of Formula (70) wherein R is Me, R³ is -NMePr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 5 a compound of Formula (70) wherein R is Me, R³ is -NMeBu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 10 a compound of Formula (70) wherein R is Me, R³ is -NH-2-butyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H; and
- 15 a compound of Formula (70) wherein R is Me, R³ is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H.

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

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

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[7] The present invention still further provides methods of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-

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traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of the above-described compounds.

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

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of

carbon atoms. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" means a straight chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(S)" means the S enantiomer and the prefix "(R)" means the R enantiomer.

Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like.

"Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi- or polycyclic 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 substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables

are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of
5 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
10 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).

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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,
20 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
25 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
30 triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of
35 Formulae (1) and (2). Examples of pharmaceutically

acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

5 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
10 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
15 Company, Easton, PA, 1985, p. 1418.

"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
20 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,
25 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
30 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
35 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.

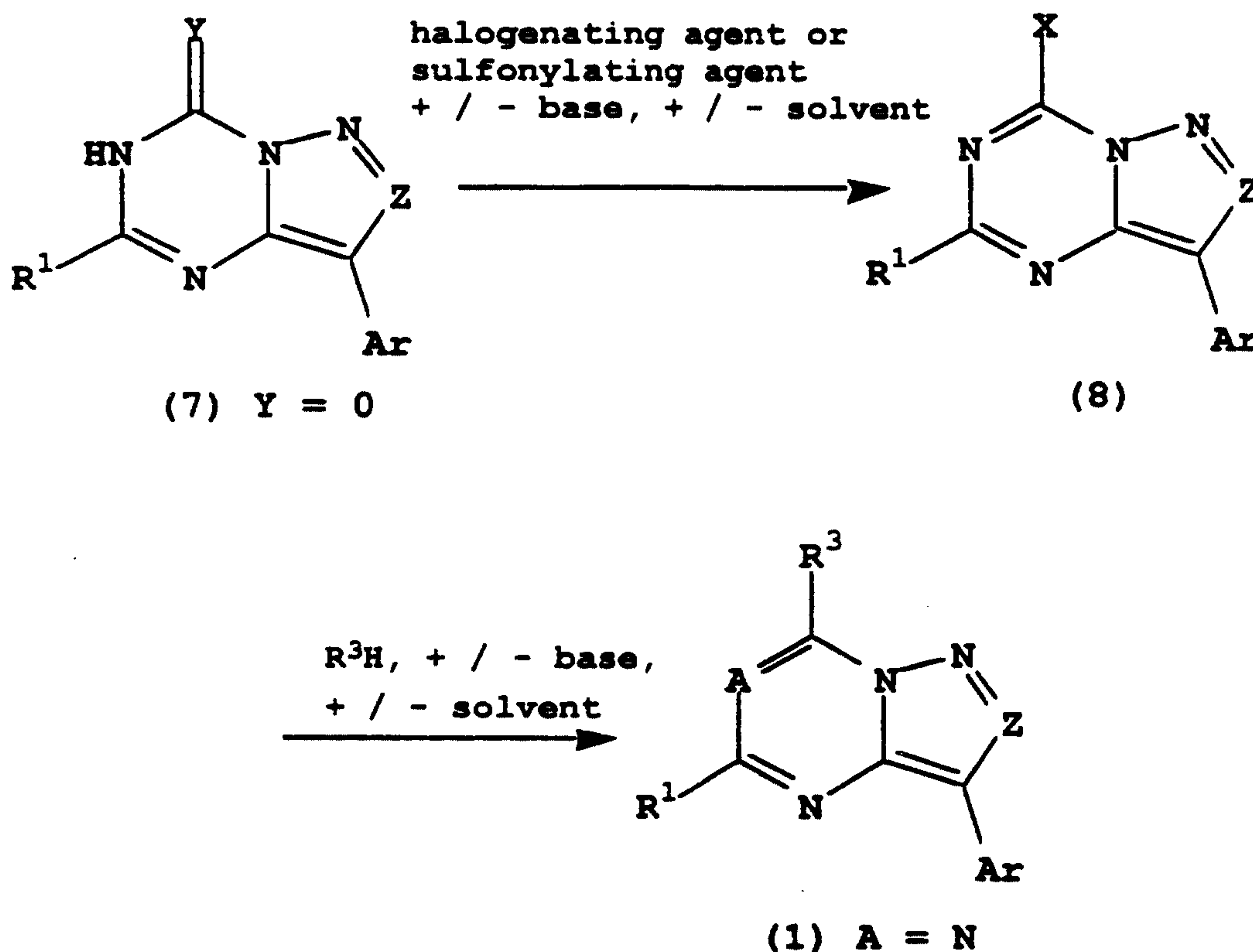
5

Syntheses

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

10

SCHEME 1



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

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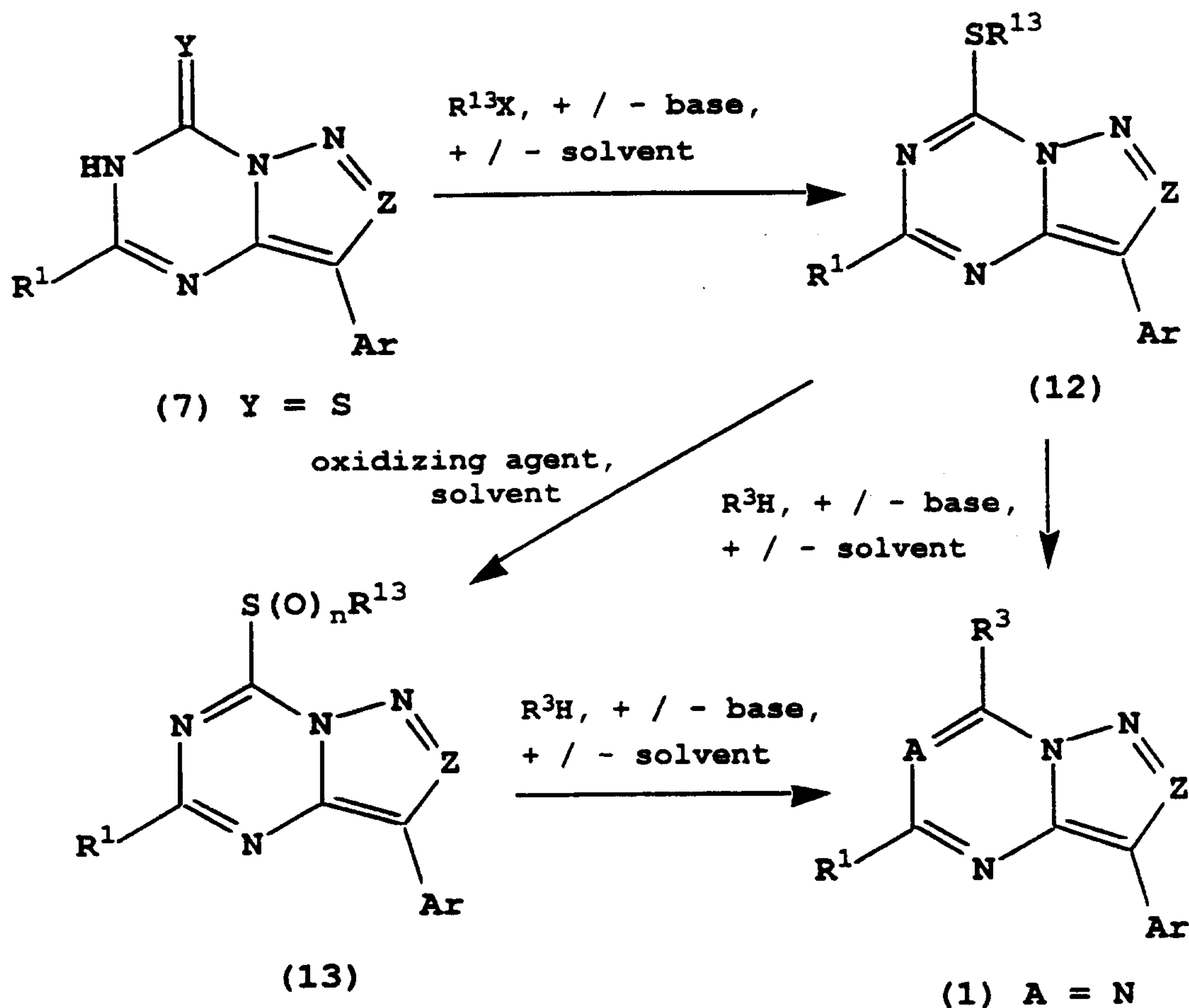
arylsulfonyloxy or haloalkane-sulfonyloxy).
Halogenating agents include, but are not limited to,
SOCl₂, POCl₃, PCl₃, PCl₅, POBr₃, PBr₃ or PBr₅.
Sulfonylating agents include, but are not limited to,
5 alkanesulfonyl halides or anhydrides (such as
methanesulfonyl chloride or methanesulfonic acid
anhydride), arylsulfonyl halides or anhydrides (such as
p-toluenesulfonyl chloride or anhydride) or
haloalkylsulfonyl halides or anhydrides (preferably
10 trifluoromethanesulfonic anhydride). Bases may
include, but are not limited to, alkali metal hydrides
(preferably sodium hydride), alkali metal alkoxides (1
to 6 carbons) (preferably sodium methoxide or sodium
ethoxide), alkaline earth metal hydrides, alkali metal
15 dialkylamides (preferably lithium di-isopropylamide),
alkali metal bis(trialkylsilyl)amides (preferably
sodium bis(trimethylsilyl)amide), trialkyl amines
(preferably N,N-di-isopropyl-N-ethyl amine or
triethylamine) or aromatic amines (preferably
20 pyridine). Inert solvents may include, but are not
limited to, lower alkanenitriles (1 to 6 carbons,
preferably acetonitrile), dialkyl ethers (preferably
diethyl ether), cyclic ethers (preferably
tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides
25 (preferably dimethylformamide), N,N-dialkylacetamides
(preferably dimethylacetamide), cyclic amides
(preferably N-methylpyrrolidin-2-one),
dialkylsulfoxides (preferably dimethylsulfoxide),
aromatic hydrocarbons (preferably benzene or toluene)
30 or haloalkanes of 1 to 10 carbons and 1 to 10 halogens
(preferably dichloromethane). Preferred reaction
temperatures range from -20°C to 100°C.

Compounds of Formula (8) may be reacted with
compounds of Formula R³H (where R³ is defined as above
35 except R³ is not SH, COR⁷, CO₂R⁷, aryl or heteroaryl)

in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80 to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, 5 alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, 10 alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but 15 are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N- 20 dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) 25 or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

Scheme 2 delineates the procedures for converting intermediate compounds of Formula (7) (where Y is S) to 30 some compounds of Formula (1).

SCHEME 2



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

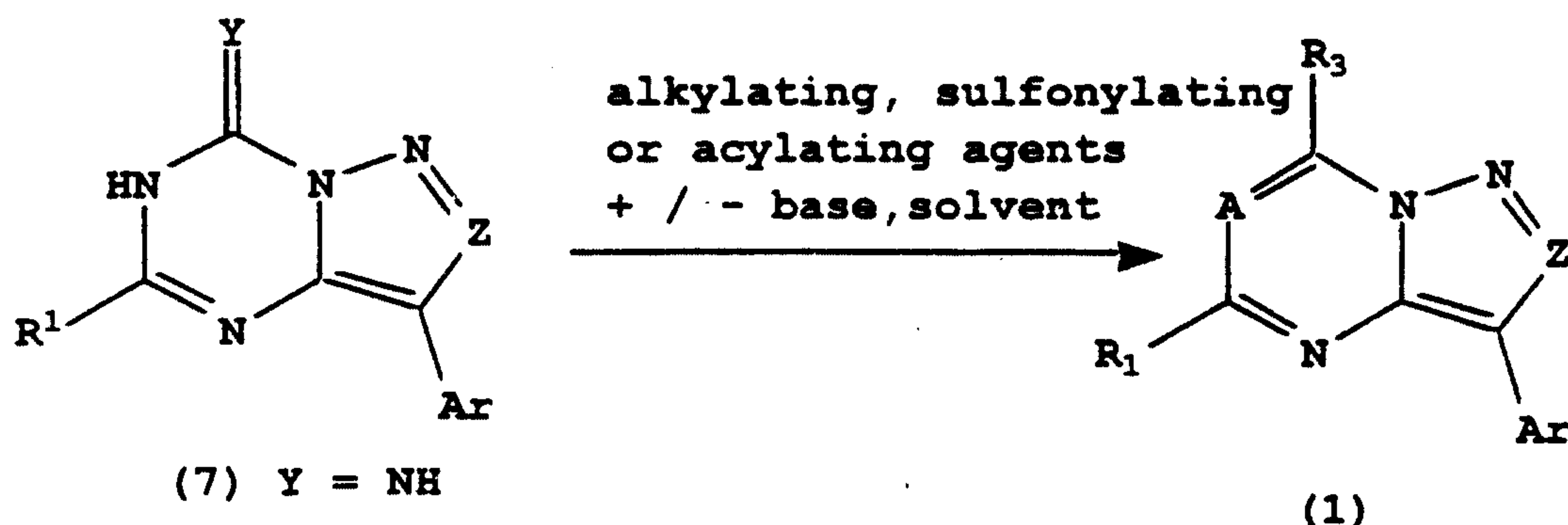
sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl
5 alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6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

Compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may then be reacted with compounds of Formula R^3H
20 to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme 1 above. Alternatively, compounds of Formula (12) (Formula (1) where R^3 is
25 SR^{13}) may be oxidized to compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) by treatment with an oxidizing agent in the presence of an inert solvent at temperatures ranging from -80°C to
30 250°C. Oxidizing agents include, but are not limited to, hydrogen peroxide, alkane or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid), dioxirane, oxone, or sodium periodate. Inert solvents may include, but are not limited to, alkanones (3 to 10 carbons, preferably acetone), water, alkyl

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

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

SCHEME 3



A = N;

 $R_3 = NR^6R^7, NR^8COR^7,$ $N(COR^7)_2, NR^8CONR^6R^7$ $NR^8CO_2R^{13}$

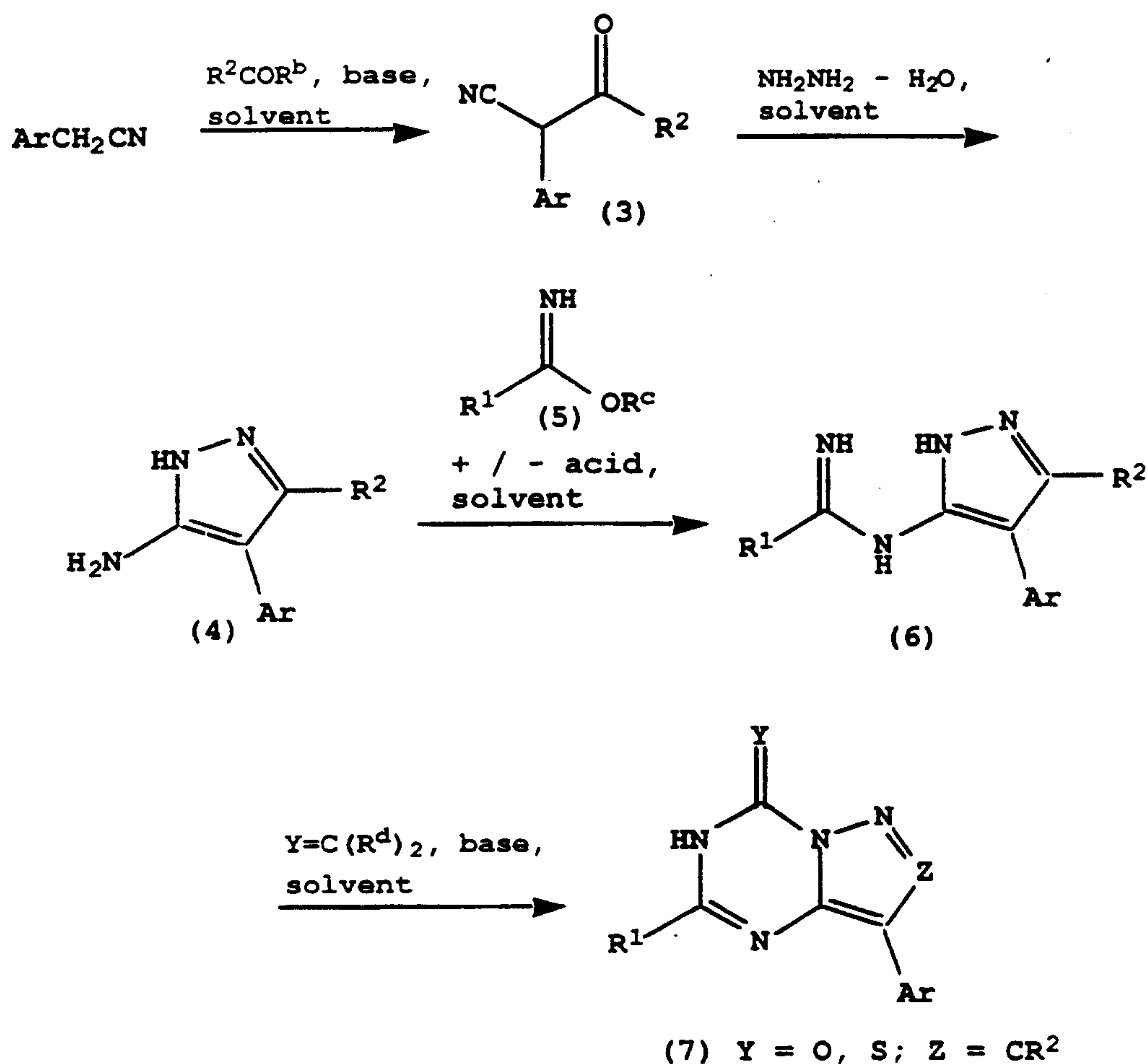
Reaction of compounds of Formula (7), where Y is NH, with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of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

mesylates or -triflates. Acylating agents may include, but are not limited to, C₁-C₁₀ alkanoyl halides or anhydrides, C₁-C₁₀ haloalkanoyl halides or anhydrides with 1 - 10 halogens, C₂-C₈ alkoxyalkanoyl halides or anhydrides, C₃-C₆ cycloalkanoyl halides or anhydrides, C₄-C₁₂ cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C₁-C₄) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C₁-C₄) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C₁-C₄) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C₁-C₁₀ alkylsulfonyl halides or anhydrides, C₁-C₁₀ haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C₂-C₈ alkoxyalkylsulfonyl halides or anhydrides, C₃-C₆ cycloalkylsulfonyl halides or anhydrides, C₄-C₁₂ cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C₁-C₄ alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C₁-C₄ alkyl)sulfonyl halides or anhydrides, heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C₁-C₄ alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower

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

Scheme 4 delineates procedures, which may be employed to prepare intermediate compounds of Formula (7), where Y is O, S and Z is CR².

SCHEME 4



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

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

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

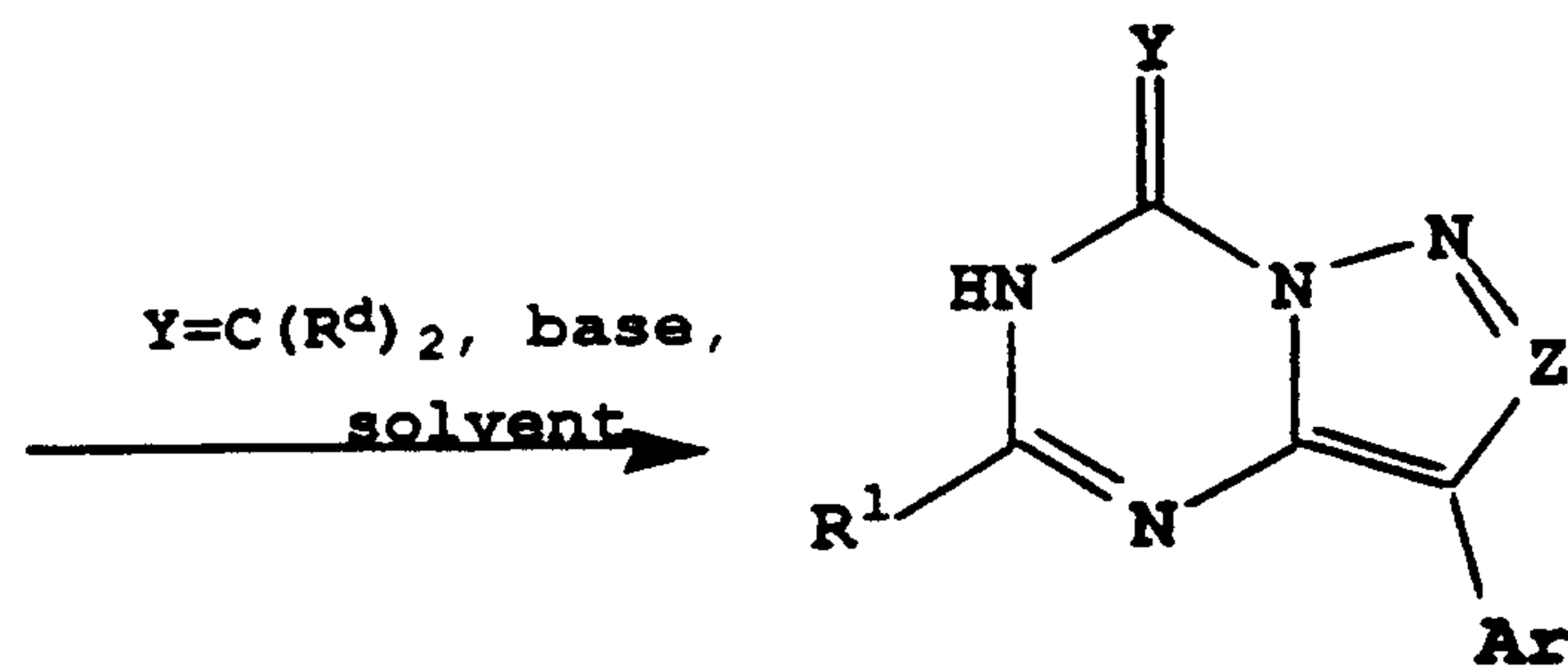
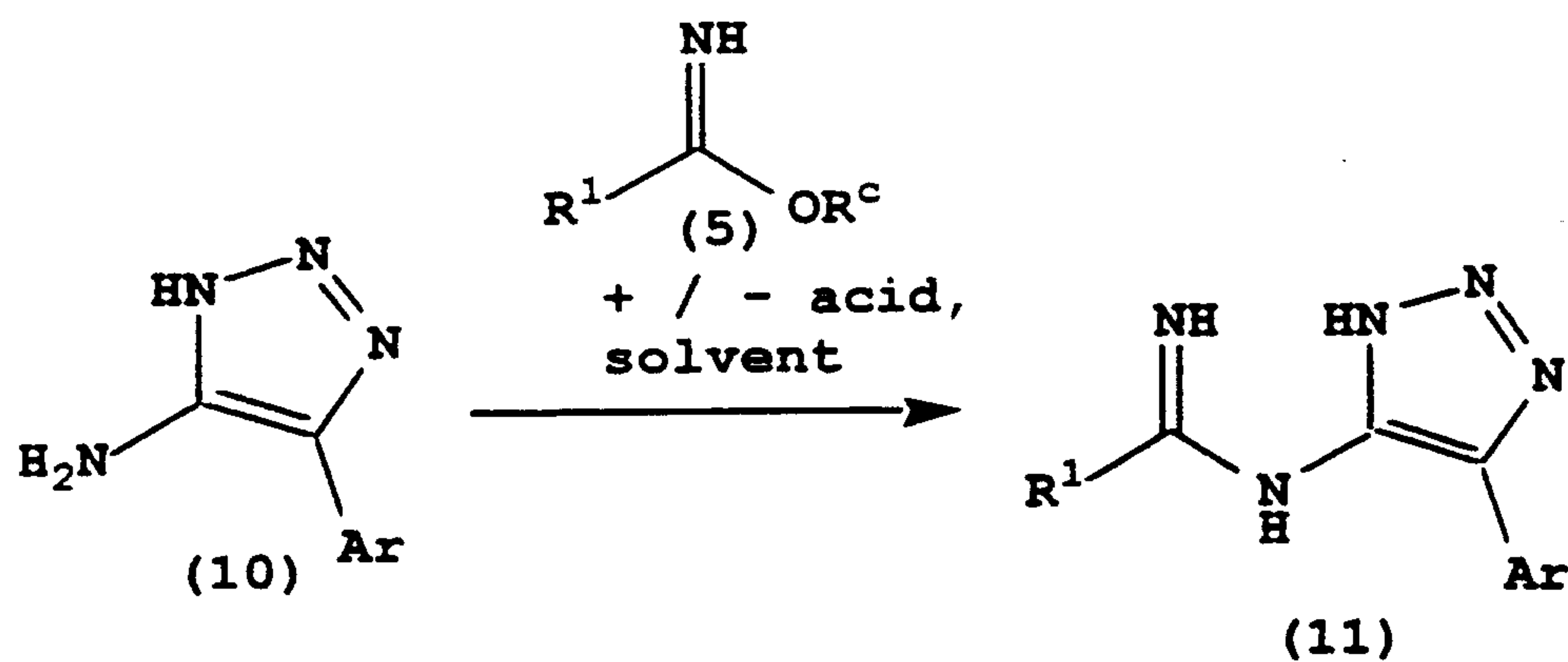
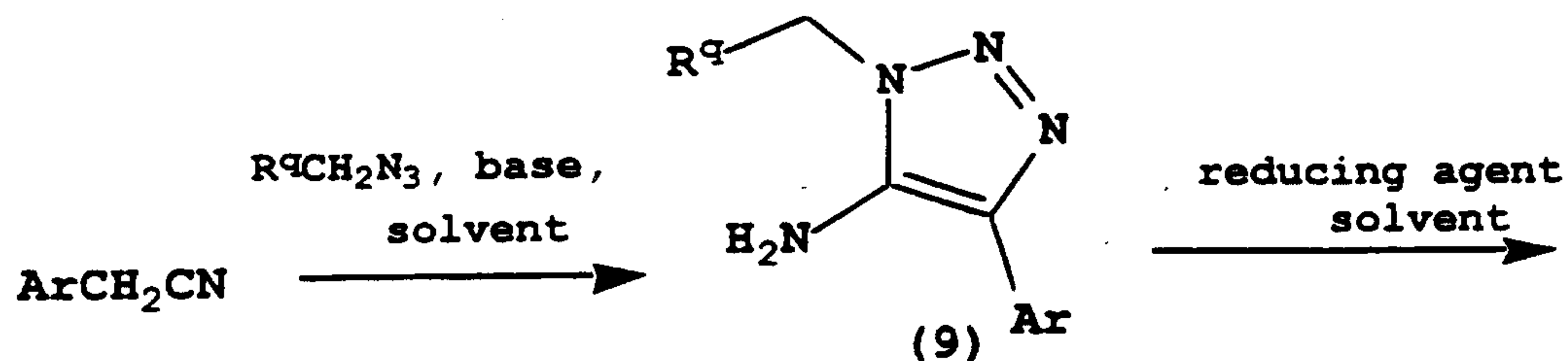
presence or absence of an acid in the presence of an inert solvent at temperatures ranging from 0°C to 200°C to produce compounds of Formula (6). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such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

