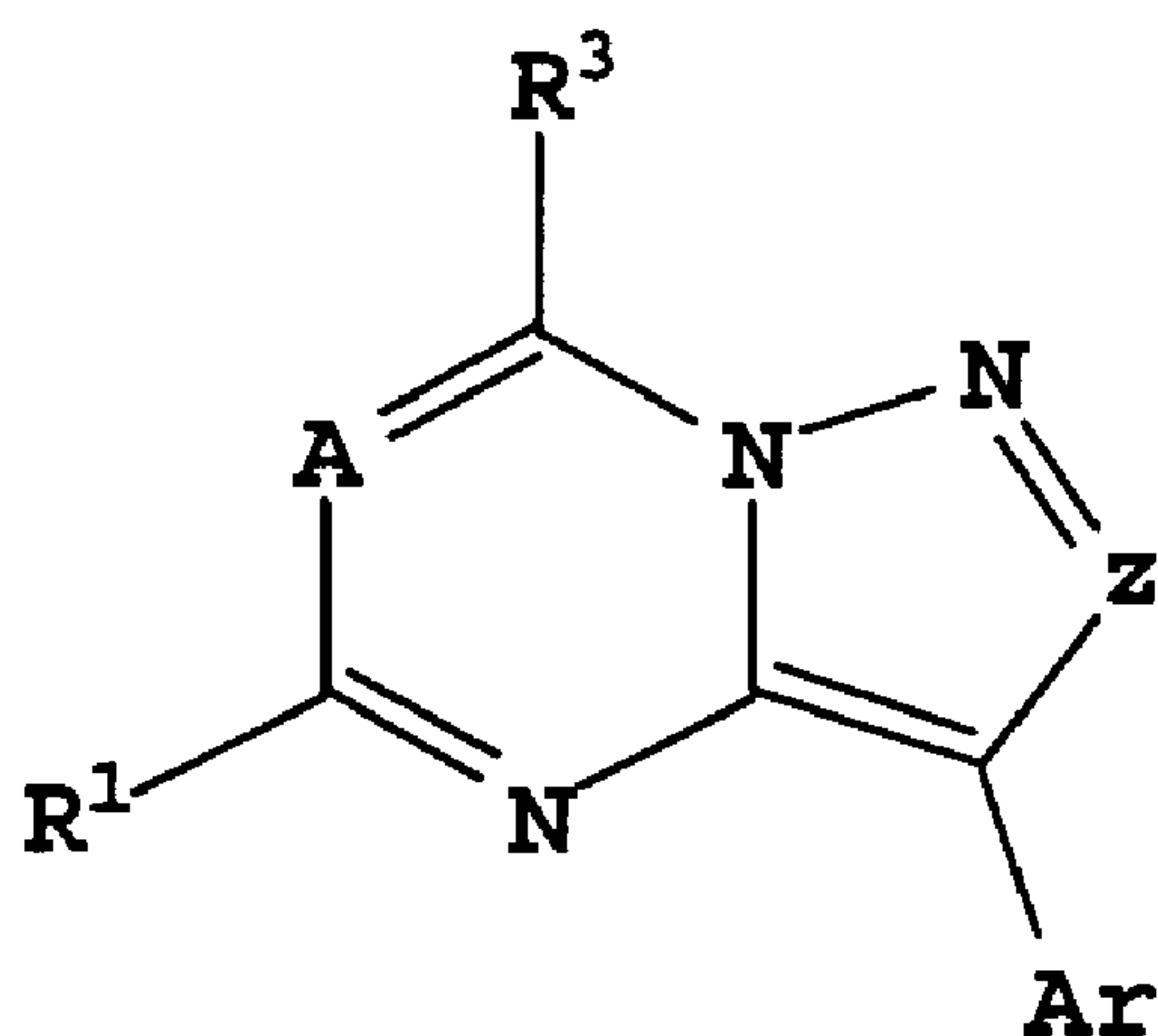




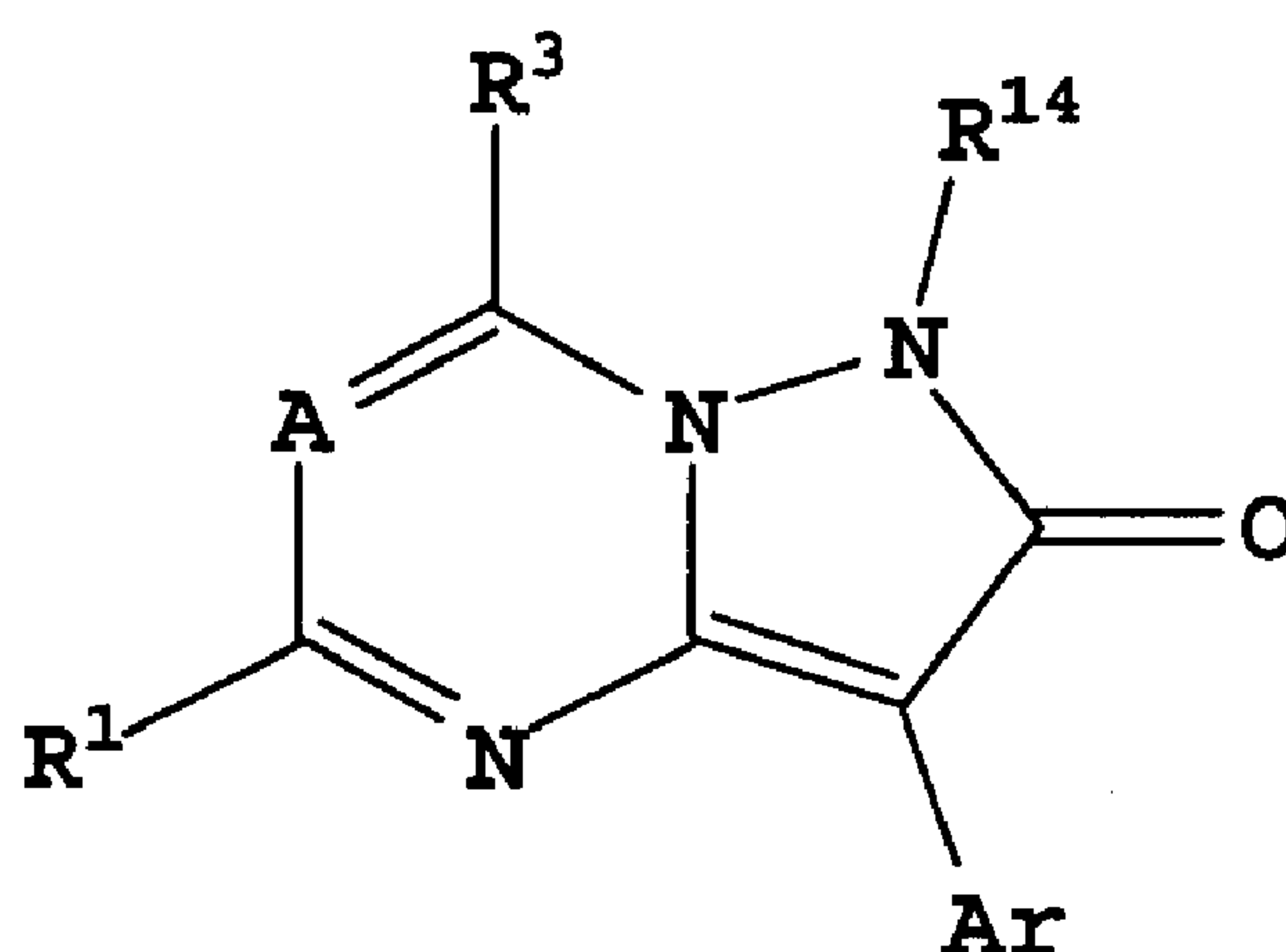
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(54) Titre : AZOLO TRIAZINES ET PYRIMIDINES
(54) Title: AZOLO TRIAZINES AND PYRIMIDINES



(I)



(II)

(57) Abrégé/Abstract:

Corticotropin releasing factor (CRF) antagonists of formula I or II: (see formula I) (see formula II) wherein A is CR, 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.