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

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

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

SCHEME 5



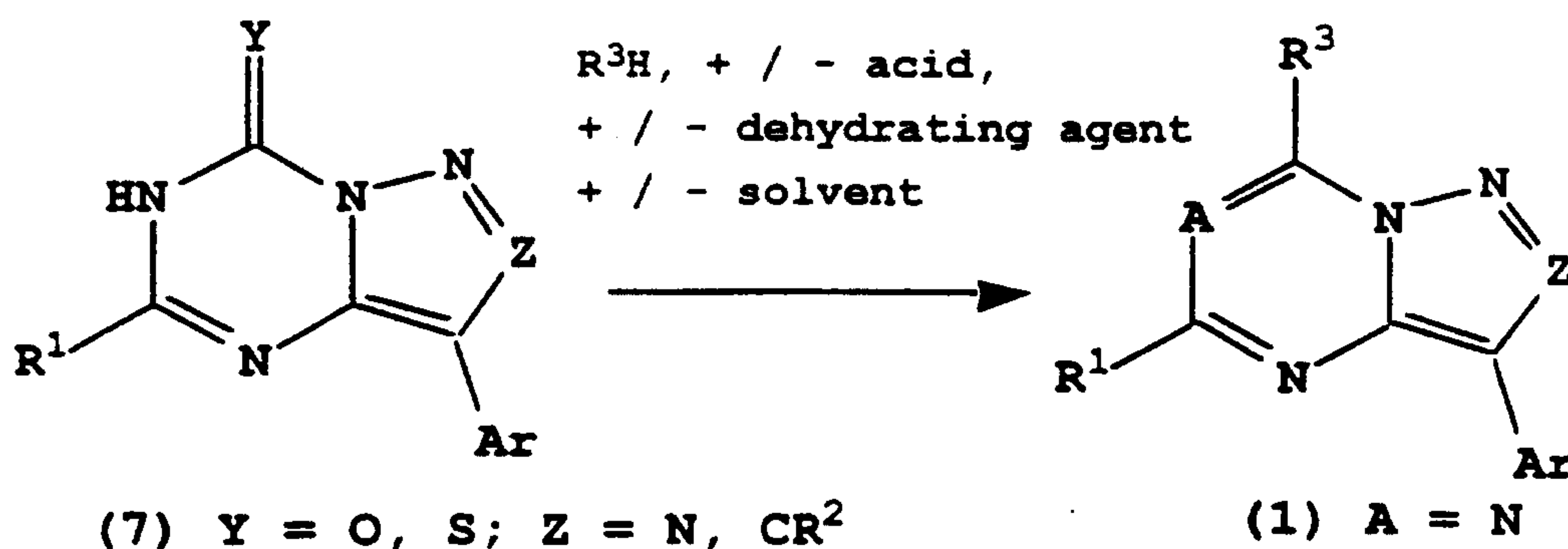
(7) Y = O, S; Z = N

Compounds of ArCH_2CN are reacted with compounds of Formula $\text{R}^q\text{CH}_2\text{N}_3$ (where R^q is a phenyl group optionally substituted by H, alkyl (1 to 6 carbons) or alkoxy (1 to 6 carbons) in the presence or absence of a base in an inert solvent at temperatures ranging from 0°C to 200°C to generate compounds of Formula (9). Bases may

include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide, sodium ethoxide or potassium t-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from ambient temperature to 100°C. Compounds of Formula (9) may be treated with a reducing agent in an inert solvent at -100°C to 100°C to afford products of Formula (10). Reducing agents include, but are not limited to, (a) hydrogen gas in combination with noble metal catalysts such as Pd-on-carbon, PtO₂, Pt-on-carbon, Rh-on-alumina or Raney nickel, (b) alkali metals (preferably sodium) in combination with liquid ammonia or (c) ceric ammonium nitrate. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably

- diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). The preferred reaction temperatures are -50°C to 60°C. Compounds of Formula (9) are then converted to compounds of Formula (7) (where Z is N) via intermediates of Formula (11) using the reagents and reaction conditions outlined in Scheme 4 for the conversion of compounds of Formula (4) to compounds of Formula (7) (where Z is CR²).
- Compounds of Formula (1) may also be prepared from compounds of Formula (7) (where Y is O, S and Z is defined above) as outlined in Scheme 6:

SCHEME 6



- Compounds of Formula (7) may be reacted with compounds of Formula R³H in the presence of a dehydrating agent in an inert solvent at reaction temperatures ranging from 0°C to 250°C. Dehydrating agents include, but are not limited to, P₂O₅, molecular sieves or inorganic or organic acids. Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic

acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid.

5 Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably glyme or diglyme), cyclic ethers (preferably

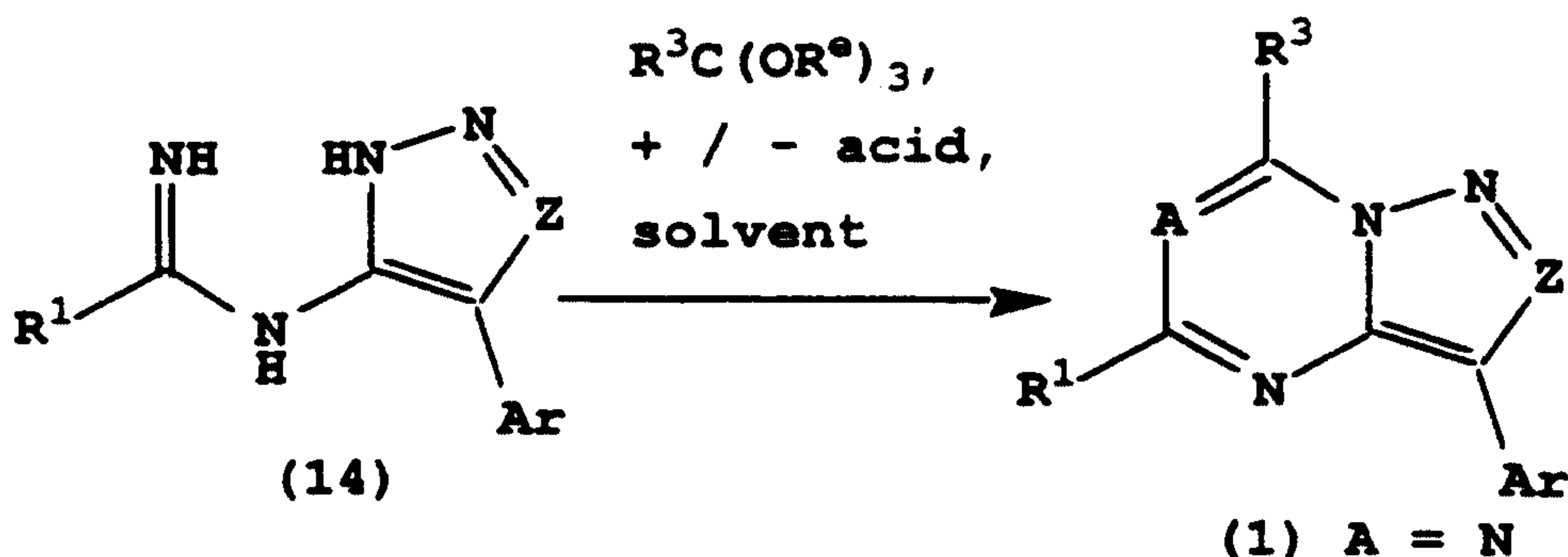
10 tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide),

15 aromatic hydrocarbons (preferably benzene or toluene) or halocarbons of 1 to 10 carbons and 1 to 10 halogens (preferably chloroform). Preferred reaction temperatures range from ambient temperature to 150°C.

Some compounds of Formula (1) (where A is N) may

20 also be prepared by the methods shown in Scheme 7:

SCHEME 7



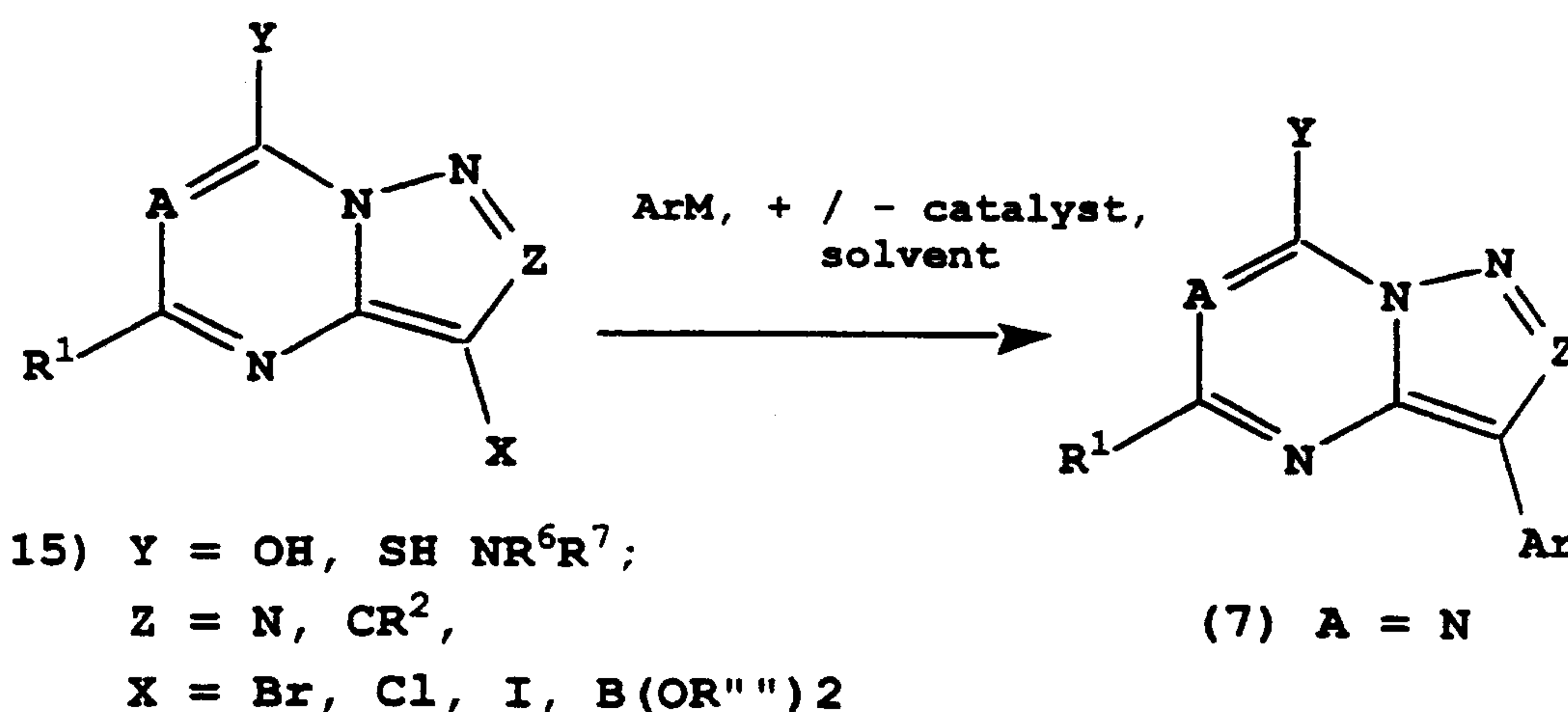
Intermediate compounds of Formula (14), where Z is defined above, may be reacted with compounds of Formula

25 R³C(OR^e)₃, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may

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

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

SCHEME 8

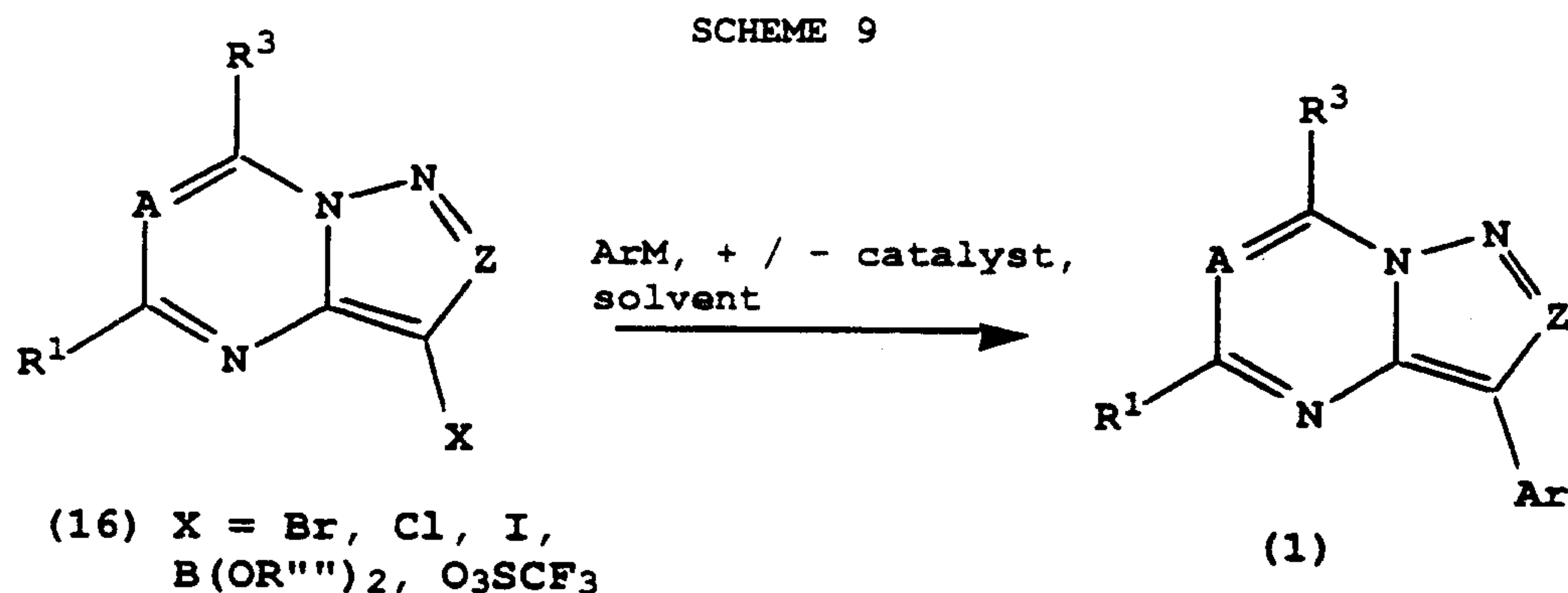


Compounds of Formula (15), (where Y is OH, SH, NR^6R^7 ; Z is defined above, X is Br, Cl, I, O_3SCF_3 or $\text{B}(\text{OR}''')_2$ and R''' is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl_2 , CeBr_2 or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C . Those skilled in the art will recognize that the reagents ArM may be generated in situ. Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as $\text{Pd}(\text{PPh}_3)_4$), palladium halides or alkanoates (such as $\text{PdCl}_2(\text{PPh}_3)_2$ or $\text{Pd}(\text{OAc})_2$) or nickel complexes (such as $\text{NiCl}_2(\text{PPh}_3)_2$). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C .

The choices of M and X are known to those skilled in the art (cf. Imamoto, T., Organocerium Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 231-250; Knochel, P., Organozinc, Organocadmium and Organomercury Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon

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

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



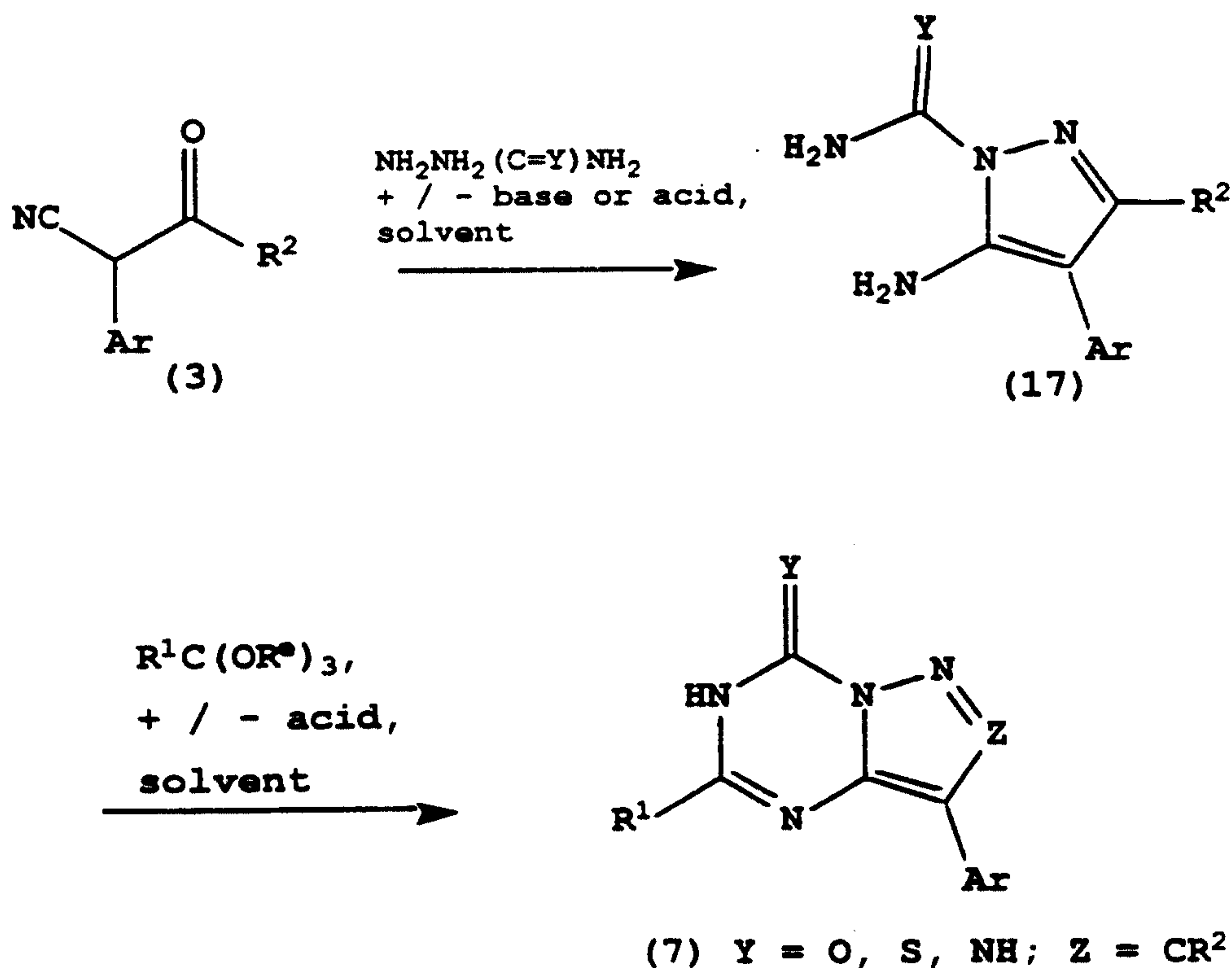
- 10 Compounds of Formula (16), where A, Z, R^1 and R^3 are defined above and X is Br, Cl, I, O_3SCF_3 or B(OR''')_2 and R''' is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl , ZnBr , ZnI , MgBr , MgCl , MgI , CeCl_2 ,
 15 CeBr_2 or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C . Those skilled in the art will recognize that the reagents ArM may be generated in
 20 situ (see the above references in Comprehensive Organic Synthesis). Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as $\text{Pd(PPh}_3)_4$), palladium halides or alkanoates (such as $\text{PdCl}_2(\text{PPh}_3)_2$ or Pd(OAc)_2) or nickel complexes (such as
 25 $\text{NiCl}_2(\text{PPh}_3)_2$). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines

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

Intermediate compounds of Formula (7) (where Y is O, S, NH, Z is CR² and R¹, R² and Ar are defined as above) may be prepared as illustrated in Scheme 10.

15

SCHEME 10



Compounds of Formula (3) may be reacted with compounds

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

Preferred reaction temperatures range from 0°C to 150°C. Compounds of Formula (17) may then be reacted with compounds of Formula $R^3C(OR^e)_3$, where R^e may be

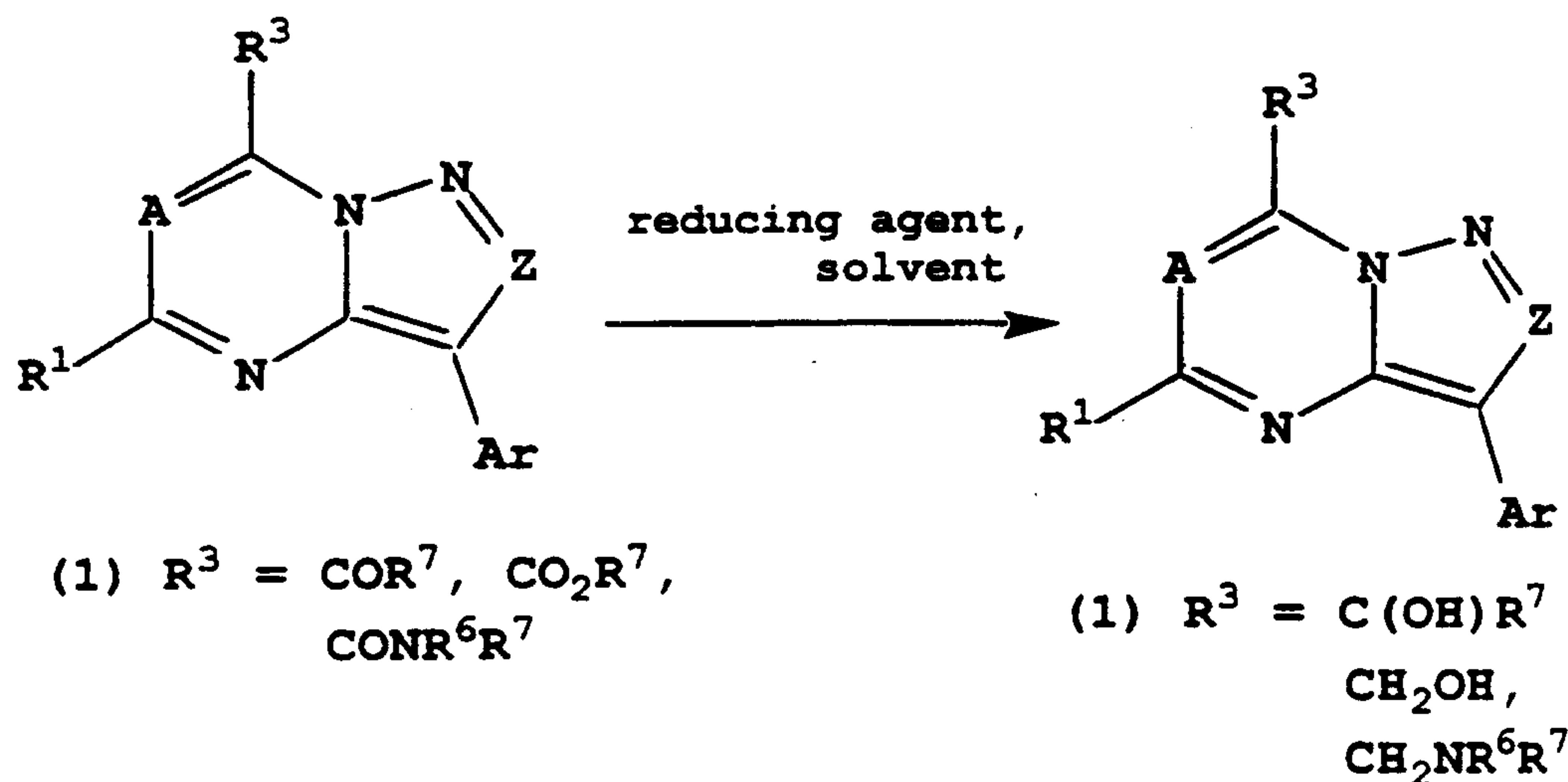
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alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably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

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

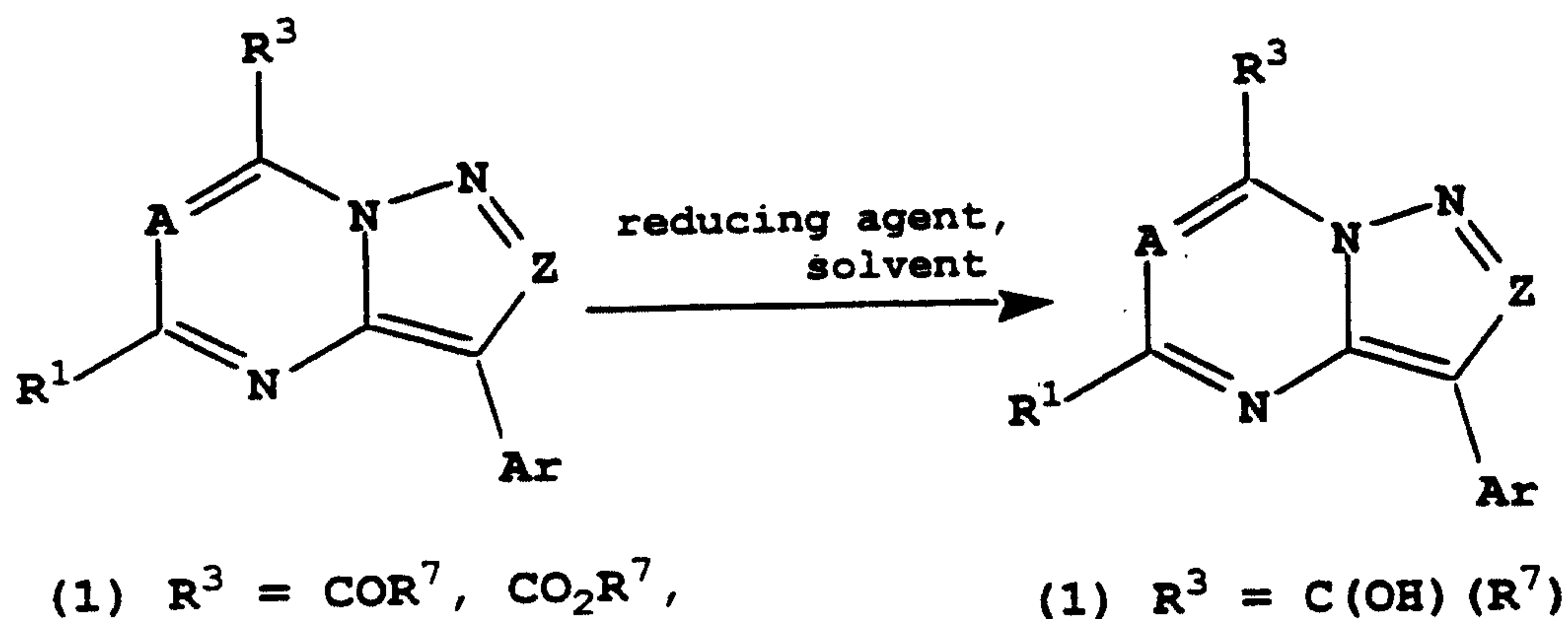
SCHEME 11



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

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

SCHEME 12

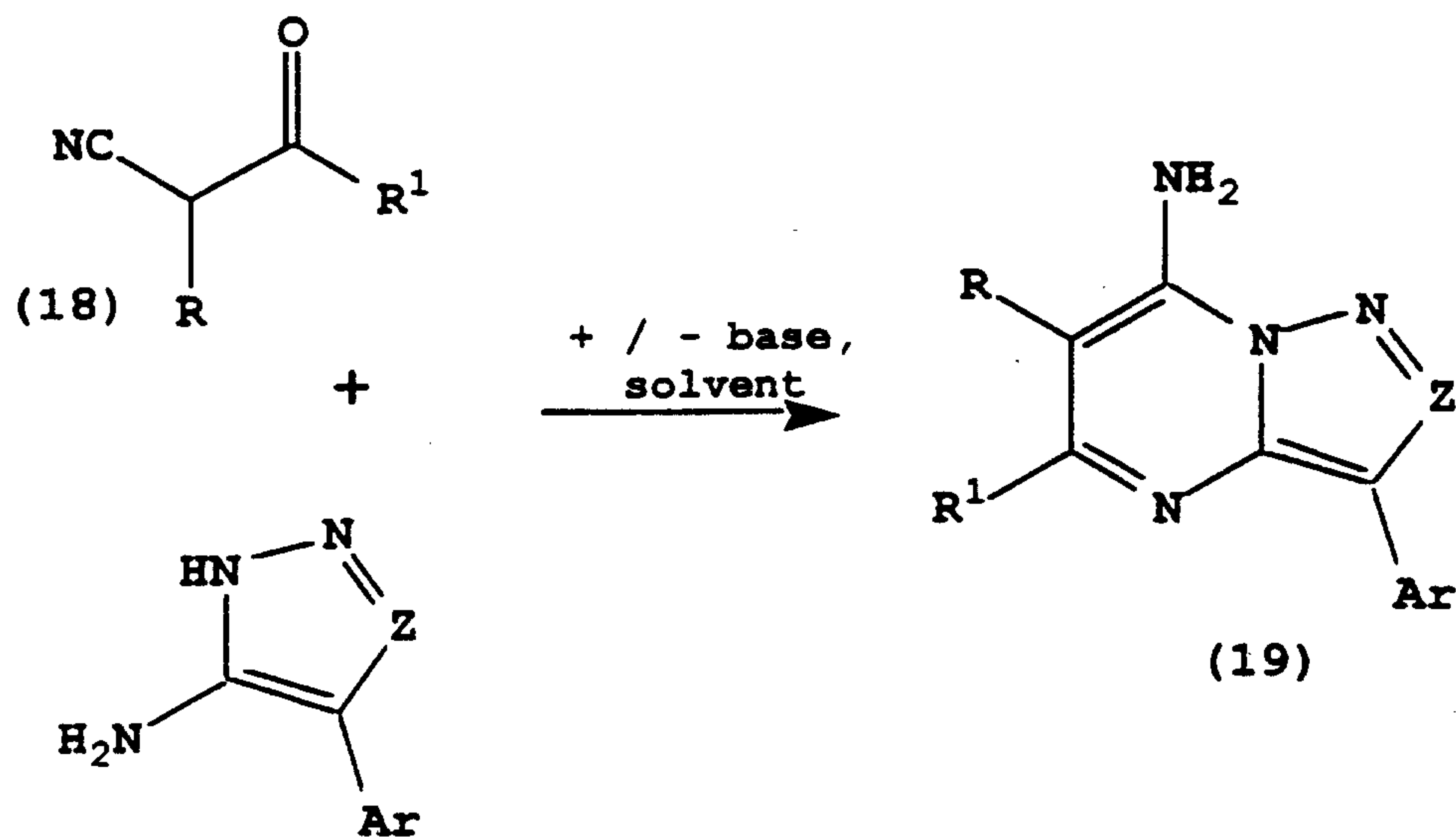
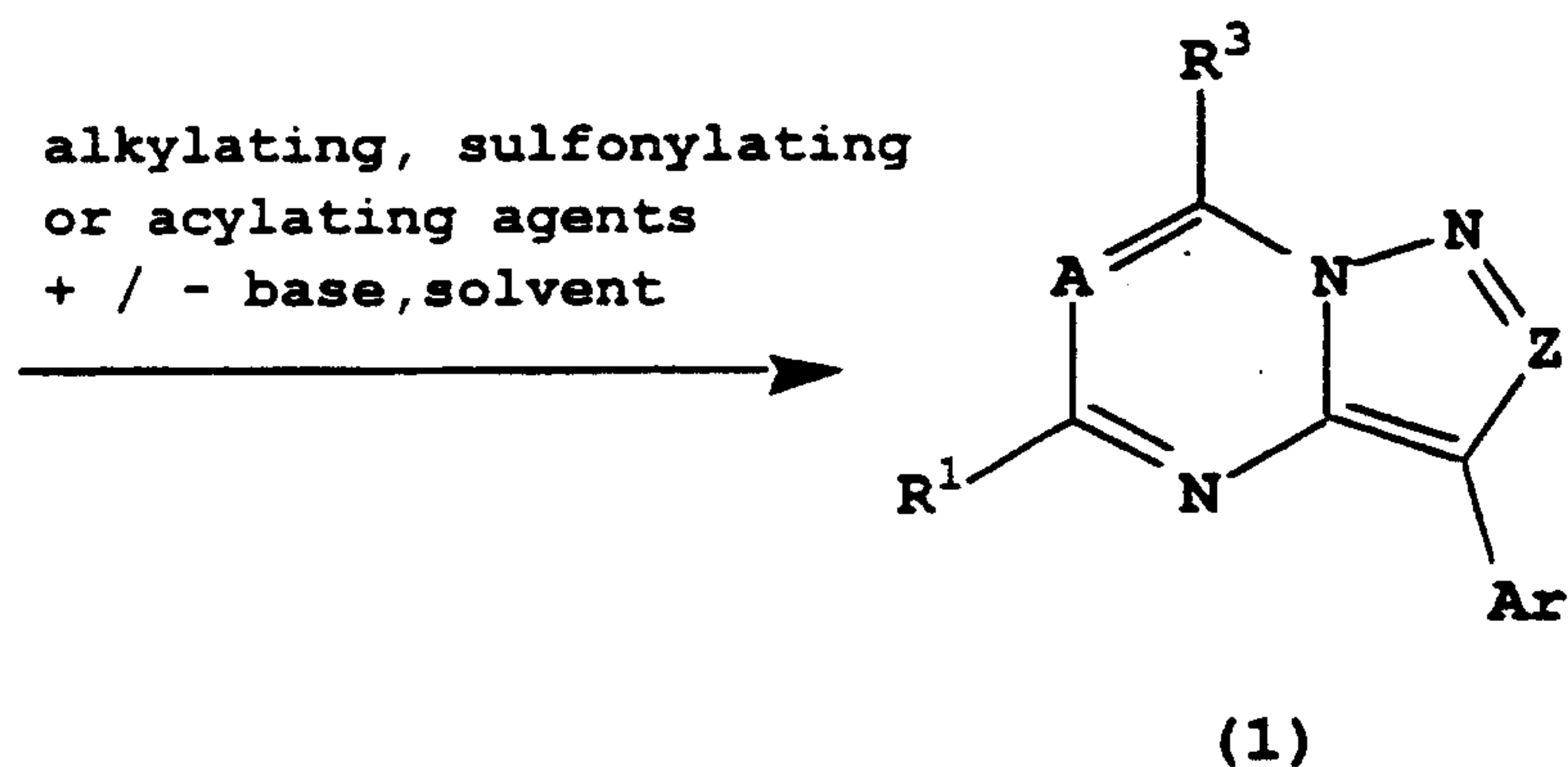


M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl₂, CeBr₂ or copper halides. Inert

5 solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

10 Compounds of Formula (1), where R³ may be - NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R¹³, -NR⁶R⁷, - NR⁸SO₂R⁷, may be synthesized as depicted in Scheme 13.

SCHEME 13

(4) $\text{Z} = \text{CR}_2$ (10) $\text{Z} = \text{N}$ 

(1)

 $\text{A} = \text{CR}$ $\text{R}_3 = \text{NR}^6\text{R}^7, \text{NR}^8\text{COR}^7,$ $\text{N}(\text{COR}^7)_2,$ $\text{NR}_8\text{CONR}^6\text{R}^7,$ $\text{NR}_8\text{CO}_2\text{R}_{13}$

Reaction of compounds of Formula (18), where R and R¹ are defined above, with compounds of Formula (4) or
 5 (10) in the presence or absence of base in an inert solvent may produce compounds of Formula (19) at

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

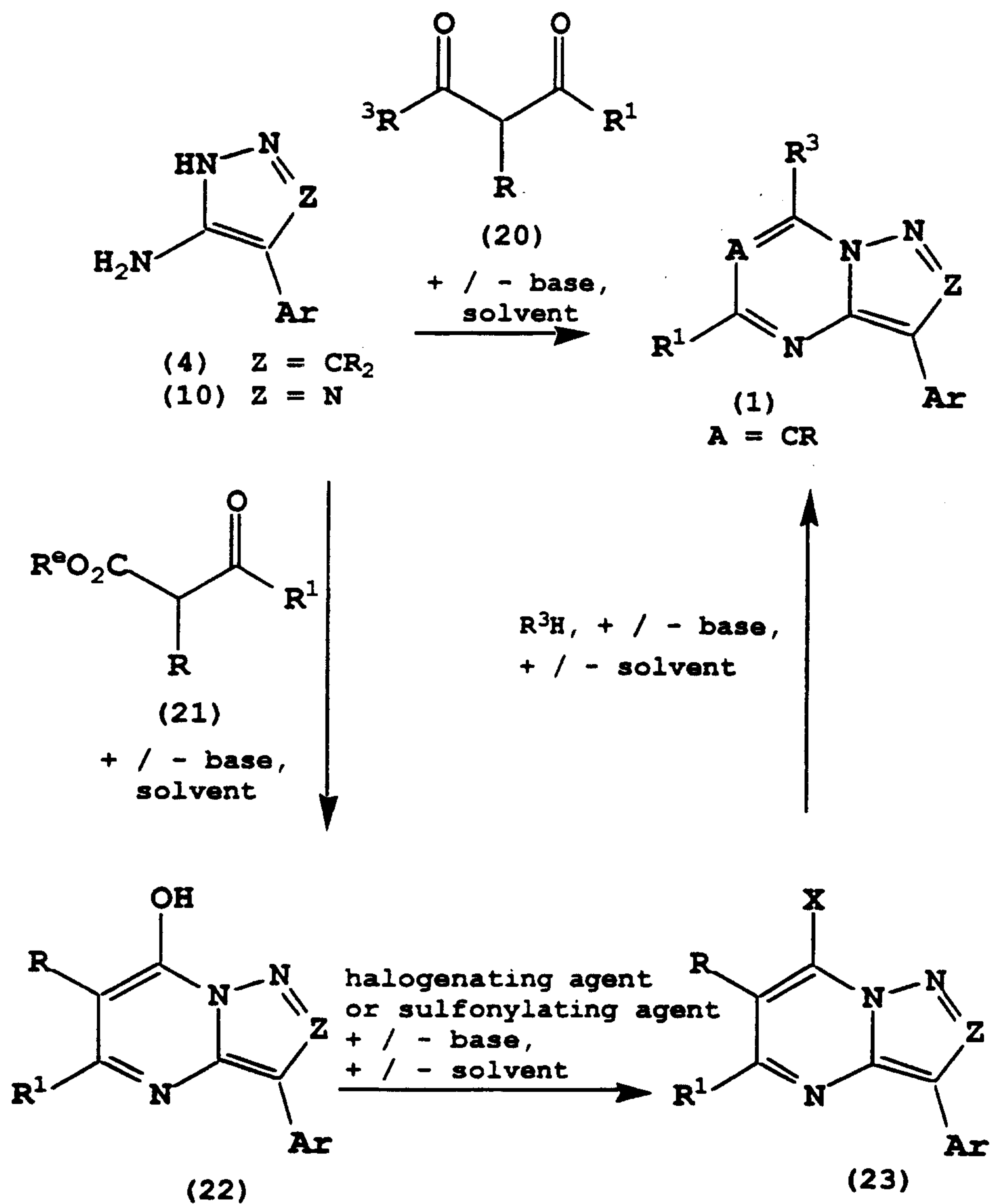
Compounds of Formula (19) may then be reacted with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C₁-C₁₀ alkyl -halides, -tosylates, -mesylates or -triflates; C₁-C₁₀ haloalkyl(1 - 10 halogens)-halides, -tosylates, -

mesylates or -triflates; C₂-C₈ alkoxyalkyl-halides, -
tosylates, -mesylates or -triflates; C₃-C₆ cycloalkyl-
halides, -tosylates, -mesylates or -triflates; C₄-
C₁₂ cycloalkylalkyl-halides, -tosylates, -mesylates or
5 -triflates; aryl(C₁-C₄ alkyl)-halides, -tosylates, -
mesylates or -triflates; heteroaryl(C₁-C₄ alkyl)-
halides, -tosylates, -mesylates or -triflates; or
heterocyclyl(C₁-C₄ alkyl)-halides, -tosylates, -
mesylates or -triflates. Acylating agents may include,
10 but are not limited to, C₁-C₁₀ alkanoyl halides or
anhydrides, C₁-C₁₀ haloalkanoyl halides or anhydrides
with 1 - 10 halogens, C₂-C₈ alkoxyalkanoyl halides or
anhydrides, C₃-C₆ cycloalkanoyl halides or anhydrides,
C₄-C₁₂ cycloalkylalkanoyl halides or anhydrides, aroyl
15 halides or anhydrides, aryl(C₁-C₄) alkanoyl halides or
anhydrides, heteroaroyl halides or anhydrides,
heteroaryl(C₁-C₄) alkanoyl halides or anhydrides,
heterocyclylcarboxylic acid halides or anhydrides or
heterocyclyl(C₁-C₄) alkanoyl halides or anhydrides.
20 Sulfonylating agents include, but are not limited to,
C₁-C₁₀ alkylsulfonyl halides or anhydrides, C₁-C₁₀
haloalkylsulfonyl halides or anhydrides with 1 - 10
halogens, C₂-C₈ alkoxyalkylsulfonyl halides or
anhydrides, C₃-C₆ cycloalkylsulfonyl halides or
25 anhydrides, C₄-C₁₂ cycloalkylalkylsulfonyl halides or
anhydrides, arylsulfonyl halides or anhydrides,
aryl(C₁-C₄ alkyl)-, heteroarylsulfonyl halides or
anhydrides, heteroaryl(C₁-C₄ alkyl)sulfonyl halides or
anhydrides, heterocyclylsulfonyl halides or anhydrides
30 or heterocyclyl(C₁-C₄ alkyl)sulfonyl halides or
anhydrides. Bases may include, but are not limited to,
alkali metal hydrides (preferably sodium hydride),
alkali metal alkoxides (1 to 6 carbons) (preferably

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

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

SCHEME 14



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

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

25 Compounds of Formula (4) or (10) may be treated with compounds of Formula (21), where R¹ is defined above and R^e is alkyl (1 - 6 carbons), in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula
30 (1), where A is CR and R is defined above. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal
35 dialkylamides (preferably lithium di-isopropylamide),

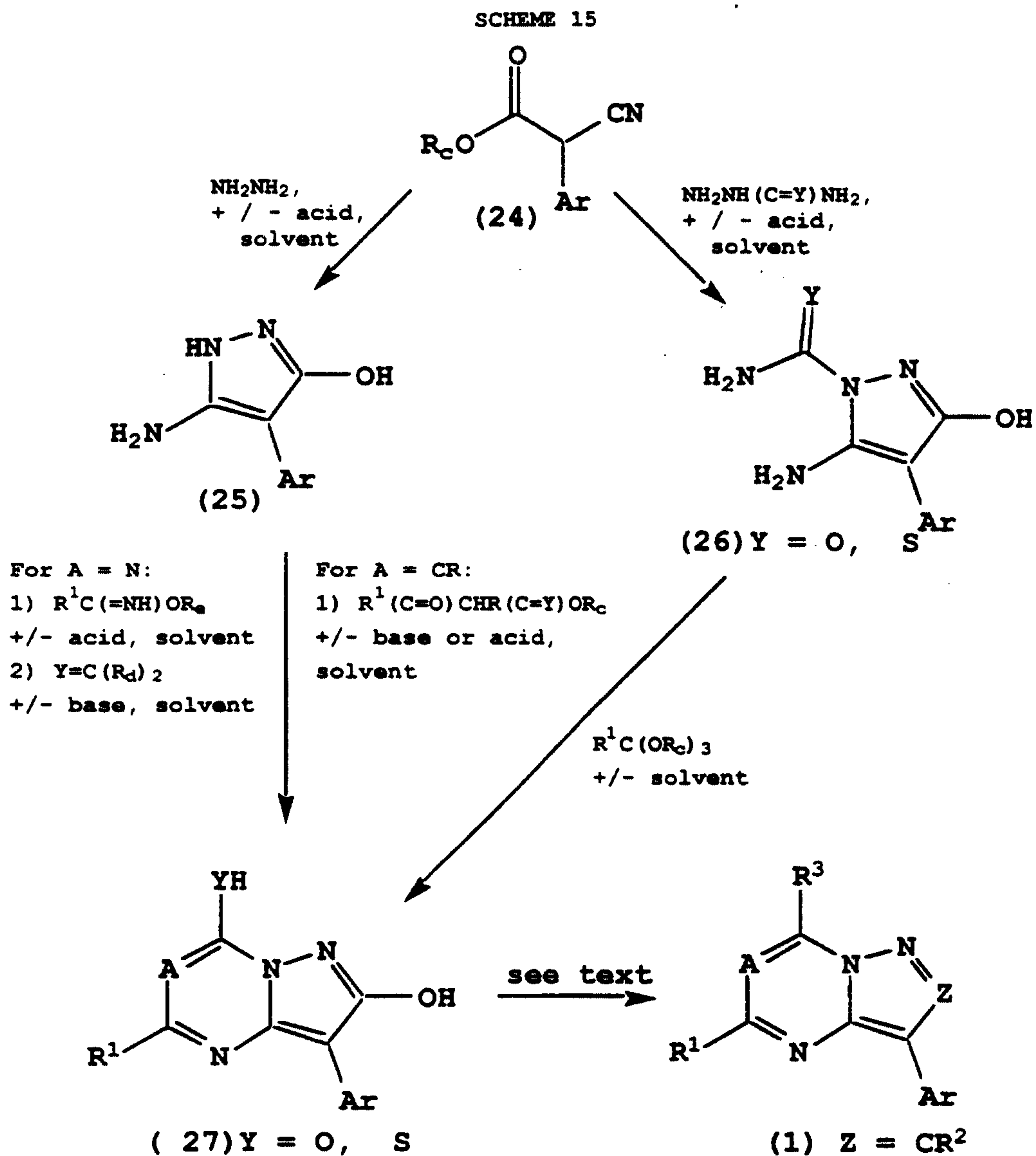
alkali metal carbonates, alkali metal
bis(trialkylsilyl)amides (preferably sodium
bis(trimethylsilyl)amide), trialkyl amines (preferably
di-isopropylethyl amine) or aromatic amines (preferably
5 pyridine). Inert solvents may include, but are not
limited to, alkyl alcohols (1 to 8 carbons, preferably
methanol or ethanol), lower alkanenitriles (1 to 6
carbons, preferably acetonitrile), dialkyl ethers
(preferably diethyl ether), cyclic ethers (preferably
10 tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides
(preferably dimethylformamide), N,N-dialkylacetamides
(preferably dimethylacetamide), cyclic amides
(preferably N-methylpyrrolidin-2-one),
dialkylsulfoxides (preferably dimethylsulfoxide) or
15 aromatic hydrocarbons (preferably benzene or toluene).
Preferred reaction temperatures range from 0°C to
100°C. Compounds of Formula (22) may be treated with a
halogenating agent or sulfonylating agent in the
presence or absence of a base in the presence or
20 absence of an inert solvent at reaction temperatures
ranging from -80°C to 250°C to give products of Formula
(23) (where X is halogen, alkanesulfonyloxy,
arylsulfonyloxy or haloalkane-sulfonyloxy).
Halogenating agents include, but are not limited to,
25 SOCl₂, POCl₃, PCl₃, PCl₅, POBr₃, PBr₃ or PBr₅.
Sulfonylating agents include, but are not limited to,
alkanesulfonyl halides or anhydrides (such as
methanesulfonyl chloride or methanesulfonic acid
anhydride), arylsulfonyl halides or anhydrides (such as
30 p-toluenesulfonyl chloride or anhydride) or
haloalkylsulfonyl halides or anhydrides (preferably
trifluoromethanesulfonic anhydride). Bases may
include, but are not limited to, alkali metal hydrides
(preferably sodium hydride), alkali metal alkoxides (1
35 to 6 carbons) (preferably sodium methoxide or sodium

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

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

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

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



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

$R^1C(=NH)OR_e$, where R^1 is defined above and R_e is a lower alkyl group) in the presence or absence of an acid in an inert solvent, followed by reaction with a compound of formula $YisC(R_d)_2$ (where Y is O or S and R^d is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent to give compounds of Formula (27) (where A is N and Y is O, S). The conditions for these transformations are the same as those employed for the conversions of compound of Formula (4) to compound of Formula (7) in Scheme 4.

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

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

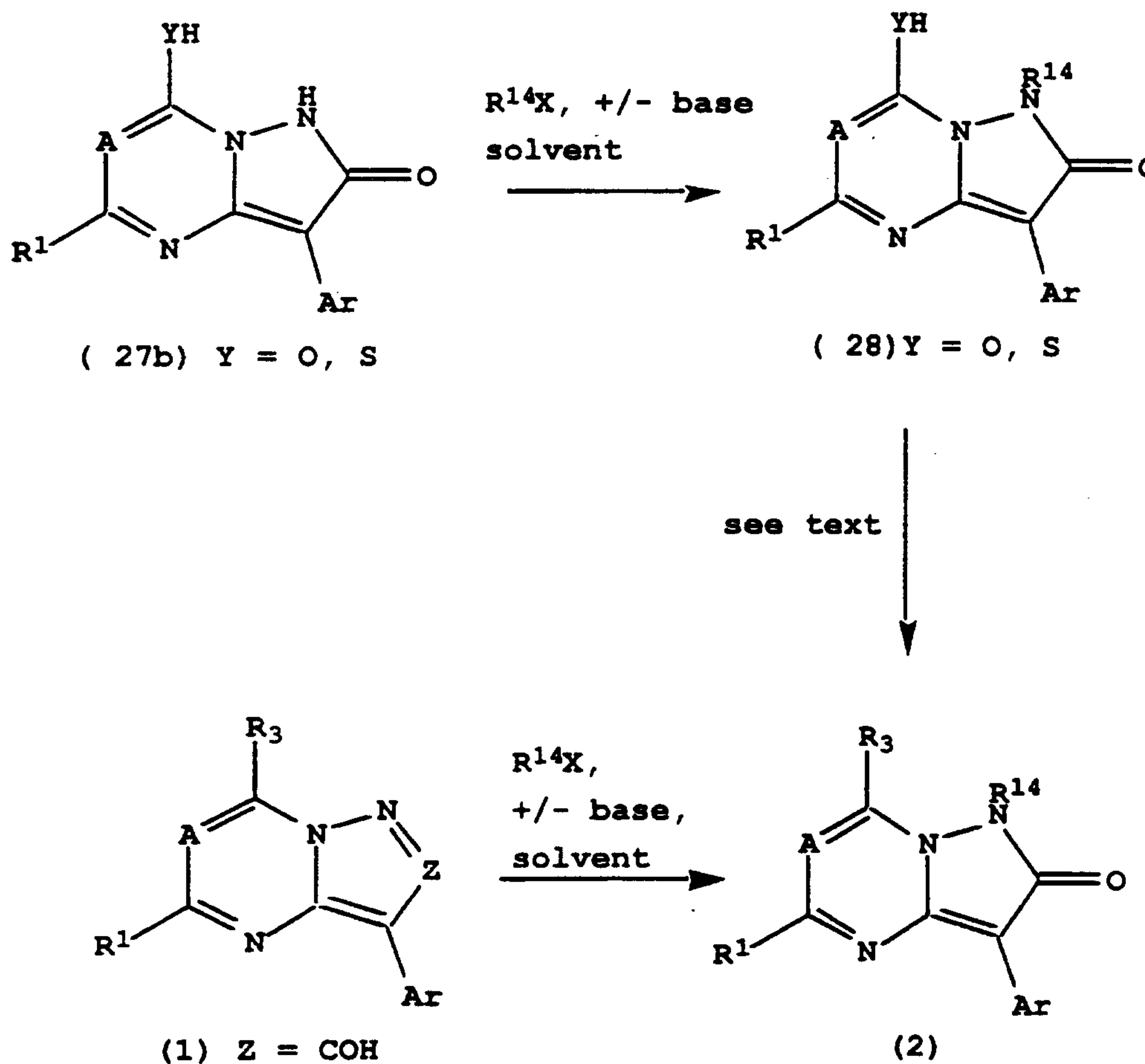
give compounds of Formula (1). The reaction conditions and reagents used for these conversions are similar to the ones employed for the conversion of intermediate compounds of Formulae (22) to (23) to (1) in Scheme 14
5 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8)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

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

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

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

SCHEME 16



Compounds of Formula (27b) may be treated with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures of Formula (28). Compounds of Formula (28) (Y is O) may then be converted to compounds of Formula (1) by treatment with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H in the presence or absence of a base in an inert solvent to give

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

Compounds of Formula (1), where Z is COH, may be converted to compounds of Formula (2) as illustrated in
20 Scheme 16. Treatment with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures (2). It will be recognized by one
25 skilled in the art that the methods used in Scheme 16 may also be used to prepare compounds of Formula (1) where Z is COR⁷.

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

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

EXAMPLES

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

Reagents were purchased from commercial sources

and, where necessary, purified prior to use according to the general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988).

5 Chromatography was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

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

15

EXAMPLE 1

Preparation of

2,7-dimethyl-8-(2,4-dimethylphenyl) [1,5-a]
20 -pyrazolo-[1,3,5]-triazin-4(3H)-one
(Formula 7, where Y is O, R₁ is CH₃, Z is C-CH₃,
Ar is 2,4-dimethylphenyl)

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

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

5

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

A mixture of 1-cyano-1-(2,4-dimethylphenyl)propan-2-one (43.8g, 0.23 mol), hydrazine-hydrate (22 mL, 0.46 mol), glacial acetic acid (45 mL, 0.78 mol) and toluene
10 (500 mL) were stirred at reflux temperature for 18 hours in an apparatus fitted with a Dean-Stark trap. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. The residue was dissolved in 6N HCl and the resulting solution was
15 extracted with ether three times. A concentrated ammonium hydroxide solution was added to the aqueous layer until pH = 11. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over MgSO_4 and filtered.
20 Solvent was removed in vacuo to give a pale brown viscous oil (34.6g, 75% yield): NMR (CDCl_3 , 300 MHz): 7.10 (s, 1H), 7.05 (d, 2H, J=1), 2.37 (s, 3H), 2.10 (s, 3H); CI-MS: 202 (M + H).

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

Ethyl acetamidate hydrochloride (60g, 0.48 mol) was added quickly to a rapidly stirred mixture of potassium carbonate (69.5g, 0.50 mol), dichloromethane
30 (120 mL) and water (350 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 120 mL). The combined organic layers were dried over MgSO_4 and filtered. Solvent was removed by simple distillation and the pot residue, a

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

Glacial acetic acid (9.7 mL, 0.17 mol) was added to a stirred mixture of 5-amino-4-(2,4-dimethylphenyl)-3-methylpyrazole (34g, 0.17 mol), ethyl acetamidate (22g, 0.25 mol) and acetonitrile (500 mL). The resulting reaction mixture was stirred at room temperature for 3 days; at the end of which time, it was concentrated in vacuo to about one-third of its original volume. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. The white solid was dried in vacuo (31.4g, 61% yield): NMR (DMSO-d₆, 300 MHz): 7.00 (s, 1H), 6.90 (dd, 2H, J=7, 1), 2.28 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H); CI-MS: 243 (M + H).

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

Sodium pellets (23g, 1 mol) were added portionwise to ethanol (500 mL) with vigorous stirring. After all the sodium reacted, 5-acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt (31.2g, 0.1 mol) and diethyl carbonate (97 mL, 0.8 mol) were added. The resulting reaction mixture was heated to reflux temperature and stirred for 18 hours. The mix was cooled to room temperature and solvent was removed in vacuo. The residue was dissolved in water and a 1N HCl solution was added slowly until pH = 5-6. The aqueous layer was extracted with ethyl acetate three times; the combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a pale tan solid (26g, 98% yield): NMR (CDCl₃, 300 MHz): 7.15(s, 1H), 7.09 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H); CI-MS: 269 (M + H).

EXAMPLE 2

Preparation of

5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-
[1,2,3]-triazolo-[1,3,5]-triazin-7(6H)-one
(Formula 7, where Y is O, R₁ is CH₃, Z is N,
Ar is 2,4,6-trimethylphenyl)

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

A mixture of 2,4,6-trimethylbenzyl cyanide (1.0g, 6.3 mmol), benzyl azide (0.92g, 6.9 mmol) and potassium t-butoxide (0.78g, 6.9 mmol) in tetrahydrofuran (10mL) was stirred at ambient temperature for 2.5 days. The resulting suspension was diluted with water and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a brown oil. Trituration with ether and filtration afforded a yellow solid (1.12g, 61% yield): NMR (CDCl₃, 300 MHz): 7.60-7.30 (m, 5H), 7.30-7.20 (m, 2H), 5.50 (s, 2H), 3.18 (br s, 2H), 2.30 (s, 3H), 2.10 (s, 6H); CI-MS: 293 (M + H).

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

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

combined organic layers were dried over MgSO_4 and filtered. Solvent was removed in vacuo to give a yellow solid (520 mg), which was homogeneous by thin layer chromatography (ethyl acetate):

5 NMR (CDCl_3 , 300 MHz): 6.97 (s, 2H), 3.68-3.50 (br.s, 2H), 2.32 (s, 3H), 2.10 (s, 6H); CI-MS: 203 (M + H).

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

10 A mixture of 4-(2,4,6-trimethylphenyl)-5-aminotriazole (400 mg, 1.98 mmol), ethyl acetamide (261 mg, 3 mmol) and glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (6 mL) was stirred at ambient temperature for 4 hours. The resulting suspension was
15 filtered and the collected solid was washed with copious amounts of ether. Drying in vacuo afforded a white solid (490 mg, 82% yield): NMR (DMSO-d_6 , 300 MHz): 7.90-7.70 (br s, 0.5H), 7.50-7.20 (br. s, 0.5H), 6.90 (s, 2H), 6.90 (s, 2H), 3.50-3.10 (br s, 3H), 2.30-
20 2.20 (br s, 3H), 2.05 (d, 1H, $J = 7$), 1.96 (s, 6H), 1.87 (s, 6H); CI-MS: 244 (M + H).

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

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

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The combined organic layers were dried over MgSO_4 and filtered. Solvent was removed in vacuo to give a yellow residue. Trituration with ether and filtration afforded a yellow solid (300 mg, 69% yield): NMR (CDCl₃, 300 MHz): 6.98 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H), 2.10 (s, 6H); CI-MS: 270 (M + H).

EXAMPLE 3

Preparation of 4-(di(carbomethoxy)methyl)-
 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-
 1,3,5-triazine
 (Formula 1, where R^3 is $\text{CH}(\text{CHCO}_2\text{CH}_3)_2$, R_1 is CH_3 , Z is
 C- CH_3 , Ar is 2,4-dimethylphenyl)

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

A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed in vacuo. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over MgSO_4 and filtered. Solvent was removed in vacuo to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (R_f = 0.5). Solvent was removed in vacuo to afford a yellow oil (1.0g, 68% yield): NMR (CDCl₃, 300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7, 1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

B. 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine
Sodium hydride (60% in oil, 80 mg, 2 mmol) was
5 washed with hexanes twice, decanted after each washing
and taken up in anhydrous tetrahydrofuran (THF, 1 mL).
A solution of diethyl malonate (0.32g, 2 mmol) in THF
(2 mL) was added dropwise over 5 min, during which time
vigorous gas evolution ensued. A solution of 4-chloro-
10 2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-
pyrazolotriazine (0.5g, 1.75 mmol) in THF (2 mL)
was added and the reaction mixture was then stirred
under a nitrogen atmosphere for 48 hours. The
resulting suspension was poured onto water and
15 extracted three times with ethyl acetate. The combined
organic layers were washed once with brine, dried over
MgSO₄ and filtered. Solvent was removed in vacuo to
give a brown oil. Column chromatography (ethyl
acetate:hexanes::1:9) afforded, after removal of
20 solvent in vacuo, a pale yellow solid (R_f = 0.2, 250
mg, 35% yield): mp 50-52°C; NMR (CDCl₃, 300 MHz): 12.35
(br.s, 1H, 7.15-7.00 (m, 3H), 4.40 (q, 2H, J = 7), 4.30
(q, 2H, J = 7), 2.4, 2.35, 2.3, 2.2, 2.1 (5 s, 12H),
1.4 (t, 3H, J = 7), 1.35-1.25 (m, 3H); CI-HRMS: Calcd:
25 411.2032, Found: 411.2023.

EXAMPLE 6

Preparation of 4-(1,3-dimethoxy-2-propylamino)-
30 2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-
1,3,5-triazine
(Formula 1, where R³ is NHCH(CH₂OCH₃)₂, R₁ is CH₃, Z is
C-CH₃, Ar is 2,4-dichlorophenyl)

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

A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl) [1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed in vacuo. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (R_f = 0.5). Solvent was removed in vacuo to afford a yellow oil (1.0g, 68% yield): NMR (CDCl₃, 300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7, 1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

20

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

A mixture of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl) [1,5-a]-pyrazolo-1,3,5-triazine (Part A, 570 mg, 1.74 mmol), 1,3-dimethoxypropyl-2-aminopropane (25mg, 2.08 mmol) and ethanol (10 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was poured onto water (25 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo. Column chromatography (CH₂Cl₂:CH₃OH::50:1) afforded one fraction. Removal of solvent in vacuo gave a solid (250 mg, 35% yield): mp 118-120°C; NMR (CDCl₃, 300 MHz): 7.50 (s, 1H), 7.28 (dd, 2H, J = 8, 1),

30

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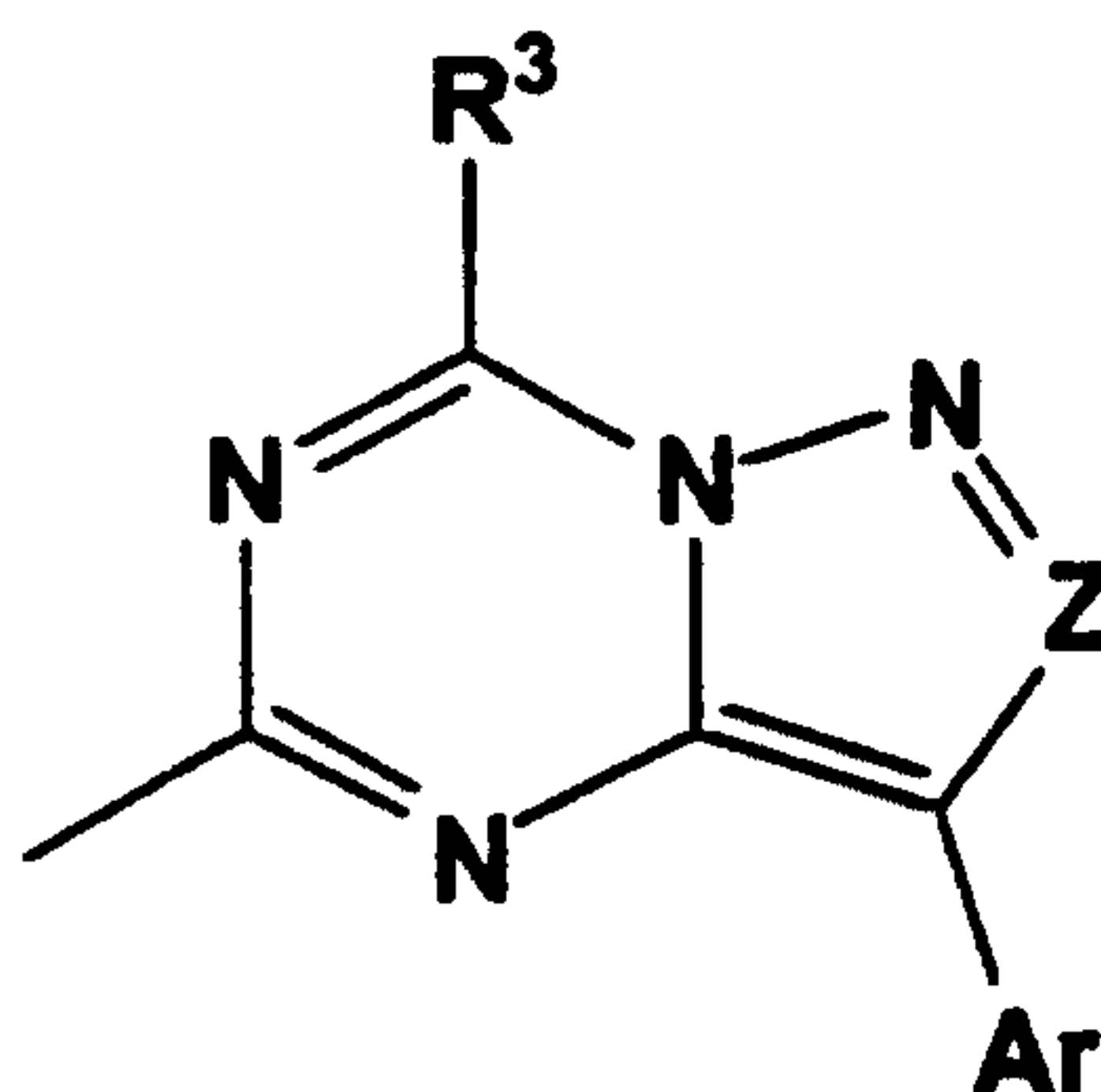
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6.75 (d, 1H, J = 8), 4.70-4.58 (m, 1H), 3.70-3.55 (m, 4H), 3.43 (s, 6H), 2.50 (s, 3H), 2.35 (s, 3H); CI-HRMS: Calcd: 409.1072, Found: 409.1085; Analysis Calcd. for C₁₈H₂₁Cl₂N₅O₂: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

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

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

TABLE 1



<u>Ex.</u>	<u>Z</u>	<u>R₃</u>	<u>Ar</u>	<u>mp (°C)</u>
25 6 ^a	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	118-120
391 ^{bz}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph	oil

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395 ^{bu}	C-Me	NEt ₂	2-Me-4,6-(MeO) ₂ Ph	114
396 ^{bv}	C-Me	NH-3-pentyl	2-Me-4,6-(MeO) ₂ Ph	145-146

5

NOTES FOR TABLE 1:

- a) Analysis Calcd: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.
- 10 bu) Analysis Calcd: C: 65.90, H: 7.72, N, 18.27; Found: C: 65.77, H: 7.62, N: 18.26.
- bv) Analysis Calcd: C: 65.02, H: 7.38, N, 18.96; Found: C: 65.01, H: 7.43, N: 18.68.
- 15 bz) CI-HRMS: Calcd: 430.2454; Found: 430.2468 (M + H);

EXAMPLE 431

20 Preparation of 2,4,7-dimethyl-8-(4-methoxy-2-methylphenyl) [1,5-a]-pyrazolo-1,3,5-triazine
(Formula 1, where R³ is CH₃, R₁ is CH₃, Z is C-CH₃, Ar is 2,4-dimethylphenyl)

25 5-Acetamidino-4-(4-methoxy-2-methylphenyl)-3-methylpyrazole, acetic acid salt (602 mg, 2 mmol) was mixed with a saturated NaHCO₃ solution (10 mL). The aqueous mixture was extracted with EtOAc three times. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The residue was
30 taken up in toluene (10 mL) and trimethyl orthoacetate (0.36 g, 3 mmol) was added to the suspension. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and stirred for 16 hours. After being cooled to ambient temperature, the reaction

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mixture was concentrated in vacuo to give an oily solid. Column chromatography (CHCl₃:MeOH::9:1) afforded, after removal of solvent in vacuo, a yellow viscous oil (R_f = 0.6, 210 mg, 37% yield): NMR (CDCl₃, 300 MHz): 7.15 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.85 (dd, 1H, J = 8,1), 3.85 (s, 3H), 2.95 (s, 3H), 2.65 (s, 3H), 2.4 (s, 3H), 2.15 (s, 3H); CI-HRMS: Calcd: 283.1559, Found: 283.1554 (M + H).

10

EXAMPLE 432

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

5-Amino-4-(2-chloro-4-methylphenyl)-3-methylpyrazole (1.86 g, 8.4 mmol) was dissolved in glacial acetic acid (30 mL) with stirring. Ethyl acetoacetate (1.18 mL, 9.2 mmol) was then added dropwise to the resulting solution. The reaction mixture was then heated to reflux temperature and stirred for 16 hours, then cooled to room temperature. Ether (100 mL) was added and the resulting precipitate was collected by filtration. Drying in vacuo afforded a white solid (1.0 g, 42% yield): NMR (CDCl₃, 300Hz): 8.70 (br.s 1H), 7.29 (s, 1H), 7.21-7.09 (m, 2H), 5.62 (s, 1H), 2.35 (s, 6H), 2.29 (s, 3H); CI-MS: 288 (M+H).

EXAMPLE 433

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

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

A mixture of 7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (1.0 g, 3.5 mmol), phosphorus oxychloride (2.7 g, 1.64 mL, 17.4 mmol), N,N-diethylaniline (0.63 g, 0.7 mL, 4.2 mmol) and toluene (20 mL) was stirred at reflux temperature for 3 hours, then it was cooled to ambient temperature. The volatiles were removed in vacuo. Flash chromatography (EtOAc:hexane::1:2) on the residue gave 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (900 mg, 84% yield) as a yellow oil: NMR (CDCl₃, 300Hz): 7.35 (s, 1H), 7.28-7.26 (m, 1H), 71.6 (d, 1H, J = 7), 6.80 (s, 1H), 2.55 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H); CI- MS: 306 (M+H).

EXAMPLE 434

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

A solution of 3-pentylamine (394mg, 6.5 mmol) and 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (200 mg, 0.65 mmol) in dimethylsulfoxide (DMSO, 10 mL) was stirred at 150°C for 2 hours; then it was cooled to ambient temperature. The reaction mixture was then poured onto water (100 mL) and mixed. Three extractions with dichloromethane, washing the combined organic layers with brine, drying over MgSO₄, filtration and removal of solvent in vacuo produced a yellow solid. Flash chromatography (EtOAc:hexanes::1:4) afforded a white

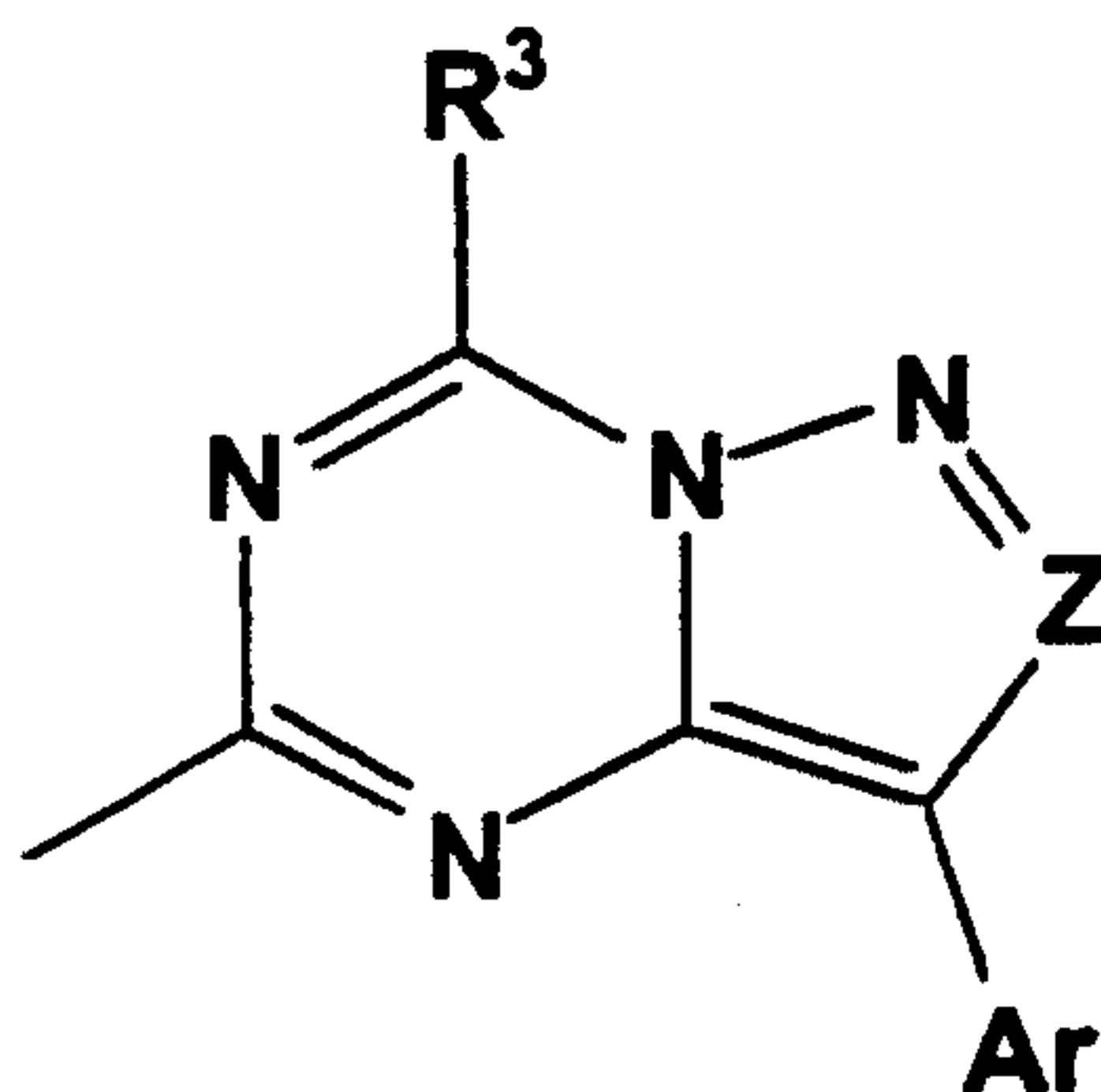
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solid (140 mg, 60% yield): mp 139-141°C; NMR (CDCl₃, 300Hz): 7.32 (s, 1H), 7.27 (d, 1H, J = 8), 7.12 (d, 1H, J = 7), 6.02 (d, 1H, J = 9), 5.78 (s, 1H), 3.50-3.39 (m, 1H), 2.45 (s, 3H), 2.36 (s, 6H), 1.82-1.60 (m, 4H), 1.01 (t, 6H, J = 8); Analysis Calcd for C₂₀H₂₅ClN₄: C, 67.31, H, 7.06, N, 15.70, Cl: 9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

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

Table 7



20	<u>Ex.</u>	<u>Z</u>	<u>R₃</u>	<u>Ar</u>	<u>mp (°C)</u>
	1200 ^a	C-Me	2-ethylpiperidyl	2-Me-4-OMePh	58-59.5
	1201 ^b	C-Me	cyclobutylamino	2-Me-4-OMePh	94.5-96
25	1202 ^c	C-Me	N(Me)CH ₂ CH=CH ₂	2-Me-4-OMePh	oil
	1203 ^d	C-Me	N(CH ₂ CH=CH ₂) ₂	2-Me-4-OMePh	oil

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	1204	C-Me	N(Et)CH ₂ c-Pr	2-Me-4-OMePh	
	1205 ^e	C-Me	NHCH ₂ -2-tetrahydrofuryl	2-Me-4-OMePh	
		amorphous			
5	1206 ^{ay}	C-Me	N(Pr)CH ₂ c-Pr	2-Me-4-OMePh	oil
	1207 ^{az}	C-Me	N(Me)Pr	2-Me-4-OMePh	oil
	1208 ^f	C-Me	N(Me)Et	2-Me-4-OMePh	oil
	1209 ^g	C-Me	N(Me)Bu	2-Me-4-OMePh	oil
10	1210 ^h	C-Me	N(Me)propargyl	2-Me-4-OMePh	oil
	1211 ⁱ	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Me-4-OMePh	oil
	1212 ^j	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Me-4-OMePh	oil
	1213 ^k	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Me-4-OMePh	oil
	1214	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Me-4-OMePh	
15	1215	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Me-4-OMePh	
	1216	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Me-4-OMePh	
	1217 ^m	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Me-4-OMePh	oil
	1218	C-Me	NHCH(c-Pr) ₂	2-Me-4-OMePh	
	1219 ⁿ	C-Me	NH-2-hexyl	2-Me-4-OMePh	oil
20	1220 ^o	C-Me	NH-2-propyl	2-Me-4-OMePh	oil
	1221 ^p	C-Me	NHCH ₂ -2-tetrahydrofuryl	2-Me-4-OMePh	
		amorphous			
	1222 ^q	C-Me	NEt(cyclohexyl)	2-Me-4-OMePh	oil
	1223	C-Me	2-ethylpiperidyl	2,5-Me ₂ -4-OMePh	
25	1224	C-Me	cyclobutylamino	2,5-Me ₂ -4-OMePh	
	1225	C-Me	N(Me)CH ₂ CH=CH ₂	2,5-Me ₂ -4-OMePh	
	1226	C-Me	N(Et)CH ₂ c-Pr	2,5-Me ₂ -4-OMePh	
	1227	C-Me	N(Pr)CH ₂ c-Pr	2,5-Me ₂ -4-OMePh	
	1228	C-Me	N(Me)Pr	2,5-Me ₂ -4-OMePh	
30	1229	C-Me	N(Me)Et	2,5-Me ₂ -4-OMePh	

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	1230	C-Me	N (Me) Bu	2,5-Me ₂ -4-OMePh
	1231	C-Me	N (Me) propargyl	2,5-Me ₂ -4-OMePh
	1232	C-Me	NH (CH (CH ₃) CH (CH ₃) CH ₃)	2,5-Me ₂ -4-OMePh
	1233	C-Me	N (CH ₂ CH ₂ OMe) CH ₂ CH=CH ₂	2,5-Me ₂ -4-OMePh
5	1234	C-Me	N (CH ₂ CH ₂ OMe) Me	2,5-Me ₂ -4-OMePh
	1235	C-Me	N (CH ₂ CH ₂ OMe) Et	2,5-Me ₂ -4-OMePh
	1236	C-Me	N (CH ₂ CH ₂ OMe) Pr	2,5-Me ₂ -4-OMePh
	1237	C-Me	N (CH ₂ CH ₂ OMe) CH ₂ c-Pr	2,5-Me ₂ -4-OMePh
	1238	C-Me	NH (CH (CH ₃) CH ₂ CH ₃)	2,5-Me ₂ -4-OMePh
10	1239	C-Me	NHCH (c-Pr) ₂	2,5-Me ₂ -4-OMePh
	1240	C-Me	2-ethylpiperidyl	2,4-(OMe) ₂ Ph
	1241	C-Me	cyclobutylamino	2,4-(OMe) ₂ Ph
	1245	C-Me	N (Me) CH ₂ CH=CH ₂	2,4-(OMe) ₂ Ph
	1255^r	C-Me	N (CH ₂ CH=CH ₂) ₂	2,4-(OMe) ₂ Ph64.8-
15	65.6			
	1256	C-Me	N (Et) CH ₂ c-Pr	2,4-(OMe) ₂ Ph
	1257	C-Me	N (Pr) CH ₂ c-Pr	2,4-(OMe) ₂ Ph
	1258	C-Me	N (Me) Pr	2,4-(OMe) ₂ Ph
	1259	C-Me	N (Me) Et	2,4-(OMe) ₂ Ph
20	1260	C-Me	N (Me) Bu	2,4-(OMe) ₂ Ph
	1261	C-Me	N (Me) propargyl	2,4-(OMe) ₂ Ph
	1262	C-Me	NH (CH (CH ₃) CH (CH ₃) CH ₃)	2,4-(OMe) ₂ Ph
	1263	C-Me	N (CH ₂ CH ₂ OMe) CH ₂ CH=CH ₂	2,4-(OMe) ₂ Ph
	1264	C-Me	N (CH ₂ CH ₂ OMe) Me	2,4-(OMe) ₂ Ph
25	1265	C-Me	N (CH ₂ CH ₂ OMe) Et	2,4-(OMe) ₂ Ph
	1266	C-Me	N (CH ₂ CH ₂ OMe) Pr	2,4-(OMe) ₂ Ph
	1267	C-Me	N (CH ₂ CH ₂ OMe) CH ₂ c-Pr	2,4-(OMe) ₂ Ph
	1268^s	C-Me	NH (CH (CH ₃) CH ₂ CH ₃)	2,4-(OMe) ₂ Ph137.8-
	138.3			
30	1269	C-Me	NHCH (c-Pr) ₂	2,4-(OMe) ₂ Ph

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	1270 ^t	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-(OMe) ₂ Ph	oil
	1271 ^u	C-Me	NHCH(Et) ₂	2,4-(OMe) ₂ Ph	128-
	129.4				
	1272	C-Me	N(Et) ₂	2,4-(OMe) ₂ Ph	
5	1273 ^v	C-Me	N(Pr) ₂	2,4-(OMe) ₂ Ph	
	1274	C-Me	2-ethylpiperidyl	2,4-(OMe) ₂ -5-MePh	
	1275	C-Me	cyclobutylamino	2,4-(OMe) ₂ -5-MePh	
	1276	C-Me	N(Me)CH ₂ CH=CH ₂	2,4-(OMe) ₂ -5-MePh	
	1277	C-Me	N(Et)CH ₂ c-Pr	2,4-(OMe) ₂ -5-MePh	
10	1278	C-Me	N(Pr)CH ₂ c-Pr	2,4-(OMe) ₂ -5-MePh	
	1279	C-Me	N(Me)Pr	2,4-(OMe) ₂ -5-MePh	
	1280	C-Me	N(Me)Et	2,4-(OMe) ₂ -5-MePh	
	1281	C-Me	N(Me)Bu	2,4-(OMe) ₂ -5-MePh	
	1282	C-Me	N(Me)propargyl	2,4-(OMe) ₂ -5-MePh	
15	1283	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃) ₂	2,4-(OMe) ₂ -5-MePh	
	1284	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2,4-(OMe) ₂ -5-MePh	
	1285	C-Me	N(CH ₂ CH ₂ OMe)Me	2,4-(OMe) ₂ -5-MePh	
	1286	C-Me	N(CH ₂ CH ₂ OMe)Et	2,4-(OMe) ₂ -5-MePh	
	1287	C-Me	N(CH ₂ CH ₂ OMe)Pr	2,4-(OMe) ₂ -5-MePh	
20	1288	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2,4-(OMe) ₂ -5-MePh	
	1289	C-Me	NH(CH(CH ₃)CH ₂ CH ₃) ₂	2,4-(OMe) ₂ -5-MePh	
	1290	C-Me	NHCH(c-Pr) ₂	2,4-(OMe) ₂ -5-MePh	
	1291	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-(OMe) ₂ -5-MePh	
	1292	C-Me	NHCH(Et) ₂	2,4-(OMe) ₂ -5-MePh	
25	1293	C-Me	N(Et) ₂	2,4-(OMe) ₂ -5-MePh	
	1294	C-Me	2-ethylpiperidyl	2,4-(OMe) ₂ -5-ClPh	
	1295	C-Me	cyclobutylamino	2,4-(OMe) ₂ -5-ClPh	
	1296	C-Me	N(Me)CH ₂ CH=CH ₂	2,4-(OMe) ₂ -5-ClPh	
	1297	C-Me	N(Et)CH ₂ c-Pr	2,4-(OMe) ₂ -5-ClPh	
30	1298	C-Me	N(Pr)CH ₂ c-Pr	2,4-(OMe) ₂ -5-ClPh	

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	1299	C-Me	N(Me) Pr	2,4-(OMe) ₂ -5-ClPh	
	1300	C-Me	N(Me) Et	2,4-(OMe) ₂ -5-ClPh	
	1301	C-Me	N(Me) Bu	2,4-(OMe) ₂ -5-ClPh	
	1302	C-Me	N(Me) propargyl	2,4-(OMe) ₂ -5-ClPh	
5	1303	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2,4-(OMe) ₂ -5-ClPh	
	1304	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2,4-(OMe) ₂ -5-ClPh	
	1305	C-Me	N(CH ₂ CH ₂ OMe) Me	2,4-(OMe) ₂ -5-ClPh	
	1306	C-Me	N(CH ₂ CH ₂ OMe) Et	2,4-(OMe) ₂ -5-ClPh	
	1307	C-Me	N(CH ₂ CH ₂ OMe) Pr	2,4-(OMe) ₂ -5-ClPh	
10	1308	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2,4-(OMe) ₂ -5-ClPh	
	1309	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2,4-(OMe) ₂ -5-ClPh	
	1310	C-Me	NHCH(c-Pr) ₂	2,4-(OMe) ₂ -5-ClPh	
	1311	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-(OMe) ₂ -5-ClPh	
	1312	C-Me	NHCH(Et) ₂	2,4-(OMe) ₂ -5-ClPh	
15	1313	C-Me	N(Et) ₂	2,4-(OMe) ₂ -5-ClPh	
	1314 ^y	C-Me	2-ethylpiperidyl	2-Me-4,6-(OMe) ₂ Ph	
					145-149
	1315 ^z	C-Me	cyclobutylamino	2-Me-4,6-(OMe) ₂ Ph	
					131-133
20	1316 ^{aa}	C-Me	N(Me)CH ₂ CH=CH ₂	2-Me-4,6-(OMe) ₂ Ph	oil
	1317	C-Me	N(Et)CH ₂ c-Pr	2-Me-4,6-(OMe) ₂ Ph	
	1318 ^{ab}	C-Me	N(Pr)CH ₂ c-Pr	2-Me-4,6-(OMe) ₂ Ph	oil
25	1319 ^{ac}	C-Me	N(Me) Pr	2-Me-4,6-(OMe) ₂ Ph	oil
	1320 ^{ad}	C-Me	N(Me) Et	2-Me-4,6-(OMe) ₂ Ph	oil
	1321 ^{ae}	C-Me	N(Me) Bu	2-Me-4,6-(OMe) ₂ Ph	oil

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	1322	C-Me	N(Me) propargyl	2-Me-4,6-(OMe) ₂ Ph	
	1323	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Me-4,6-(OMe) ₂ Ph	
	1324	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Me-4,6-(OMe) ₂ Ph	
	1325	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Me-4,6-(OMe) ₂ Ph	
5	1326 ^{af}	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Me-4,6-(OMe) ₂ Ph	oil
	1327	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Me-4,6-(OMe) ₂ Ph	
	1328 ^{ag}	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Me-4,6-(OMe) ₂ Ph	oil
10	1329 ^{ax}	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Me-4,6-(OMe) ₂ Ph	
					107-110
	1330	C-Me	NHCH(c-Pr) ₂	2-Me-4,6-(OMe) ₂ Ph	
	1331 ^w	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(OMe) ₂ Ph	
	1332	C-Me	NHCH(Et) ₂	2-Me-4,6-(OMe) ₂ Ph	
15	1333	C-Me	N(Et) ₂	2-Me-4,6-(OMe) ₂ Ph	
	1334 ^x	C-Me	NEt(Bu)	2-Me-4,6-(OMe) ₂ Ph	oil
	1335	C-Me	2-ethylpiperidyl	2-Cl-4,6-(OMe) ₂ Ph	
	1336	C-Me	cyclobutylamino	2-Cl-4,6-(OMe) ₂ Ph	
	1337	C-Me	N(Me)CH ₂ CH=CH ₂	2-Cl-4,6-(OMe) ₂ Ph	
20	1338	C-Me	N(Et)CH ₂ c-Pr	2-Cl-4,6-(OMe) ₂ Ph	
	1339	C-Me	N(Pr)CH ₂ c-Pr	2-Cl-4,6-(OMe) ₂ Ph	
	1340	C-Me	N(Me)Pr	2-Cl-4,6-(OMe) ₂ Ph	
	1341	C-Me	N(Me)Et	2-Cl-4,6-(OMe) ₂ Ph	
	1342	C-Me	N(Me)Bu	2-Cl-4,6-(OMe) ₂ Ph	
25	1343	C-Me	N(Me) propargyl	2-Cl-4,6-(OMe) ₂ Ph	
	1344	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Cl-4,6-(OMe) ₂ Ph	
	1345	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Cl-4,6-(OMe) ₂ Ph	
	1346	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Cl-4,6-(OMe) ₂ Ph	
	1347	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Cl-4,6-(OMe) ₂ Ph	
30	1348	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Cl-4,6-(OMe) ₂ Ph	

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	1349	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Cl-4,6-(OMe) ₂ Ph
	1350	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Cl-4,6-(OMe) ₂ Ph
	1351	C-Me	NHCH(c-Pr) ₂	2-Cl-4,6-(OMe) ₂ Ph
	1352	C-Me	NHCH(Et) ₂	2-Cl-4,6-(OMe) ₂ Ph
5	1353	C-Me	N(Et) ₂	2-Cl-4,6-(OMe) ₂ Ph
	1354	C-Me	2-ethylpiperidyl	2-Cl-4-OMe-Ph
	1355	C-Me	cyclobutylamino	2-Cl-4-OMe-Ph
	1356	C-Me	N(Me)CH ₂ CH=CH ₂	2-Cl-4-OMe-Ph
	1357	C-Me	N(Et)CH ₂ c-Pr	2-Cl-4-OMe-Ph
10	1358	C-Me	N(Pr)CH ₂ c-Pr	2-Cl-4-OMe-Ph
	1359	C-Me	N(Me)Pr	2-Cl-4-OMe-Ph
	1360	C-Me	N(Me)Et	2-Cl-4-OMe-Ph
	1361	C-Me	N(Me)Bu	2-Cl-4-OMe-Ph
	1362	C-Me	N(Me)propargyl	2-Cl-4-OMe-Ph
15	1363	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Cl-4-OMe-Ph
	1364	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Cl-4-OMe-Ph
	1365	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Cl-4-OMe-Ph
	1366	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Cl-4-OMe-Ph
	1367	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Cl-4-OMe-Ph
20	1368	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Cl-4-OMe-Ph
	1369	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Cl-4-OMe-Ph
	1370	C-Me	NHCH(c-Pr) ₂	2-Cl-4-OMe-Ph
	1371	C-Me	2-ethylpiperidyl	2-Me-4,5-(OMe) ₂ Ph
	1372	C-Me	cyclobutylamino	2-Me-4,5-(OMe) ₂ Ph
25	1373	C-Me	N(Me)CH ₂ CH=CH ₂	2-Me-4,5-(OMe) ₂ Ph
	1374	C-Me	N(Et)CH ₂ c-Pr	2-Me-4,5-(OMe) ₂ Ph
	1375	C-Me	N(Pr)CH ₂ c-Pr	2-Me-4,5-(OMe) ₂ Ph
	1376	C-Me	N(Me)Pr	2-Me-4,5-(OMe) ₂ Ph
	1377	C-Me	N(Me)Et	2-Me-4,5-(OMe) ₂ Ph
30	1378	C-Me	N(Me)Bu	2-Me-4,5-(OMe) ₂ Ph
	1379	C-Me	N(Me)propargyl	2-Me-4,5-(OMe) ₂ Ph

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	1380	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Me-4,5-(OMe) ₂ Ph	
	1381	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Me-4,5-(OMe) ₂ Ph	
	1382	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Me-4,5-(OMe) ₂ Ph	
	1383	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Me-4,5-(OMe) ₂ Ph	
5	1384	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Me-4,5-(OMe) ₂ Ph	
	1385	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Me-4,5-(OMe) ₂ Ph	
	1386	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Me-4,5-(OMe) ₂ Ph	
	1387	C-Me	NHCH(c-Pr) ₂	2-Me-4,5-(OMe) ₂ Ph	
	1388	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,5-(OMe) ₂ Ph	
10	1389	C-Me	NHCH(Et) ₂	2-Me-4,5-(OMe) ₂ Ph	
	1390	C-Me	N(Et) ₂	2-Me-4,5-(OMe) ₂ Ph	
	1391	C-Me	NEt(Bu)	2-Me-4,5-(OMe) ₂ Ph	
	1392	C-Me	2-ethylpiperidyl	2-Cl-4,5-(OMe) ₂ Ph	
	1393 ^{ab}	C-Me	cyclobutylamino	2-Cl-4,5-(OMe) ₂ Ph	
15					121-122
	1394 ^{ai}	C-Me	N(Me)CH ₂ CH=CH ₂	2-Cl-4,5-(OMe) ₂ Ph	
					122-126
	1395	C-Me	N(Et)CH ₂ c-Pr	2-Cl-4,5-(OMe) ₂ Ph	
	1396 ^{aj}	C-Me	N(Pr)CH ₂ c-Pr	2-Cl-4,5-(OMe) ₂ Ph	oil
20					
	1397 ^{ak}	C-Me	N(Me)Pr	2-Cl-4,5-(OMe) ₂ Ph	
					115-117
	1398 ^{al}	C-Me	N(Me)Et	2-Cl-4,5-(OMe) ₂ Ph	
					115-119
25	1399 ^{am}	C-Me	N(Me)Bu	2-Cl-4,5-(OMe) ₂ Ph	oil
	1400	C-Me	N(Me)propargyl	2-Cl-4,5-(OMe) ₂ Ph	
	1401	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Cl-4,5-(OMe) ₂ Ph	
	1402	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Cl-4,5-(OMe) ₂ Ph	
30	1403	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Cl-4,5-(OMe) ₂ Ph	

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	1404 ^{an}	C-Me	N(CH ₂ CH ₂ OMe) Et	2-Cl-4,5-(OMe) ₂ Ph	oil
	1405	C-Me	N(CH ₂ CH ₂ OMe) Pr	2-Cl-4,5-(OMe) ₂ Ph	
	1406 ^{ao}	C-Me	N(CH ₂ CH ₂ OMe) CH ₂ c-Pr	2-Cl-4,5-(OMe) ₂ Ph	oil
5	1407	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Cl-4,5-(OMe) ₂ Ph	
	1408	C-Me	NHCH(c-Pr) ₂	2-Cl-4,5-(OMe) ₂ Ph	
	1409 ^{ap}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,5-(OMe) ₂ Ph	oil
10	1410 ^{aq}	C-Me	NHCH(Et) ₂	2-Cl-4,5-(OMe) ₂ Ph	
					104-106
	1411 ^{ar}	C-Me	N(Et) ₂	2-Cl-4,5-(OMe) ₂ Ph	oil
	1412 ^{as}	C-Me	NEt(Bu)	2-Cl-4,5-(OMe) ₂ Ph	oil
	1413	C-Me	2-ethylpiperidyl	2-Cl-4-OMe-5-MePh	
15	1414	C-Me	cyclobutylamino	2-Cl-4-OMe-5-MePh	
	1415	C-Me	N(Me)CH ₂ CH=CH ₂	2-Cl-4-OMe-5-MePh	
	1416	C-Me	N(Et)CH ₂ c-Pr	2-Cl-4-OMe-5-MePh	
	1417	C-Me	N(Pr)CH ₂ c-Pr	2-Cl-4-OMe-5-MePh	
	1418	C-Me	N(Me)Pr	2-Cl-4-OMe-5-MePh	
20	1419	C-Me	N(Me)Et	2-Cl-4-OMe-5-MePh	
	1420	C-Me	N(Me)Bu	2-Cl-4-OMe-5-MePh	
	1421	C-Me	N(Me)propargyl	2-Cl-4-OMe-5-MePh	
	1422	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Cl-4-OMe-5-MePh	
	1423	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Cl-4-OMe-5-MePh	
25	1424	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Cl-4-OMe-5-MePh	
	1425	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Cl-4-OMe-5-MePh	
	1426	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Cl-4-OMe-5-MePh	
	1427	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Cl-4-OMe-5-MePh	
	1428	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Cl-4-OMe-5-MePh	
30	1429	C-Me	NHCH(c-Pr) ₂	2-Cl-4-OMe-5-MePh	
	1430	C-Me	NHCH(Et) ₂	2-Cl-4-OMe-5-MePh	

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	1431	C-Me	N(Et) ₂	2-Cl-4-OMe-5-MePh
	1432	C-Me	NEt(Bu)	2-Cl-4-OMe-5-MePh
	1433	C-Me	2-ethylpiperidyl	2-Cl-6-OMe-4-MePh
	1434	C-Me	cyclobutylamino	2-Cl-6-OMe-4-MePh
5	1435	C-Me	N(Me)CH ₂ CH=CH ₂	2-Cl-6-OMe-4-MePh
	1436	C-Me	N(Et)CH ₂ c-Pr	2-Cl-6-OMe-4-MePh
	1437	C-Me	N(Pr)CH ₂ c-Pr	2-Cl-6-OMe-4-MePh
	1438	C-Me	N(Me)Pr	2-Cl-6-OMe-4-MePh
	1439	C-Me	N(Me)Et	2-Cl-6-OMe-4-MePh
10	1440	C-Me	N(Me)Bu	2-Cl-6-OMe-4-MePh
	1441	C-Me	N(Me)propargyl	2-Cl-6-OMe-4-MePh
	1442	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Cl-6-OMe-4-MePh
	1443	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Cl-6-OMe-4-MePh
	1444	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Cl-6-OMe-4-MePh
15	1445	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Cl-6-OMe-4-MePh
	1446	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Cl-6-OMe-4-MePh
	1447	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Cl-6-OMe-4-MePh
	1448	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Cl-6-OMe-4-MePh
	1449	C-Me	NHCH(c-Pr) ₂	2-Cl-6-OMe-4-MePh
20	1450	C-Me	NHCH(Et) ₂	2-Cl-6-OMe-4-MePh
	1451	C-Me	N(Et) ₂	2-Cl-6-OMe-4-MePh
	1452	C-Me	NEt(Bu)	2-Cl-6-OMe-4-MePh
	1453	C-Me	2-ethylpiperidyl	2,6-Me ₂ -4-OMePh
	1454	C-Me	cyclobutylamino	2,6-Me ₂ -4-OMePh
25	1455	C-Me	N(Me)CH ₂ CH=CH ₂	2,6-Me ₂ -4-OMePh
	1456	C-Me	N(Et)CH ₂ c-Pr	2,6-Me ₂ -4-OMePh
	1457	C-Me	N(Pr)CH ₂ c-Pr	2,6-Me ₂ -4-OMePh
	1458	C-Me	N(Me)Pr	2,6-Me ₂ -4-OMePh
	1459	C-Me	N(Me)Et	2,6-Me ₂ -4-OMePh
30	1460	C-Me	N(Me)Bu	2,6-Me ₂ -4-OMePh
	1461	C-Me	N(Me)propargyl	2,6-Me ₂ -4-OMePh

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	1462	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2,6-Me ₂ -4-OMePh	
	1463	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2,6-Me ₂ -4-OMePh	
	1464	C-Me	N(CH ₂ CH ₂ OMe)Me	2,6-Me ₂ -4-OMePh	
	1465	C-Me	N(CH ₂ CH ₂ OMe)Et	2,6-Me ₂ -4-OMePh	
5	1466	C-Me	N(CH ₂ CH ₂ OMe)Pr	2,6-Me ₂ -4-OMePh	
	1467	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2,6-Me ₂ -4-OMePh	
	1468	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2,6-Me ₂ -4-OMePh	
	1469	C-Me	NHCH(c-Pr) ₂	2,6-Me ₂ -4-OMePh	
	1470	C-Me	NHCH(Et) ₂	2,6-Me ₂ -4-OMePh	
10	1471	C-Me	N(Et) ₂	2,6-Me ₂ -4-OMePh	
	1472	C-Me	NEt(Bu)	2,6-Me ₂ -4-OMePh	
	1473	C-Me	2-ethylpiperidyl	2-Cl-4-OMe-5-FPh	
	1474	C-Me	cyclobutylamino	2-Cl-4-OMe-5-FPh	
	1475 ^{be}	C-Me	N(Me)CH ₂ CH=CH ₂	2-Cl-4-OMe-5-FPh	oil
15					
	1476	C-Me	N(Et)CH ₂ c-Pr	2-Cl-4-OMe-5-FPh	
	1478	C-Me	N(Pr)CH ₂ c-Pr	2-Cl-4-OMe-5-FPh	
	1479 ^{bb}	C-Me	N(Me)Pr	2-Cl-4-OMe-5-FPh	oil
20	1480 ^{bc}	C-Me	N(Me)Et	2-Cl-4-OMe-5-FPh	oil
	1481	C-Me	N(Me)Bu	2-Cl-4-OMe-5-FPh	
	1482	C-Me	N(Me)propargyl	2-Cl-4-OMe-5-FPh	
	1483	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Cl-4-OMe-5-FPh	
25	1484	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Cl-4-OMe-5-FPh	
	1485	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Cl-4-OMe-5-FPh	
	1486	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Cl-4-OMe-5-FPh	
	1487	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Cl-4-OMe-5-FPh	
	1488	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Cl-4-OMe-5-FPh	
30	1489 ^{bd}	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Cl-4-OMe-5-FPh	
					solid

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	1490	C-Me	NHCH(c-Pr) ₂	2-Cl-4-OMe-5-FPh	
	1491 ^{be}	C-Me	NHCH(Et) ₂	2-Cl-4-OMe-5-FPh	oil
	1492 ^{bf}	C-Me	N(Et) ₂	2-Cl-4-OMe-5-FPh	
5					96-98
	1493 ^{bg}	C-Me	NEt(Bu)	2-Cl-4-OMe-5-FPh	oil
	1494	C-Me	2-ethylpiperidyl	2-Cl-4-OMe-6-MePh	
	1495	C-Me	cyclobutylamino	2-Cl-4-OMe-6-MePh	
	1496	C-Me	N(Me)CH ₂ CH=CH ₂	2-Cl-4-OMe-6-MePh	
10	1497	C-Me	N(Et)CH ₂ c-Pr	2-Cl-4-OMe-6-MePh	
	1498	C-Me	N(Pr)CH ₂ c-Pr	2-Cl-4-OMe-6-MePh	
	1499	C-Me	N(Me)Pr	2-Cl-4-OMe-6-MePh	
	1500	C-Me	N(Me)Et	2-Cl-4-OMe-6-MePh	
	1501	C-Me	N(Me)Bu	2-Cl-4-OMe-6-MePh	
15	1502	C-Me	N(Me)propargyl	2-Cl-4-OMe-6-MePh	
	1503	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Cl-4-OMe-6-MePh	
	1504	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Cl-4-OMe-6-MePh	
	1505	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Cl-4-OMe-6-MePh	
	1506	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Cl-4-OMe-6-MePh	
20	1507	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Cl-4-OMe-6-MePh	
	1508	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Cl-4-OMe-6-MePh	
	1509	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Cl-4-OMe-6-MePh	
	1510	C-Me	NHCH(c-Pr) ₂	2-Cl-4-OMe-6-MePh	
	1511	C-Me	NHCH(Et) ₂	2-Cl-4-OMe-6-MePh	
25	1512	C-Me	N(Et) ₂	2-Cl-4-OMe-6-MePh	
	1513	C-Me	NEt(Bu)	2-Cl-4-OMe-6-MePh	
	1514	C-Me	2-ethylpiperidyl	6-Me ₂ N-4-Me- pyrid-3-yl	
	1515	C-Me	cyclobutylamino	6-Me ₂ N-4-Me- pyrid-3-yl	
30	1516	C-Me	N(Me)CH ₂ CH=CH ₂	6-Me ₂ N-4-Me- pyrid-3-yl	

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	1517	C-Me	N(Et)CH ₂ c-Pr	6-Me ₂ N-4-Me- pyrid-3-yl	
	1518	C-Me	N(Pr)CH ₂ c-Pr	6-Me ₂ N-4-Me- pyrid-3-yl	
5	1519	C-Me	N(Me)Pr	6-Me ₂ N-4-Me- pyrid-3-yl	
	1520	C-Me	N(Me)Et	6-Me ₂ N-4-Me- pyrid-3-yl	
	1521	C-Me	N(Me)Bu	6-Me ₂ N-4-Me- pyrid-3-yl	
10	1522	C-Me	N(Me)propargyl	6-Me ₂ N-4-Me- pyrid-3-yl	
	1523	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	6-Me ₂ N-4-Me- pyrid-3-yl	
15	1524	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	6-Me ₂ N-4-Me- pyrid-3-yl	
	1525	C-Me	N(CH ₂ CH ₂ OMe)Me	6-Me ₂ N-4-Me- pyrid-3-yl	
	1526 ^{at}	C-Me	N(CH ₂ CH ₂ OMe)Et	6-Me ₂ N-4-Me- pyrid-3-yl	oil
20	1527	C-Me	N(CH ₂ CH ₂ OMe)Pr	6-Me ₂ N-4-Me- pyrid-3-yl	
	1528	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	6-Me ₂ N-4-Me- pyrid-3-yl	
25	1529	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	6-Me ₂ N-4-Me- pyrid-3-yl	
	1530	C-Me	NHCH(c-Pr) ₂	6-Me ₂ N-4-Me- pyrid-3-yl	
	1531 ^{au}	C-Me	N(CH ₂ CH ₂ OMe) ₂	6-Me ₂ N-4-Me- pyrid-3-yl	
30					103-104
	1532 ^{av}	C-Me	NHCH(Et) ₂	6-Me ₂ N-4-Me-	

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				pyrid-3-yl	153-154
	1533 ^{aw}	C-Me	N(Et) ₂	6-Me ₂ N-4-Me- pyrid-3-yl	
5					117-118
	1534	C-Me	2-ethylpiperidyl	6-MeO-4-Me- pyrid-3-yl	
	1535	C-Me	cyclobutylamino	6-MeO-4-Me- pyrid-3-yl	
10	1536	C-Me	N(Me)CH ₂ CH=CH ₂	6-MeO-4-Me- pyrid-3-yl	
	1537	C-Me	N(Et)CH ₂ c-Pr	6-MeO-4-Me- pyrid-3-yl	
	1538	C-Me	N(Pr)CH ₂ c-Pr	6-MeO-4-Me- pyrid-3-yl	
15					
	1539	C-Me	N(Me)Pr	6-MeO-4-Me- pyrid-3-yl	
	1540	C-Me	N(Me)Et	6-MeO-4-Me- pyrid-3-yl	
20	1541	C-Me	N(Me)Bu	6-MeO-4-Me- pyrid-3-yl	
	1542	C-Me	N(Me)propargyl	6-MeO-4-Me- pyrid-3-yl	
	1543	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	6-MeO-4-Me- pyrid-3-yl	
25					
	1544	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	6-MeO-4-Me- pyrid-3-yl	
	1545	C-Me	N(CH ₂ CH ₂ OMe)Me	6-MeO-4-Me- pyrid-3-yl	
30	1546	C-Me	N(CH ₂ CH ₂ OMe)Et	6-MeO-4-Me- pyrid-3-yl	
	1547	C-Me	N(CH ₂ CH ₂ OMe)Pr	6-MeO-4-Me- pyrid-3-yl	

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	1548	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	6-MeO-4-Me- pyrid-3-yl
	1549	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	6-MeO-4-Me- pyrid-3-yl
5	1550	C-Me	NHCH(c-Pr) ₂	6-MeO-4-Me- pyrid-3-yl
	1551	C-Me	N(CH ₂ CH ₂ OMe) ₂	6-MeO-4-Me- pyrid-3-yl
	1552	C-Me	NHCH(Et) ₂	6-MeO-4-Me- pyrid-3-yl
10	1553	C-Me	N(Et) ₂	6-MeO-4-Me- pyrid-3-yl
	1554	C-Me	2-ethylpiperidyl	4,6-Me ₂ - pyrid-3-yl
15	1555	C-Me	cyclobutylamino	4,6-Me ₂ - pyrid-3-yl
	1556	C-Me	N(Me)CH ₂ CH=CH ₂	4,6-Me ₂ - pyrid-3-yl
	1557	C-Me	N(Et)CH ₂ c-Pr	4,6-Me ₂ - pyrid-3-yl
20	1558	C-Me	N(Pr)CH ₂ c-Pr	4,6-Me ₂ - pyrid-3-yl
	1559	C-Me	N(Me)Pr	4,6-Me ₂ - pyrid-3-yl
25	1560	C-Me	N(Me)Et	4,6-Me ₂ - pyrid-3-yl
	1561	C-Me	N(Me)Bu	4,6-Me ₂ - pyrid-3-yl
	1562	C-Me	N(Me)propargyl	4,6-Me ₂ - pyrid-3-yl
30	1563	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	4,6-Me ₂ - pyrid-3-yl

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	1564	C-Me	$N(CH_2CH_2OMe)CH_2CH=CH_2$	4,6-Me ₂ - pyrid-3-yl
	1565	C-Me	$N(CH_2CH_2OMe)Me$	4,6-Me ₂ - pyrid-3-yl
5	1566	C-Me	$N(CH_2CH_2OMe)Et$	4,6-Me ₂ - pyrid-3-yl
	1567	C-Me	$N(CH_2CH_2OMe)Pr$	4,6-Me ₂ - pyrid-3-yl
	1568	C-Me	$N(CH_2CH_2OMe)CH_2c-Pr$	4,6-Me ₂ - pyrid-3-yl
10	1569	C-Me	$NH(CH(CH_3)CH_2CH_3)$	4,6-Me ₂ - pyrid-3-yl
	1570	C-Me	$NHCH(c-Pr)_2$	4,6-Me ₂ - pyrid-3-yl
15	1571	C-Me	$N(CH_2CH_2OMe)_2$	4,6-Me ₂ - pyrid-3-yl
	1572	C-Me	$NHCH(Et)_2$	4,6-Me ₂ - pyrid-3-yl
	1573	C-Me	$N(Et)_2$	4,6-Me ₂ - pyrid-3-yl
20	1574	C-Me	2-ethylpiperidyl	2,6-Me ₂ - pyrid-3-yl
	1575	C-Me	cyclobutylamino	2,6-Me ₂ - pyrid-3-yl
25	1576	C-Me	$N(Me)CH_2CH=CH_2$	2,6-Me ₂ - pyrid-3-yl
	1577	C-Me	$N(Et)CH_2c-Pr$	2,6-Me ₂ - pyrid-3-yl
	1578	C-Me	$N(Pr)CH_2c-Pr$	2,6-Me ₂ - pyrid-3-yl
30	1579	C-Me	$N(Me)Pr$	2,6-Me ₂ - pyrid-3-yl

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	1580	C-Me	N (Me) Et	2,6-Me ₂ - pyrid-3-yl
	1581	C-Me	N (Me) Bu	2,6-Me ₂ - pyrid-3-yl
5	1582	C-Me	N (Me) propargyl	2,6-Me ₂ - pyrid-3-yl
	1583	C-Me	NH (CH (CH ₃) CH (CH ₃) CH ₃)	2,6-Me ₂ - pyrid-3-yl
	1584	C-Me	N (CH ₂ CH ₂ OMe) CH ₂ CH=CH ₂	2,6-Me ₂ - pyrid-3-yl
10	1585	C-Me	N (CH ₂ CH ₂ OMe) Me	2,6-Me ₂ - pyrid-3-yl
	1586	C-Me	N (CH ₂ CH ₂ OMe) Et	2,6-Me ₂ - pyrid-3-yl
15	1587	C-Me	N (CH ₂ CH ₂ OMe) Pr	2,6-Me ₂ - pyrid-3-yl
	1588	C-Me	N (CH ₂ CH ₂ OMe) CH ₂ c-Pr	2,6-Me ₂ - pyrid-3-yl
	1589	C-Me	NH (CH (CH ₃) CH ₂ CH ₃)	2,6-Me ₂ - pyrid-3-yl
20	1590	C-Me	NHCH (c-Pr) ₂	2,6-Me ₂ - pyrid-3-yl
	1591	C-Me	N (CH ₂ CH ₂ OMe) ₂	2,6-Me ₂ - pyrid-3-yl
25	1592	C-Me	NHCH (Et) ₂	2,6-Me ₂ - pyrid-3-yl
	1593	C-Me	N (Et) ₂	2,6-Me ₂ - pyrid-3-yl
	1594	C-Me	2-ethylpiperidyl	4-MeO-6-Me- pyrid-3-yl
30	1595	C-Me	cyclobutylamino	4-MeO-6-Me- pyrid-3-yl
	1596	C-Me	N (Me) CH ₂ CH=CH ₂	4-MeO-6-Me-

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				pyrid-3-yl
	1597	C-Me	N(Et)CH ₂ c-Pr	4-MeO-6-Me-
				pyrid-3-yl
	1598	C-Me	N(Pr)CH ₂ c-Pr	4-MeO-6-Me-
5				pyrid-3-yl
	1599	C-Me	N(Me)Pr	4-MeO-6-Me-
				pyrid-3-yl
	1600	C-Me	N(Me)Et	4-MeO-6-Me-
				pyrid-3-yl
10	1601	C-Me	N(Me)Bu	4-MeO-6-Me-
				pyrid-3-yl
	1602	C-Me	N(Me)propargyl	4-MeO-6-Me-
				pyrid-3-yl
	1603	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	4-MeO-6-Me-
15				pyrid-3-yl
	1604	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	4-MeO-6-Me-
				pyrid-3-yl
	1605	C-Me	N(CH ₂ CH ₂ OMe)Me	4-MeO-6-Me-
				pyrid-3-yl
20	1606	C-Me	N(CH ₂ CH ₂ OMe)Et	4-MeO-6-Me-
				pyrid-3-yl
	1607	C-Me	N(CH ₂ CH ₂ OMe)Pr	4-MeO-6-Me-
				pyrid-3-yl
	1608	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	4-MeO-6-Me-
25				pyrid-3-yl
	1609	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	4-MeO-6-Me-
				pyrid-3-yl
	1610	C-Me	NHCH(c-Pr) ₂	4-MeO-6-Me-
				pyrid-3-yl
30	1611	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-MeO-6-Me-
				pyrid-3-yl
	1612	C-Me	NHCH(Et) ₂	4-MeO-6-Me-
				pyrid-3-yl

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	1613	C-Me	N(Et) ₂	4-MeO-6-Me- pyrid-3-yl
	1614	C-Me	2-ethylpiperidyl	2-Br-4,5-(OMe) ₂ Ph
	1615	C-Me	cyclobutylamino	2-Br-4,5-(OMe) ₂ Ph
5	1616	C-Me	N(Me)CH ₂ CH=CH ₂	2-Br-4,5-(OMe) ₂ Ph
	1617	C-Me	N(Et)CH ₂ c-Pr	2-Br-4,5-(OMe) ₂ Ph
	1618	C-Me	N(Pr)CH ₂ c-Pr	2-Br-4,5-(OMe) ₂ Ph
	1619	C-Me	N(Me)Pr	2-Br-4,5-(OMe) ₂ Ph
	1620	C-Me	N(Me)Et	2-Br-4,5-(OMe) ₂ Ph
10	1621	C-Me	N(Me)Bu	2-Br-4,5-(OMe) ₂ Ph
	1622	C-Me	N(Me)propargyl	2-Br-4,5-(OMe) ₂ Ph
	1623	C-Me	NH(CH(CH ₃)CH(CH ₃)CH ₃)	2-Br-4,5-(OMe) ₂ Ph
	1624	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH=CH ₂	2-Br-4,5-(OMe) ₂ Ph
	1625	C-Me	N(CH ₂ CH ₂ OMe)Me	2-Br-4,5-(OMe) ₂ Ph
15	1626	C-Me	N(CH ₂ CH ₂ OMe)Et	2-Br-4,5-(OMe) ₂ Ph
	1627	C-Me	N(CH ₂ CH ₂ OMe)Pr	2-Br-4,5-(OMe) ₂ Ph
	1628	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ c-Pr	2-Br-4,5-(OMe) ₂ Ph
	1629	C-Me	NH(CH(CH ₃)CH ₂ CH ₃)	2-Br-4,5-(OMe) ₂ Ph
	1630	C-Me	NHCH(c-Pr) ₂	2-Br-4,5-(OMe) ₂ Ph
20	1631	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,5-(OMe) ₂ Ph
	1632	C-Me	NHCH(Et) ₂	2-Br-4,5-(OMe) ₂ Ph
	1633	C-Me	N(Et) ₂	2-Br-4,5-(OMe) ₂ Ph
	1634	C-Me	NEt(Bu)	2-Br-4,5-(OMe) ₂ Ph

25 Notes for Table 7:

- a) CI-MS: 330 (M + H)⁺;
 b) CI-MS: 338 (M + H)⁺;
 c) CI-MS: 338 (M + H)⁺;
 d) CI-MS: 400 (M + H)⁺;
 30 f) CI-MS: 326 (M + H)⁺;
 g) CI-MS: 354 (M + H)⁺;

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- h) CI-MS: 336 (M + H)⁺;
i) CI-MS: 354 (M + H)⁺;
j) CI-MS: 378 (M + H)⁺;
k) CI-HRMS: Calcd 356.2087 (M + H)⁺, Found: 356.2071;
5 m) CI-MS: 340 (M + H)⁺;
n) CI-MS: 368 (M + H)⁺;
o) CI-MS: 326 (M + H)⁺;
p) CI-MS: 368 (M + H)⁺;
q) CI-MS: 394 (M + H)⁺;
10 r) CI-HRMS: Calcd 380.2087 (M + H)⁺, Found: 380.2078;
s) CI-HRMS: Calcd 356.2008 (M + H)⁺, Found: 356.1997;
t) CI-HRMS: Calcd 416.2220 (M + H)⁺, Found: 416.2005;
u) CI-HRMS: Calcd 370.2243 (M + H)⁺, Found: 370.2246;
v) CI-HRMS: Calcd 380.2400 (M + H)⁺, Found: 384.2382;
15 w) CI-HRMS: Calcd 429.2376 (M + H)⁺, Found: 429.2358;
x) CI-HRMS: Calcd 397.2478 (M + H)⁺, Found: 397.2484;
y) CI-HRMS: Calcd 410.5438 (M + H)⁺, Found: 410.2558;
z) CI-HRMS: Calcd 368.4625 (M + H)⁺, Found: 368.2100;
aa) CI-HRMS: Calcd 368.2090 (M + H)⁺, Found: 368.4625;
20 ab) CI-MS 410 (M + H)⁺;
ac) CI-HRMS: Calcd 370.4785 (M + H)⁺, Found: 370.2246;
ad) CI-HRMS: Calcd 356.4514 (M + H)⁺, Found: 356.2086;
ae) CI-MS 384 (M + H)⁺;
af) CI-MS 400 (M + H)⁺;
25 ag) CI-MS 426 (M + H)⁺;
ah) CI-HRMS: Calcd 388.1553 (M + H)⁺, Found: 388.1554;
ai) CI-HRMS: Calcd 388.1540 (M + H)⁺, Found: 358.1546;
aj) CI-HRMS: Calcd 430.2005 (M + H)⁺, Found: 430.2006;
ak) CI-HRMS: Calcd 390.1683 (M + H)⁺, Found: 390.1682;
30 al) CI-HRMS: Calcd 376.1554 (M + H)⁺, Found: 376.1548;
am) CI-HRMS: Calcd 404.1853 (M + H)⁺, Found: 404.1850;
an) CI-HRMS: Calcd 420.1810 (M + H)⁺, Found: 420.1809;

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

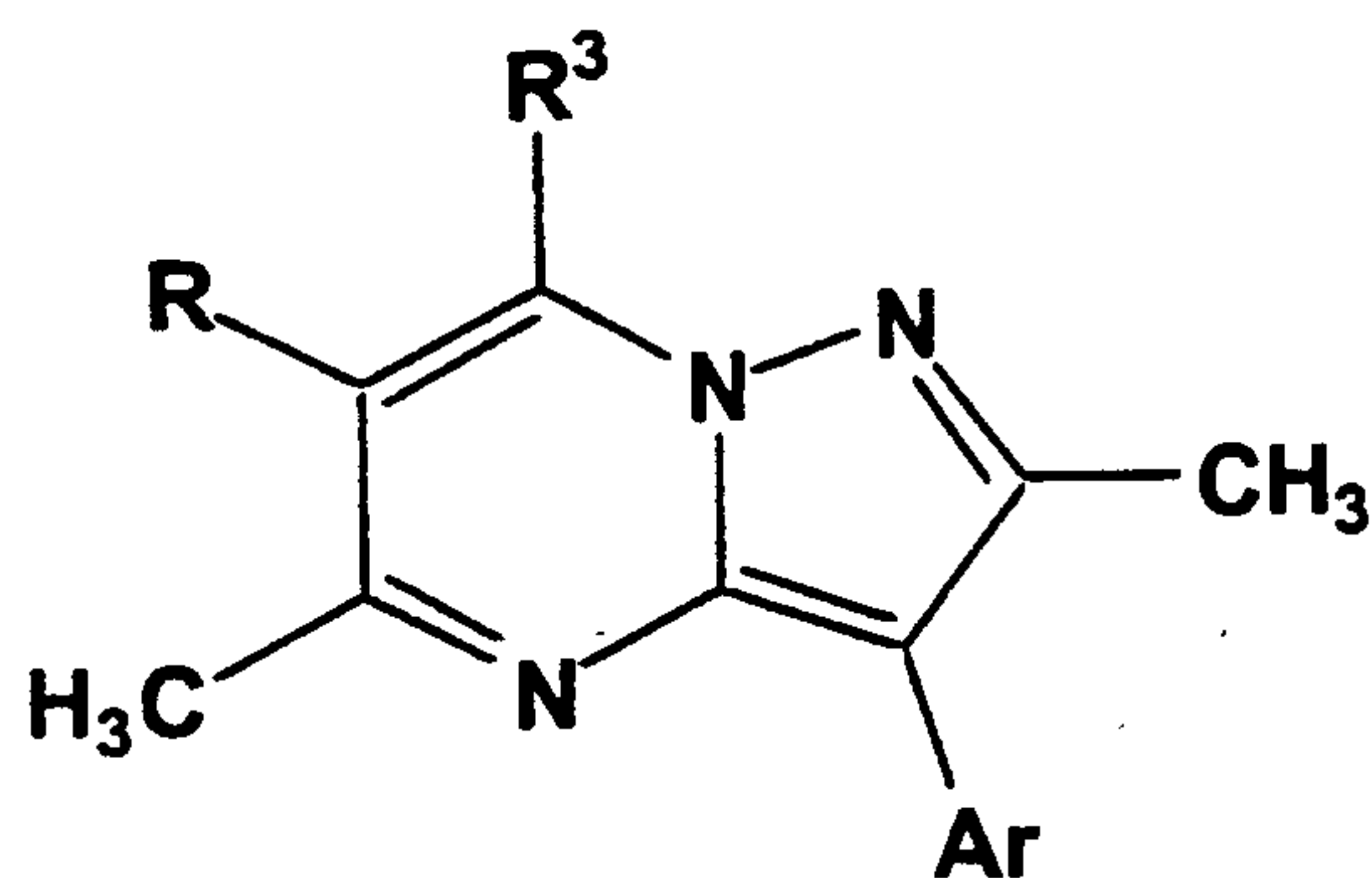
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The examples delineated in TABLE 8 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is
25 propyl, Me is methyl, Et is ethyl, Bu is butyl, cPr is cyclopropyl, Ex is Example,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

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	<u>Ex.</u>	<u>R</u>	<u>R³</u>	<u>Ar</u>	<u>mp (°C)</u>
5	2000	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	
	2001	Me	N(Bu)Et	2,4-Cl ₂ -Ph	
	2002	Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	
	2003	Me	N(Pr)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph	
	2004	Me	NH-3-pentyl	2,4-Cl ₂ -Ph	
10	2005	Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	
	2006	Me	NHCH(Et) ₂	2,4-Me ₂ -Ph	
	2007	Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
	2008	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
	2009	Me	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
15	2010	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl,4-MePh	
	2011	Me	NHCH(CH ₂ OMe) ₂	2-Cl,4-MePh	
	2012	Me	NHCH(Et) ₂	2-Cl,4-MePh	
	2013	Me	NEt ₂	2,4-Me ₂ -Ph	
	2014	Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
20	2015	Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
	2016	Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	
	2017	Me	NHCH(Et) ₂	2-Me,4-MeOPh	
	2018	Me	NHCH(CH ₂ OMe) ₂	2-Me,4-MeOPh	
	2019	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me,4-MeOPh	115-
25	116 ^a				
	2020	Me	(S)-NHCH(CH ₂ CH ₂ OMe)-	2-Me,4-MeOPh	

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	2021		(CH ₂ OMe)	
	2022	Me	(S) -NHCH(CH ₂ CH ₂ OMe) -	2,4-Me ₂ -Ph
	2023		(CH ₂ OMe)	
	2024	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me,4-ClPh
5	2025	Me	NHEt	2,4-Me ₂ -Ph
	2026	Me	NHCH(Et) ₂	2-Me,4-ClPh
	2027	Me	NHCH(CH ₂ OMe) ₂	2-Me,4-ClPh
	2028	Me	N(Ac)Et	2,4-Me ₂ -Ph
	2029	Me	(S) -NHCH(CH ₂ CH ₂ OMe) -	2-Me,4-ClPh
10	2030		(CH ₂ OMe)	
	2031	Me	N(Pr)CH ₂ CH ₂ CN	2-Me,4-MeOPh
	2032	Me	NEt ₂	2-Me,4-MeOPh
	2033	Me	(S) -NHCH(CH ₂ CH ₂ OMe) -	2-Cl,4-MePh
	2034		(CH ₂ OMe)	
15	2035	Me	NEt ₂	2-Cl,4-MePh
	2036	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Me,4-MeOPh
	2037	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl,4-MePh
	2038	Me	NHCH(Et)CH ₂ OMe	2-Me,4-MeOPh
	2039	Me	NHCH(Et)CH ₂ OMe	2-Cl,4-MePh
20	2040	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh
	2041	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh
	2042	Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh
	2043	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh
	2044	Me	NEt ₂	2-Cl-4-MeOPh
25	2045	Me	NH-3-pentyl	2-Cl-4-MeOPh
	2046	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	2047	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	2048	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	2049	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
30	2050	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2051	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2052	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph

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	2053	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,5-(MeO) ₂ Ph
	2054	Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4,5-(MeO) ₂ Ph
	2055	Me	$N(c-Pr)CH_2CH_2CN$	2-Cl-4,5-(MeO) ₂ Ph
	2056	Me	NEt_2	2-Cl-4,5-(MeO) ₂ Ph
5	2057	Me	$NH-3-pentyl$	2-Cl-4,5-(MeO) ₂ Ph
	2058	Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4,5-(MeO) ₂ Ph
	2059	Me	$NHCH(Me)CH_2CH_2OMe$	2-Cl-4,5-(MeO) ₂ Ph
	2060	Me	$NHCH(CH_2OMe)_2$	2-Br-4,5-(MeO) ₂ Ph
	2061	Me	$N(CH_2CH_2OMe)_2$	2-Br-4,5-(MeO) ₂ Ph
10	2062	Me	$NHCH(Et)CH_2CH_2OMe$	2-Br-4,5-(MeO) ₂ Ph
	2063	Me	$N(c-Pr)CH_2CH_2CN$	2-Br-4,5-(MeO) ₂ Ph
	2064	Me	NEt_2	2-Br-4,5-(MeO) ₂ Ph
	2065	Me	$NH-3-pentyl$	2-Br-4,5-(MeO) ₂ Ph
	2066	Me	$NHCH(Et)CH_2CH_2OMe$	2-Br-4,5-(MeO) ₂ Ph
15	2067	Me	$NHCH(Me)CH_2CH_2OMe$	2-Br-4,5-(MeO) ₂ Ph
	2068	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-(MeO) ₂ Ph
	2069	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-(MeO) ₂ Ph
	2070	Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4,6-(MeO) ₂ Ph
	2071	Me	$N(c-Pr)CH_2CH_2CN$	2-Cl-4,6-(MeO) ₂ Ph
20	2072	Me	NEt_2	2-Cl-4,6-(MeO) ₂ Ph
	2073	Me	$NH-3-pentyl$	2-Cl-4,6-(MeO) ₂ Ph
	2074	Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4,6-(MeO) ₂ Ph
	2075	Me	$NHCH(Me)CH_2CH_2OMe$	2-Cl-4,6-(MeO) ₂ Ph
	2076	Me	$NHCH(CH_2OMe)_2$	2-Me-4,6-(MeO) ₂ Ph
25	2077	Me	$N(CH_2CH_2OMe)_2$	2-Me-4,6-(MeO) ₂ Ph
	2078	Me	$NHCH(Et)CH_2CH_2OMe$	2-Me-4,6-(MeO) ₂ Ph
	2079	Me	$N(c-Pr)CH_2CH_2CN$	2-Me-4,6-(MeO) ₂ Ph
	2080	Me	NEt_2	2-Me-4,6-(MeO) ₂ Ph
	2081	Me	$NH-3-pentyl$	2-Me-4,6-(MeO) ₂ Ph
30	2082	Me	$NHCH(Et)CH_2CH_2OMe$	2-Me-4,6-(MeO) ₂ Ph
	2083	Me	$NHCH(Me)CH_2CH_2OMe$	2-Me-4,6-(MeO) ₂ Ph
	2084	Me	$N(c-Pr)CH_2CH_2CN$	2-Br-4,6-(MeO) ₂ Ph

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	2085	Me	NEt ₂	2-Br-4,6-(MeO) ₂ Ph
	2086	Me	NH-3-pentyl	2-Br-4,6-(MeO) ₂ Ph
	2087	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4,6-(MeO) ₂ Ph
	2088	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4,6-(MeO) ₂ Ph
5	2089	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2090	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2091	Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	2092	Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	2093	Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
10	2094	Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	2095	Me	NEt ₂	2-MeO-4-MePh
	2096	Me	NH-3-pentyl	2-MeO-4-MePh
	2097	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2098	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
15	2099	Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	2100	Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	2101	Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
	2102	Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	2103	Me	NEt ₂	2-MeO-4-MePh
20	2104	Me	NH-3-pentyl	2-MeO-4-MePh
	2105	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2106	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2107	Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-ClPh
	2108	Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
25	2109	Me	NHCH(Et)CH ₂ OMe	2-MeO-4-ClPh
	2110	Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-ClPh
	2111	Me	NEt ₂	2-MeO-4-ClPh
	2112	Me	NH-3-pentyl	2-MeO-4-ClPh
	2113	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-ClPh
30	2114	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-ClPh
	2115	Cl	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
	2116	Cl	N(Bu)Et	2,4-Cl ₂ -Ph

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	2117	Cl	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	
	2118	Cl	N(Pr)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph	
	2119	Cl	NH-3-pentyl	2,4-Cl ₂ -Ph	
	2120	Cl	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	
5	2121	Cl	NHCH(Et) ₂	2,4-Me ₂ -Ph	
	2122	Cl	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
	2123	Cl	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
	2124	Cl	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
	2125	Cl	N(CH ₂ CH ₂ OMe) ₂	2-Cl,4-MePh	
10	2126	Cl	NHCH(CH ₂ OMe) ₂	2-Cl,4-MePh	
	2127	Cl	NHCH(Et) ₂	2-Cl,4-MePh	
	2128	Cl	NEt ₂	2,4-Me ₂ -Ph	
	2129	Cl	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
	2130	Cl	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
15	2131	Cl	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	
	2132	Cl	NHCH(Et) ₂	2-Me,4-MeOPh	
	2133	Cl	NHCH(CH ₂ OMe) ₂	2-Me,4-MeOPh	74-76 ^b
	2134	Cl	N(CH ₂ CH ₂ OMe) ₂	2-Me,4-MeOPh	
20	2135	Cl	(S)-NHCH(CH ₂ CH ₂ OMe) -	2-Me,4-MeOPh	
	2136		(CH ₂ OMe)		
	2137	Cl	(S)-NHCH(CH ₂ CH ₂ OMe) -	2,4-Me ₂ -Ph	
	2138		(CH ₂ OMe)		
	2139	Cl	N(CH ₂ CH ₂ OMe) ₂	2-Me,4-ClPh	
25	2140	Cl	NHEt	2,4-Me ₂ -Ph	
	2141	Cl	NHCH(Et) ₂	2-Me,4-ClPh	
	2142	Cl	NHCH(CH ₂ OMe) ₂	2-Me,4-ClPh	
	2143	Cl	N(Ac)Et	2,4-Me ₂ -Ph	
	2144	Cl	(S)-NHCH(CH ₂ CH ₂ OMe) -	2-Me,4-ClPh	
30	2145		(CH ₂ OMe)		
	2146	Cl	N(Pr)CH ₂ CH ₂ CN	2-Me,4-MeOPh	
	2147	Cl	NEt ₂	2-Me,4-MeOPh	

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	2148	Cl	(S) -NHCH(CH ₂ CH ₂ OMe) -	2-Cl, 4-MePh
	2149		(CH ₂ OMe)	
	2150	Cl	NEt ₂	2-Cl, 4-MePh
	2151	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-Me, 4-MeOPh
5	2152	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-Cl, 4-MePh
	2153	Cl	NHCH(Et)CH ₂ OMe	2-Me, 4-MeOPh
	2154	Cl	NHCH(Et)CH ₂ OMe	2-Cl, 4-MePh
	2155	Cl	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh
	2156	Cl	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh
10	2157	Cl	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh
	2158	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh
	2159	Cl	NEt ₂	2-Cl-4-MeOPh
	2160	Cl	NH-3-pentyl	2-Cl-4-MeOPh
	2161	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
15	2162	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	2163	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	2164	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	2165	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2166	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
20	2167	Cl	NHCH(CH ₂ OMe) ₂	2-Cl-4, 5-(MeO) ₂ Ph
	2168	Cl	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4, 5-(MeO) ₂ Ph
	2169	Cl	NHCH(Et)CH ₂ OMe	2-Cl-4, 5-(MeO) ₂ Ph
	2170	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4, 5-(MeO) ₂ Ph
	2171	Cl	NEt ₂	2-Cl-4, 5-(MeO) ₂ Ph
25	2172	Cl	NH-3-pentyl	2-Cl-4, 5-(MeO) ₂ Ph
	2173	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4, 5-(MeO) ₂ Ph
	2174	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4, 5-(MeO) ₂ Ph
	2175	Cl	NHCH(CH ₂ OMe) ₂	2-Br-4, 5-(MeO) ₂ Ph
	2176	Cl	N(CH ₂ CH ₂ OMe) ₂	2-Br-4, 5-(MeO) ₂ Ph
30	2177	Cl	NHCH(Et)CH ₂ OMe	2-Br-4, 5-(MeO) ₂ Ph
	2178	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4, 5-(MeO) ₂ Ph
	2179	Cl	NEt ₂	2-Br-4, 5-(MeO) ₂ Ph

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	2180	Cl	NH-3-pentyl	2-Br-4,5-(MeO) ₂ Ph
	2181	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	2182	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	2183	Cl	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
5	2184	Cl	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
	2185	Cl	NHCH(Et)CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
	2186	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,6-(MeO) ₂ Ph
	2187	Cl	NEt ₂	2-Cl-4,6-(MeO) ₂ Ph
	2188	Cl	NH-3-pentyl	2-Cl-4,6-(MeO) ₂ Ph
10	2189	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
	2190	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
	2191	Cl	NHCH(CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	2192	Cl	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	2193	Cl	NHCH(Et)CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
15	2194	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-Me-4,6-(MeO) ₂ Ph
	2195	Cl	NEt ₂	2-Me-4,6-(MeO) ₂ Ph
	2196	Cl	NH-3-pentyl	2-Me-4,6-(MeO) ₂ Ph
	2197	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
	2198	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
20	2199	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,6-(MeO) ₂ Ph
	2200	Cl	NEt ₂	2-Br-4,6-(MeO) ₂ Ph
	2201	Cl	NH-3-pentyl	2-Br-4,6-(MeO) ₂ Ph
	2202	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4,6-(MeO) ₂ Ph
	2203	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4,6-(MeO) ₂ Ph
25	2204	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2205	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2206	Cl	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	2207	Cl	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	2208	Cl	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
30	2209	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	2210	Cl	NEt ₂	2-MeO-4-MePh
	2211	Cl	NH-3-pentyl	2-MeO-4-MePh

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	2212	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2213	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2214	Cl	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	2215	Cl	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
5	2216	Cl	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
	2217	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	2218	Cl	NEt ₂	2-MeO-4-MePh
	2219	Cl	NH-3-pentyl	2-MeO-4-MePh
	2220	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
10	2221	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2222	Cl	NHCH(CH ₂ OMe) ₂	2-MeO-4-ClPh
	2223	Cl	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
	2224	Cl	NHCH(Et)CH ₂ OMe	2-MeO-4-ClPh
	2225	Cl	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-ClPh
15	2226	Cl	NEt ₂	2-MeO-4-ClPh
	2227	Cl	NH-3-pentyl	2-MeO-4-ClPh
	2228	Cl	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-ClPh
	2229	Cl	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-ClPh
	2230	F	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
20	2231	F	N(Bu)Et	2,4-Cl ₂ -Ph
	2232	F	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
	2233	F	N(Pr)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph
	2234	F	NH-3-pentyl	2,4-Cl ₂ -Ph
	2235	F	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
25	2236	F	NHCH(Et) ₂	2,4-Me ₂ -Ph
	2237	F	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	2238	F	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	2239	F	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	2240	F	N(CH ₂ CH ₂ OMe) ₂	2-Cl,4-MePh
30	2241	F	NHCH(CH ₂ OMe) ₂	2-Cl,4-MePh
	2242	F	NHCH(Et) ₂	2-Cl,4-MePh
	2243	F	NEt ₂	2,4-Me ₂ -Ph

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	2244	F	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	2245	F	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	2246	F	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	2247	F	NHCH(Et) ₂	2-Me-4-MeOPh
5	2248	F	NHCH(CH ₂ OMe) ₂	2-Me-4-MeOPh
	2249	F	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-MeOPh
	2250	F	(S)-NHCH(CH ₂ CH ₂ OMe) -	2-Me-4-MeOPh
	2251		(CH ₂ OMe)	
	2252	F	(S)-NHCH(CH ₂ CH ₂ OMe) -	2,4-Me ₂ -Ph
10	2253		(CH ₂ OMe)	
	2254	F	N(CH ₂ CH ₂ OMe) ₂	2-Me,4-ClPh
	2255	F	NHEt	2,4-Me ₂ -Ph
	2256	F	NHCH(Et) ₂	2-Me,4-ClPh
	2257	F	NHCH(CH ₂ OMe) ₂	2-Me,4-ClPh
15	2258	F	N(Ac)Et	2,4-Me ₂ -Ph
	2259	F	(S)-NHCH(CH ₂ CH ₂ OMe) -	2-Me,4-ClPh
	2260		(CH ₂ OMe)	
	2261	F	N(Pr)CH ₂ CH ₂ CN	2-Me,4-MeOPh
	2262	F	NEt ₂	2-Me,4-MeOPh
20	2263	F	(S)-NHCH(CH ₂ CH ₂ OMe) -	2-Cl,4-MePh
	2264		(CH ₂ OMe)	
	2265	F	NEt ₂	2-Cl,4-MePh
	2266	F	N(c-Pr)CH ₂ CH ₂ CN	2-Me,4-MeOPh
	2267	F	N(c-Pr)CH ₂ CH ₂ CN	2-Cl,4-MePh
25	2268	F	NHCH(Et)CH ₂ OMe	2-Me,4-MeOPh
	2269	F	NHCH(Et)CH ₂ OMe	2-Cl,4-MePh
	2270	F	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh
	2271	F	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh
	2272	F	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh
30	2273	F	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh
	2274	F	NEt ₂	2-Cl-4-MeOPh
	2275	F	NH-3-pentyl	2-Cl-4-MeOPh

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	2276	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	2277	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	2278	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	2279	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
5	2280	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2281	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2282	F	NHCH(CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
	2283	F	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
	2284	F	NHCH(Et)CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
10	2285	F	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,5-(MeO) ₂ Ph
	2286	F	NEt ₂	2-Cl-4,5-(MeO) ₂ Ph
	2287	F	NH-3-pentyl	2-Cl-4,5-(MeO) ₂ Ph
	2288	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	2289	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
15	2290	F	NHCH(CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
	2291	F	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
	2292	F	NHCH(Et)CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	2293	F	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,5-(MeO) ₂ Ph
	2294	F	NEt ₂	2-Br-4,5-(MeO) ₂ Ph
20	2295	F	NH-3-pentyl	2-Br-4,5-(MeO) ₂ Ph
	2296	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	2297	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	2298	F	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
	2299	F	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
25	2300	F	NHCH(Et)CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
	2301	F	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,6-(MeO) ₂ Ph
	2302	F	NEt ₂	2-Cl-4,6-(MeO) ₂ Ph
	2303	F	NH-3-pentyl	2-Cl-4,6-(MeO) ₂ Ph
	2304	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
30	2305	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
	2306	F	NHCH(CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	2307	F	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph

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	2308	F	NHCH(Et)CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
	2309	F	N(c-Pr)CH ₂ CH ₂ CN	2-Me-4,6-(MeO) ₂ Ph
	2310	F	NEt ₂	2-Me-4,6-(MeO) ₂ Ph
	2311	F	NH-3-pentyl	2-Me-4,6-(MeO) ₂ Ph
5	2312	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
	2313	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
	2314	F	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,6-(MeO) ₂ Ph
	2315	F	NEt ₂	2-Br-4,6-(MeO) ₂ Ph
	2316	F	NH-3-pentyl	2-Br-4,6-(MeO) ₂ Ph
10	2317	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4,6-(MeO) ₂ Ph
	2318	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4,6-(MeO) ₂ Ph
	2319	F	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2320	F	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	2321	F	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
15	2322	F	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	2323	F	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
	2324	F	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	2325	F	NEt ₂	2-MeO-4-MePh
	2326	F	NH-3-pentyl	2-MeO-4-MePh
20	2327	F	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2328	F	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2329	F	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	2330	F	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	2331	F	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
25	2332	F	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	2333	F	NEt ₂	2-MeO-4-MePh
	2334	F	NH-3-pentyl	2-MeO-4-MePh
	2335	F	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	2336	F	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
30	2337	F	NHCH(CH ₂ OMe) ₂	2-MeO-4-ClPh
	2338	F	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
	2339	F	NHCH(Et)CH ₂ OMe	2-MeO-4-ClPh

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	2340	F	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-ClPh
	2341	F	NEt ₂	2-MeO-4-ClPh
	2342	F	NH-3-pentyl	2-MeO-4-ClPh
	2343	F	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-ClPh
5	2344	F	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-ClPh
	2345	Me	NMe(CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2346	Me	NEt(CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2347	Me	NPr(CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2348	Me	NH-2-butyl	2,4-Cl ₂ -Ph
10	2349	Me	cyclobutylamino	2,4-Cl ₂ -Ph
	2350	Me	2-ethylpiperidinyl	2,4-Cl ₂ -Ph
	2351	Me	NMe(propargyl)	2,4-Cl ₂ -Ph
	2352	Me	NEt(propargyl)	2,4-Cl ₂ -Ph
	2353	Me	NEtMe	2,4-Cl ₂ -Ph
15	2354	Me	NEtPr	2,4-Cl ₂ -Ph
	2355	Me	NMeBu	2,4-Cl ₂ -Ph
	2356	Me	NMe(CH ₂ cPr)	2,4-Cl ₂ -Ph
	2357	Me	NEt(CH ₂ cPr)	2,4-Cl ₂ -Ph
	2358	Me	NPr(CH ₂ cPr)	2,4-Cl ₂ -Ph
20	2359	Me	NMe(CH ₂ CH ₂ OMe)	2-Me-4-MeOPh
	2360	Me	NEt(CH ₂ CH ₂ OMe)	2-Me-4-MeOPh
	2361	Me	NPr(CH ₂ CH ₂ OMe)	2-Me-4-MeOPh
	2362	Me	NH-2-butyl	2-Me-4-MeOPh
	2363	Me	cyclobutylamino	2-Me-4-MeOPh
25	2364	Me	2-ethylpiperidinyl	2-Me-4-MeOPh
	2365	Me	NMe(propargyl)	2-Me-4-MeOPh
	2366	Me	NEt(propargyl)	2-Me-4-MeOPh
	2367	Me	NEtMe	2-Me-4-MeOPh
	2368	Me	NEtPr	2-Me-4-MeOPh
30	2369	Me	NMeBu	2-Me-4-MeOPh
	2370	Me	NMe(CH ₂ cPr)	2-Me-4-MeOPh
	2371	Me	NEt(CH ₂ cPr)	2-Me-4-MeOPh
	2372	Me	NPr(CH ₂ cPr)	2-Me-4-MeOPh

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	2373	Me	NMe (CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
	2374	Me	NEt (CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
	2375	Me	NPr (CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
	2376	Me	NH-2-butyl	2,4-Me ₂ -Ph
5	2377	Me	cyclobutylamino	2,4-Me ₂ -Ph
	2378	Me	2-ethylpiperidinyl	2,4-Me ₂ -Ph
	2379	Me	NMe (propargyl)	2,4-Me ₂ -Ph
	2380	Me	NEt (propargyl)	2,4-Me ₂ -Ph
	2381	Me	NEtMe	2,4-Me ₂ -Ph
10	2382	Me	NEtPr	2,4-Me ₂ -Ph
	2383	Me	NMeBu	2,4-Me ₂ -Ph
	2384	Me	NMe (CH ₂ cPr)	2,4-Me ₂ -Ph
	2385	Me	NEt (CH ₂ cPr)	2,4-Me ₂ -Ph
	2386	Me	NPr (CH ₂ cPr)	2,4-Me ₂ -Ph
15	2387	Me	NMe (CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2388	Me	NEt (CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2389	Me	NPr (CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2390	Me	NH-2-butyl	2-Cl-4-MeOPh
	2391	Me	cyclobutylamino	2-Cl-4-MeOPh
20	2392	Me	2-ethylpiperidinyl	2-Cl-4-MeOPh
	2393	Me	NMe (propargyl)	2-Cl-4-MeOPh
	2394	Me	NEt (propargyl)	2-Cl-4-MeOPh
	2395	Me	NEtMe	2-Cl-4-MeOPh
	2396	Me	NEtPr	2-Cl-4-MeOPh
25	2397	Me	NMeBu	2-Cl-4-MeOPh
	2398	Me	NMe (CH ₂ cPr)	2-Cl-4-MeOPh
	2399	Me	NEt (CH ₂ cPr)	2-Cl-4-MeOPh
	2400	Me	NPr (CH ₂ cPr)	2-Cl-4-MeOPh
	2401	Me	NMe (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
30	2402	Me	NEt (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
	2403	Me	NPr (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
	2404	Me	NH-2-butyl	2,5-Me ₂ -4-MeOPh

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	2405	Me	cyclobutylamino	2,5-Me ₂ -4-MeOPh
	2406	Me	2-ethylpiperidinyl	2,5-Me ₂ -4-MeOPh
	2407	Me	NMe(propargyl)	2,5-Me ₂ -4-MeOPh
	2408	Me	NEt(propargyl)	2,5-Me ₂ -4-MeOPh
5	2409	Me	NEtMe	2,5-Me ₂ -4-MeOPh
	2410	Me	NEtPr	2,5-Me ₂ -4-MeOPh
	2411	Me	NMeBu	2,5-Me ₂ -4-MeOPh
	2412	Me	NMe(CH ₂ cPr)	2,5-Me ₂ -4-MeOPh
	2413	Me	NEt(CH ₂ cPr)	2,5-Me ₂ -4-MeOPh
10	2414	Me	NPr(CH ₂ cPr)	2,5-Me ₂ -4-MeOPh
	2415	Cl	NMe(CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2416	Cl	NEt(CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2417	Cl	NPr(CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2418	Cl	NH-2-butyl	2,4-Cl ₂ -Ph
15	2419	Cl	cyclobutylamino	2,4-Cl ₂ -Ph
	2420	Cl	2-ethylpiperidinyl	2,4-Cl ₂ -Ph
	2421	Cl	NMe(propargyl)	2,4-Cl ₂ -Ph
	2422	Cl	NEt(propargyl)	2,4-Cl ₂ -Ph
	2423	Cl	NEtMe	2,4-Cl ₂ -Ph
20	2424	Cl	NEtPr	2,4-Cl ₂ -Ph
	2425	Cl	NMeBu	2,4-Cl ₂ -Ph
	2426	Cl	NMe(CH ₂ cPr)	2,4-Cl ₂ -Ph
	2427	Cl	NEt(CH ₂ cPr)	2,4-Cl ₂ -Ph
	2428	Cl	NPr(CH ₂ cPr)	2,4-Cl ₂ -Ph
25	2429	Cl	NMe(CH ₂ CH ₂ OMe)	2-Me-4-MeOPh
	2430	Cl	NEt(CH ₂ CH ₂ OMe)	2-Me-4-MeOPh
	2431	Cl	NPr(CH ₂ CH ₂ OMe)	2-Me-4-MeOPh
	2432	Cl	NH-2-butyl	2-Me-4-MeOPh
	2433	Cl	cyclobutylamino	2-Me-4-MeOPh
30	2434	Cl	2-ethylpiperidinyl	2-Me-4-MeOPh
	2435	Cl	NMe(propargyl)	2-Me-4-MeOPh
	2436	Cl	NEt(propargyl)	2-Me-4-MeOPh

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	2437	Cl	NEtMe	2-Me-4-MeOPh
	2438	Cl	NEtPr	2-Me-4-MeOPh
	2439	Cl	NMeBu	2-Me-4-MeOPh
	2440	Cl	NMe (CH ₂ cPr)	2-Me-4-MeOPh
5	2441	Cl	NEt (CH ₂ cPr)	2-Me-4-MeOPh
	2442	Cl	NPr (CH ₂ cPr)	2-Me-4-MeOPh
	2443	Cl	NMe (CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
	2444	Cl	NEt (CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
	2445	Cl	NPr (CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
10	2446	Cl	NH-2-butyl	2,4-Me ₂ -Ph
	2447	Cl	cyclobutylamino	2,4-Me ₂ -Ph
	2448	Cl	2-ethylpiperidinyl	2,4-Me ₂ -Ph
	2449	Cl	NMe (propargyl)	2,4-Me ₂ -Ph
	2450	Cl	NEt (propargyl)	2,4-Me ₂ -Ph
15	2451	Cl	NEtMe	2,4-Me ₂ -Ph
	2452	Cl	NEtPr	2,4-Me ₂ -Ph
	2453	Cl	NMeBu	2,4-Me ₂ -Ph
	2454	Cl	NMe (CH ₂ cPr)	2,4-Me ₂ -Ph
	2455	Cl	NEt (CH ₂ cPr)	2,4-Me ₂ -Ph
20	2456	Cl	NPr (CH ₂ cPr)	2,4-Me ₂ -Ph
	2457	Cl	NMe (CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2458	Cl	NEt (CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2459	Cl	NPr (CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2460	Cl	NH-2-butyl	2-Cl-4-MeOPh
25	2461	Cl	cyclobutylamino	2-Cl-4-MeOPh
	2462	Cl	2-ethylpiperidinyl	2-Cl-4-MeOPh
	2463	Cl	NMe (propargyl)	2-Cl-4-MeOPh
	2464	Cl	NEt (propargyl)	2-Cl-4-MeOPh
	2465	Cl	NEtMe	2-Cl-4-MeOPh
30	2466	Cl	NEtPr	2-Cl-4-MeOPh
	2467	Cl	NMeBu	2-Cl-4-MeOPh
	2468	Cl	NMe (CH ₂ cPr)	2-Cl-4-MeOPh
	2469	Cl	NEt (CH ₂ cPr)	2-Cl-4-MeOPh

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	2470	Cl	NPr (CH ₂ cPr)	2-Cl-4-MeOPh
	2471	Cl	NMe (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
	2472	Cl	NEt (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
	2473	Cl	NPr (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
5	2474	Cl	NH-2-butyl	2,5-Me ₂ -4-MeOPh
	2475	Cl	cyclobutylamino	2,5-Me ₂ -4-MeOPh
	2476	Cl	2-ethylpiperidinyl	2,5-Me ₂ -4-MeOPh
	2477	Cl	NMe (propargyl)	2,5-Me ₂ -4-MeOPh
	2478	Cl	NEt (propargyl)	2,5-Me ₂ -4-MeOPh
10	2479	Cl	NEtMe	2,5-Me ₂ -4-MeOPh
	2480	Cl	NEtPr	2,5-Me ₂ -4-MeOPh
	2481	Cl	NMeBu	2,5-Me ₂ -4-MeOPh
	2482	Cl	NMe (CH ₂ cPr)	2,5-Me ₂ -4-MeOPh
	2483	Cl	NEt (CH ₂ cPr)	2,5-Me ₂ -4-MeOPh
15	2484	Cl	NPr (CH ₂ cPr)	2,5-Me ₂ -4-MeOPh
	2485	F	NMe (CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2486	F	NEt (CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2487	F	NPr (CH ₂ CH ₂ OMe)	2,4-Cl ₂ -Ph
	2488	F	NH-2-butyl	2,4-Cl ₂ -Ph
20	2489	F	cyclobutylamino	2,4-Cl ₂ -Ph
	2490	F	2-ethylpiperidinyl	2,4-Cl ₂ -Ph
	2491	F	NMe (propargyl)	2,4-Cl ₂ -Ph
	2492	F	NEt (propargyl)	2,4-Cl ₂ -Ph
	2493	F	NEtMe	2,4-Cl ₂ -Ph
25	2494	F	NEtPr	2,4-Cl ₂ -Ph
	2495	F	NMeBu	2,4-Cl ₂ -Ph
	2496	F	NMe (CH ₂ cPr)	2,4-Cl ₂ -Ph
	2497	F	NEt (CH ₂ cPr)	2,4-Cl ₂ -Ph
	2498	F	NPr (CH ₂ cPr)	2,4-Cl ₂ -Ph
30	2499	F	NMe (CH ₂ CH ₂ OMe)	2-Me-4-MeOPh
	2500	F	NEt (CH ₂ CH ₂ OMe)	2-Me-4-MeOPh
	2501	F	NPr (CH ₂ CH ₂ OMe)	2-Me-4-MeOPh

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	2502	F	NH-2-butyl	2-Me-4-MeOPh
	2503	F	cyclobutylamino	2-Me-4-MeOPh
	2504	F	2-ethylpiperidinyl	2-Me-4-MeOPh
	2505	F	NMe(propargyl)	2-Me-4-MeOPh
5	2506	F	NEt(propargyl)	2-Me-4-MeOPh
	2507	F	NEtMe	2-Me-4-MeOPh
	2508	F	NEtPr	2-Me-4-MeOPh
	2509	F	NMeBu	2-Me-4-MeOPh
	2510	F	NMe(CH ₂ cPr)	2-Me-4-MeOPh
10	2511	F	NEt(CH ₂ cPr)	2-Me-4-MeOPh
	2512	F	NPr(CH ₂ cPr)	2-Me-4-MeOPh
	2513	F	NMe(CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
	2514	F	NEt(CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
	2515	F	NPr(CH ₂ CH ₂ OMe)	2,4-Me ₂ -Ph
15	2516	F	NH-2-butyl	2,4-Me ₂ -Ph
	2517	F	cyclobutylamino	2,4-Me ₂ -Ph
	2518	F	2-ethylpiperidinyl	2,4-Me ₂ -Ph
	2519	F	NMe(propargyl)	2,4-Me ₂ -Ph
	2520	F	NEt(propargyl)	2,4-Me ₂ -Ph
20	2521	F	NEtMe	2,4-Me ₂ -Ph
	2522	F	NEtPr	2,4-Me ₂ -Ph
	2523	F	NMeBu	2,4-Me ₂ -Ph
	2524	F	NMe(CH ₂ cPr)	2,4-Me ₂ -Ph
	2525	F	NEt(CH ₂ cPr)	2,4-Me ₂ -Ph
25	2526	F	NPr(CH ₂ cPr)	2,4-Me ₂ -Ph
	2527	F	NMe(CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2528	F	NEt(CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2529	F	NPr(CH ₂ CH ₂ OMe)	2-Cl-4-MeOPh
	2530	F	NH-2-butyl	2-Cl-4-MeOPh
30	2531	F	cyclobutylamino	2-Cl-4-MeOPh
	2532	F	2-ethylpiperidinyl	2-Cl-4-MeOPh
	2533	F	NMe(propargyl)	2-Cl-4-MeOPh
	2534	F	NEt(propargyl)	2-Cl-4-MeOPh

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	2535	F	NEtMe	2-Cl-4-MeOPh
	2536	F	NEtPr	2-Cl-4-MeOPh
	2537	F	NMeBu	2-Cl-4-MeOPh
	2538	F	NMe (CH ₂ cPr)	2-Cl-4-MeOPh
5	2539	F	NEt (CH ₂ cPr)	2-Cl-4-MeOPh
	2540	F	NPr (CH ₂ cPr)	2-Cl-4-MeOPh
	2541	F	NMe (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
	2542	F	NEt (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
	2543	F	NPr (CH ₂ CH ₂ OMe)	2,5-Me ₂ -4-MeOPh
10	2544	F	NH-2-butyl	2,5-Me ₂ -4-MeOPh
	2545	F	cyclobutylamino	2,5-Me ₂ -4-MeOPh
	2546	F	2-ethylpiperidinyl	2,5-Me ₂ -4-MeOPh
	2547	F	NMe (propargyl)	2,5-Me ₂ -4-MeOPh
	2548	F	NEt (propargyl)	2,5-Me ₂ -4-MeOPh
15	2549	F	NEtMe	2,5-Me ₂ -4-MeOPh
	2550	F	NEtPr	2,5-Me ₂ -4-MeOPh
	2551	F	NMeBu	2,5-Me ₂ -4-MeOPh
	2552	F	NMe (CH ₂ cPr)	2,5-Me ₂ -4-MeOPh
	2553	F	NEt (CH ₂ cPr)	2,5-Me ₂ -4-MeOPh
20	2554	F	NPr (CH ₂ cPr)	2,5-Me ₂ -4-MeOPh

a) CI-HRMS: Calcd: 367.2498; Found: 367.2468 (M + H)⁺b) CI-HRMS: Calcd: 387.1952; Found: 387.1939 (M + H)⁺

25

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

30

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
5 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
10 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 μ M hygromycin. Cells
15 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 1×10^8 of the suspended cells were then centrifuged to
20 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
25 $MgCl_2$, 2 mM EGTA, 1 μ g/ml aprotinin, 1 μ g/ml leupeptin and 1 μ g/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
30 resuspended to a protein concentration of 360 μ g/ml to be used in the assay.

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

of drugs range from 10^{-10} - 10^{-5} M), 100 μ l of ^{125}I -ovine-CRF (^{125}I -o-CRF) (final concentration 150 pM) and 150 μ l 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 K_i values for inhibition which are then used to assess biological activity.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM MgCl_2 , 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6} M) and 0.8 mg original wet weight tissue

(approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/³²P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 μ l of [³H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [³²P]cAMP from [³²P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

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

Compounds may be tested in any species of rodent or small mammal.

25

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

30

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,
5 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
10 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
15 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.
20 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
25 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
30 composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups,
35 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
5 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
10 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
15 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
20 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
25 contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are
30 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.

35 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
5 can be illustrated as follows:

Capsules

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

Soft Gelatin Capsules

15 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
20 ingredient. The capsules were washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was
25 100 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
30 adsorption.

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

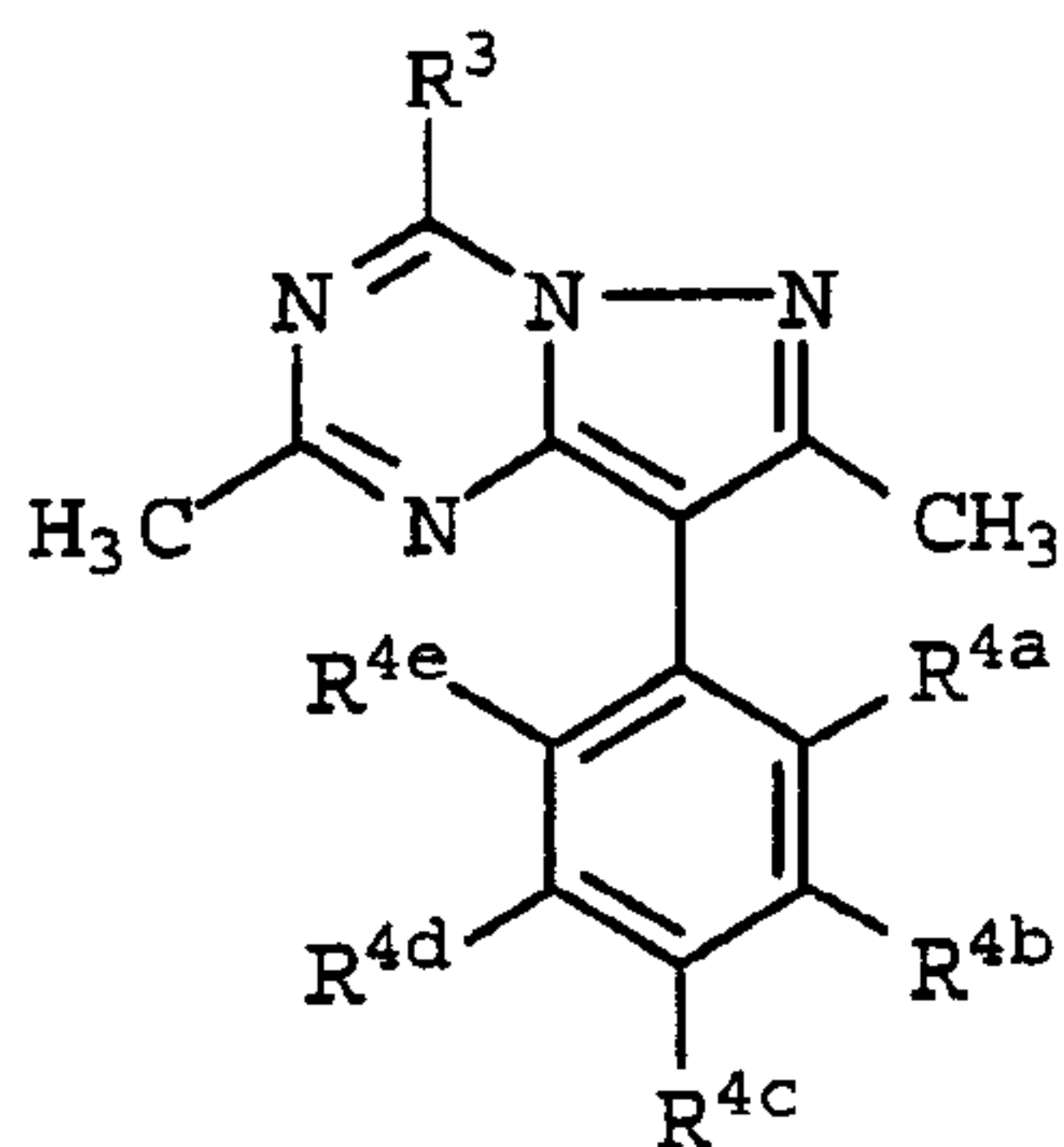
Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be
5 apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification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

CLAIMS

WHAT IS CLAIMED IS:

5

1. A compound of Formula (50)



FORMULA (50)

10

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

a compound of Formula (50) wherein R³ is 2-ethylpiperid-1-yl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R³ is cyclobutyl-amino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R³ is N(Me)CH₂CH=CH₂, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $N(\text{Pr})\text{CH}_2\text{cPr}$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is H;
- 5 a compound of Formula (50) wherein R^3 is $N(\text{Me})\text{Pr}$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 10 a compound of Formula (50) wherein R^3 is $N(\text{Me})\text{Et}$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 15 a compound of Formula (50) wherein R^3 is $N(\text{Me})\text{Bu}$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 20 a compound of Formula (50) wherein R^3 is
 $N(\text{Me})\text{propargyl}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is
 $\text{NHCH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is
 $N(\text{CH}_2\text{CH}_2\text{OMe})\text{Me}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is
 $\text{NHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $N(\text{Pr})\text{CH}_2\text{cPr}$,
 R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
 is H;

- a compound of Formula (50) wherein R^3 is $N(Me)Bu$, R^{4a} is OMe , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is H ;
- 5 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)Et$, R^{4a} is OMe , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is H ;
- 10 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-CH_2cPr$, R^{4a} is OMe , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is H ;
- 15 a compound of Formula (50) wherein R^3 is $NHCH(CH_3)CH_2CH_3$, R^{4a} is OMe , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is H ;
- 20 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is OMe , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is H ;
- a compound of Formula (50) wherein R^3 is $NHCH(Et)_2$, R^{4a} is OMe , R^{4b} is H , R^{4c} is OMe , R^{4d} is Me and R^{4e} is H ;
- 25 a compound of Formula (50) wherein R^3 is 2-ethylpiperid-1-yl, R^{4a} is Me , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is OMe ;
- 30 a compound of Formula (50) wherein R^3 is cyclobutyl-amino, R^{4a} is Me , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is OMe ;
- 35 a compound of Formula (50) wherein R^3 is $N(Me)CH_2CH=CH_2$, R^{4a} is Me , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is OMe ;
- 40 a compound of Formula (50) wherein R^3 is $N(Pr)CH_2cPr$, R^{4a} is Me , R^{4b} is H , R^{4c} is OMe , R^{4d} is H and R^{4e} is OMe ;

- a compound of Formula (50) wherein R^3 is N(Me)Pr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 5 a compound of Formula (50) wherein R^3 is N(Me)Et, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 10 a compound of Formula (50) wherein R^3 is N(Me)Bu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 15 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)Et, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 20 a compound of Formula (50) wherein R^3 is N(CH₂CH₂OMe)-CH₂cPr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- a compound of Formula (50) wherein R^3 is NHCH(CH₃)CH₂CH₃, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is OMe;
- 25 a compound of Formula (50) wherein R^3 is NHCH(Et)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is N(Me)CH₂CH=CH₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is N(Me)Pr, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is N(Me)Et, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is F and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is cyclobutyl-amino, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $N(Me)CH_2CH=CH_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $N(Pr)CH_2cPr$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $N(Me)Pr$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $N(Me)Et$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $N(Me)Bu$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)Et$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)-CH_2cPr$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $NHCH(CH_2OCH_3)_2$; R^{4a} is Cl; R^{4b} is H; R^{4c} is Cl; R^{4d}

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

5 a compound of Formula (50) wherein R³ is NEt₂; R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is OMe;

10 a compound of Formula (50) wherein R³ is NH-3-pentyl; R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is OMe;

a compound of Formula (50) wherein R³ is N(CH₂CH=CH₂)₂; R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is H;

15 a compound of Formula (50) wherein R³ is NHCH₂-2-tetrahydrofuryl; R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is H;

20 a compound of Formula (50) wherein R³ is NH-2-hexyl; R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is H;

25 a compound of Formula (50) wherein R³ is NH-2-propyl; R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is H;

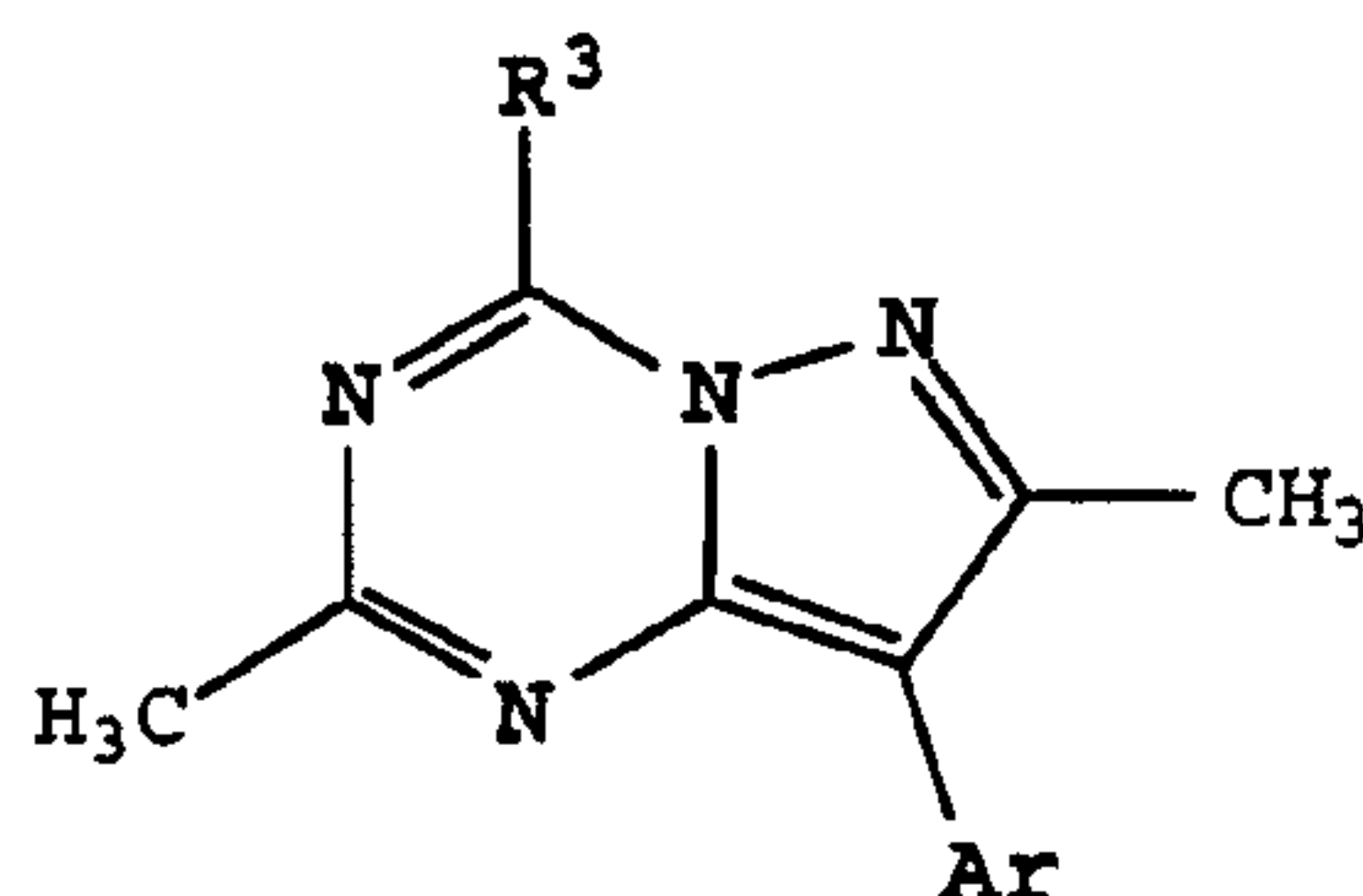
30 a compound of Formula (50) wherein R³ is NEt(cyclohexyl); R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is H;

a compound of Formula (50) wherein R³ is N(CH₂CH=CH₂)₂; R^{4a} is OMe; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $N(Et)_2$; R^{4a} is OMe; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $N(Pr)_2$; R^{4a} is OMe; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $NH(CH(CH_3)CH_2CH_3)$; R^{4a} is OMe; R^{4b} is H; R^{4c} is OMe; R^{4d} is Cl; and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$; R^{4a} is OMe; R^{4b} is H; R^{4c} is OMe; R^{4d} is Cl; and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$; R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is OMe;
- 25 a compound of Formula (50) wherein R^3 is $NEt(Bu)$; R^{4a} is Me; R^{4b} is H; R^{4c} is OMe; R^{4d} is H; and R^{4e} is OMe;
- 30 a compound of Formula (50) wherein R^3 is $N(Et)_2$; R^{4a} is Cl; R^{4b} is H; R^{4c} is OMe; R^{4d} is OMe; and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $\text{NEt}(\text{Bu})$; R^{4a} is Cl ; R^{4b} is H ; R^{4c} is OMe ; R^{4d} is OMe ; and R^{4e} is H ;
- 5 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})_2$; R^{4a} is Me ; R^{4b} is H ; R^{4c} is OMe ; R^{4d} is H ; and R^{4e} is Me ;
- 10 a compound of Formula (50) wherein R^3 is $\text{NEt}(\text{Bu})$; R^{4a} is Me ; R^{4b} is H ; R^{4c} is OMe ; R^{4d} is H ; and R^{4e} is Me ;
- 15 a compound of Formula (50) wherein R^3 is $\text{NH}(\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3)$; R^{4a} is Cl ; R^{4b} is H ; R^{4c} is OMe ; R^{4d} is F ; and R^{4e} is H ;
- 20 a compound of Formula (50) wherein R^3 is $\text{NEt}(\text{Bu})$; R^{4a} is Cl ; R^{4b} is H ; R^{4c} is OMe ; R^{4d} is F ; and R^{4e} is H ;
- a compound of Formula (50) wherein R^3 is $\text{N}(\text{Pr})\text{CH}_2\text{C-Pr}$; R^{4a} is Br ; R^{4b} is H ; R^{4c} is OMe ; R^{4d} is OMe ; and R^{4e} is H ;
- 25 a compound of Formula (50) wherein R^3 is $\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$; R^{4a} is Br ; R^{4b} is H ; R^{4c} is OMe ; R^{4d} is OMe ; and R^{4e} is H ;
- 30 a compound of Formula (50) wherein R^3 is $\text{N}(\text{Et})_2$; R^{4a} is Br ; R^{4b} is H ; R^{4c} is OMe ; R^{4d} is OMe ; and R^{4e} is H .

2. A compound of Formula (60)



FORMULA (60)

5

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

10

a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)Et$, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

15 a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)_2$, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is $NHCH(Et)_2$ Ar is 6-dimethylamino-4-methylpyrid-3-yl;

20

a compound of Formula (60) wherein R^3 is $N(Et)_2$, Ar is 6-dimethylamino-4-methylpyrid-3-yl;

25 a compound of Formula (60) wherein R^3 is $N(Me)CH_2CH=CH_2$, Ar is 6-methoxy-4-methylpyrid-3-yl;

- a compound of Formula (60) wherein R^3 is $N(\text{Pr})\text{CH}_2\text{cPr}$,
Ar is 6-methoxy -4-methylpyrid-3-yl;
- 5 a compound of Formula (60) wherein R^3 is $N(\text{Me})\text{Pr}$, Ar is
6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(\text{Me})\text{Et}$, Ar is
6-methoxy -4-methylpyrid-3-yl;
- 10 a compound of Formula (60) wherein R^3 is $N(\text{Me})\text{Bu}$, Ar is
6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is
 $N(\text{CH}_2\text{CH}_2\text{OMe})\text{Et}$, Ar is 6-methoxy -4-methylpyrid-3-yl;
15
- a compound of Formula (60) wherein R^3 is $N(\text{CH}_2\text{CH}_2\text{OMe})\text{-CH}_2\text{cPr}$, Ar is 6-methoxy -4-methylpyrid-3-yl;
- 20 a compound of Formula (60) wherein R^3 is
 $\text{NHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, Ar is 6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $N(\text{CH}_2\text{CH}_2\text{OMe})_2$,
25 Ar is 6-methoxy -4-methylpyrid-3-yl;
- a compound of Formula (60) wherein R^3 is $\text{NHCH}(\text{Et})_2$ Ar
is 6-methoxy -4-methylpyrid-3-yl;
- 30 a compound of Formula (60) wherein R^3 is $N(\text{Et})_2$, Ar is

6- methoxy -4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is

5 $N(CH_2CH_2OMe)Et$, Ar is 2-methoxy-6-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is $N(CH_2CH_2OMe)_2$,

Ar is 4-methoxy-6-methylpyrid-3-yl;

10 a compound of Formula (60) wherein R^3 is $NHCH(Et)_2$, Ar is 6- methoxy -4-methylpyrid-3-yl;

a compound of Formula (60) wherein R^3 is $N(Et)_2$, Ar is 4-methoxy-6-methylpyrid-3-yl.

15

3. A compound and geometric isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof, wherein said compound
20 is selected from the group:

4-((2-butyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine;

25 4-((2-butyl)amino)-2,7-dimethyl-8-(2,5-di methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine;

4-((3-pentyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine;

30

4-(N-cyclopropylmethyl-N-propylamino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-

triazine;

4 - (N-cyclopropylmethyl-N-propylamino) - 2,7-dimethyl-
8 - (2-methyl-4-methoxyphenyl) - [1,5-a] - pyrazolo-1,3,5-
5 triazine;

4 - (N-cyclopropylmethyl-N-propylamino) - 2,7-dimethyl-
8 - (2,5-dimethyl-4-methoxyphenyl) - [1,5-a] - pyrazolo-
1,3,5-triazine;
10

4 - (N-allyl-N- (2-methoxyethyl) amino) - 2,7-dimethyl-8-
(2-methyl-4-methoxyphenyl) - [1,5-a] - pyrazolo-1,3,5-
triazine;

15 4 - (N-allyl-N- (2-methoxyethyl) amino) - 2,7-dimethyl-8-
(2,5-dimethyl-4-methoxyphenyl) - [1,5-a] - pyrazolo-
1,3,5-triazine;

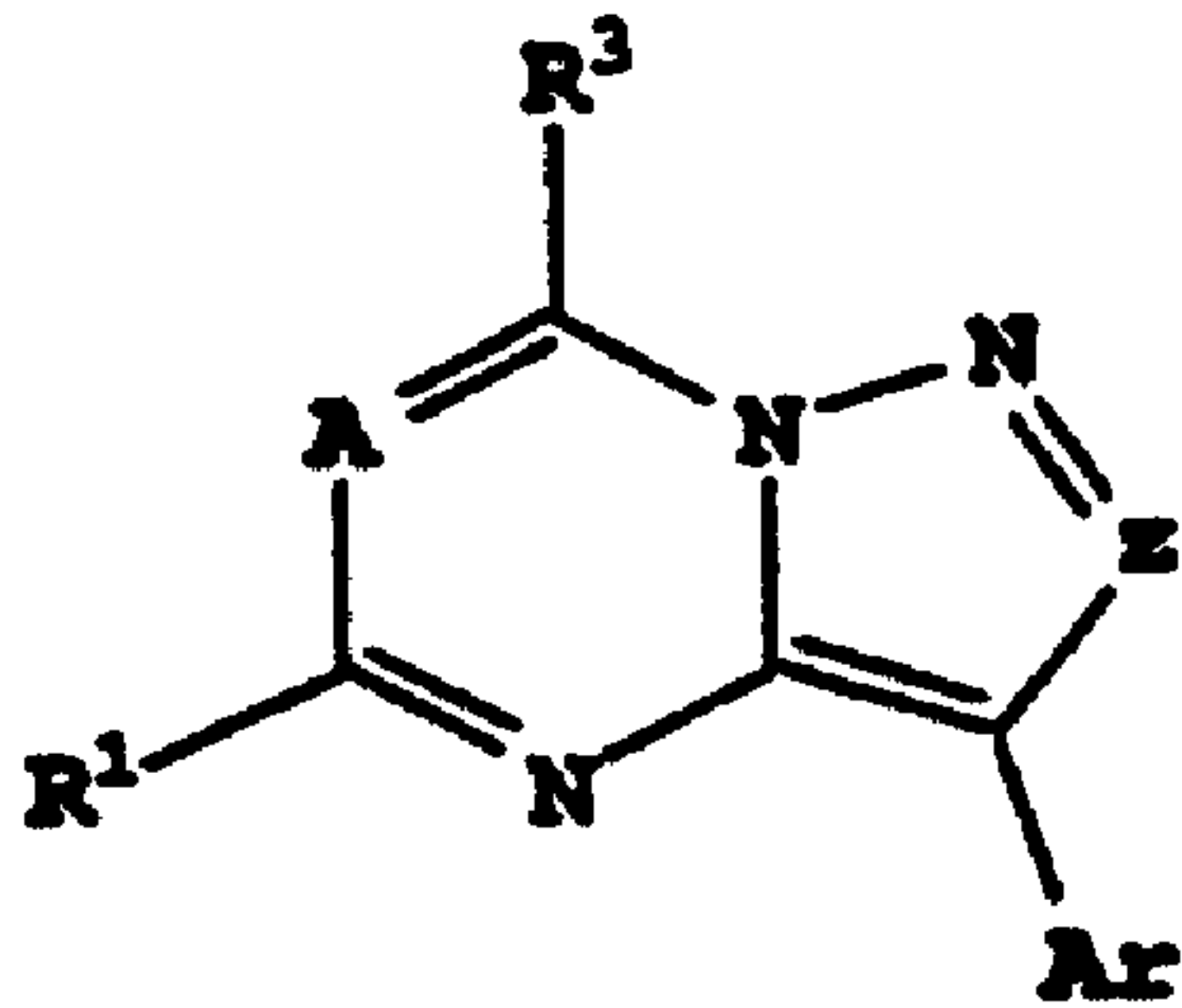
4 - (N-ethyl-N- (2-methoxyethyl) amino) - 2,7-dimethyl-8-
20 (2-methyl-4-methoxyphenyl) - [1,5-a] - pyrazolo-1,3,5-
triazine; and

4 - (N-ethyl-N- (2-methoxyethyl) amino) - 2,7-dimethyl-8-
(2,5-dimethyl-4-methoxyphenyl) - [1,5-a] - pyrazolo-1,3,5-
25 triazine.

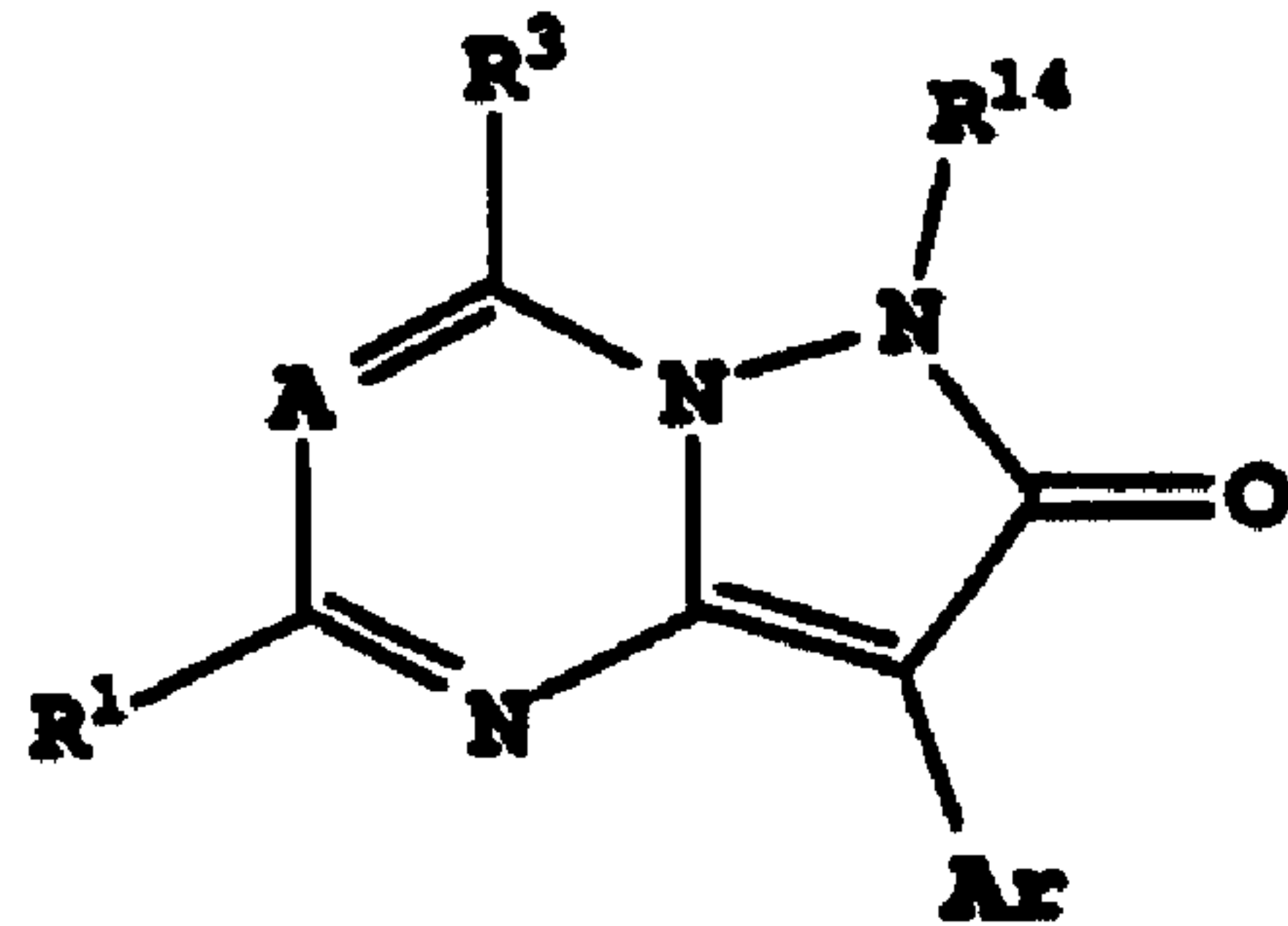
4. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a compound of
any one of claims 1 to 3.

30

5. Use of a compound of any one of claims 1 to 3 in the preparation of a medicament for treating affective disorder, anxiety, depression, or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including disorders induced or facilitated by CRF, in mammals.



(I)



(II)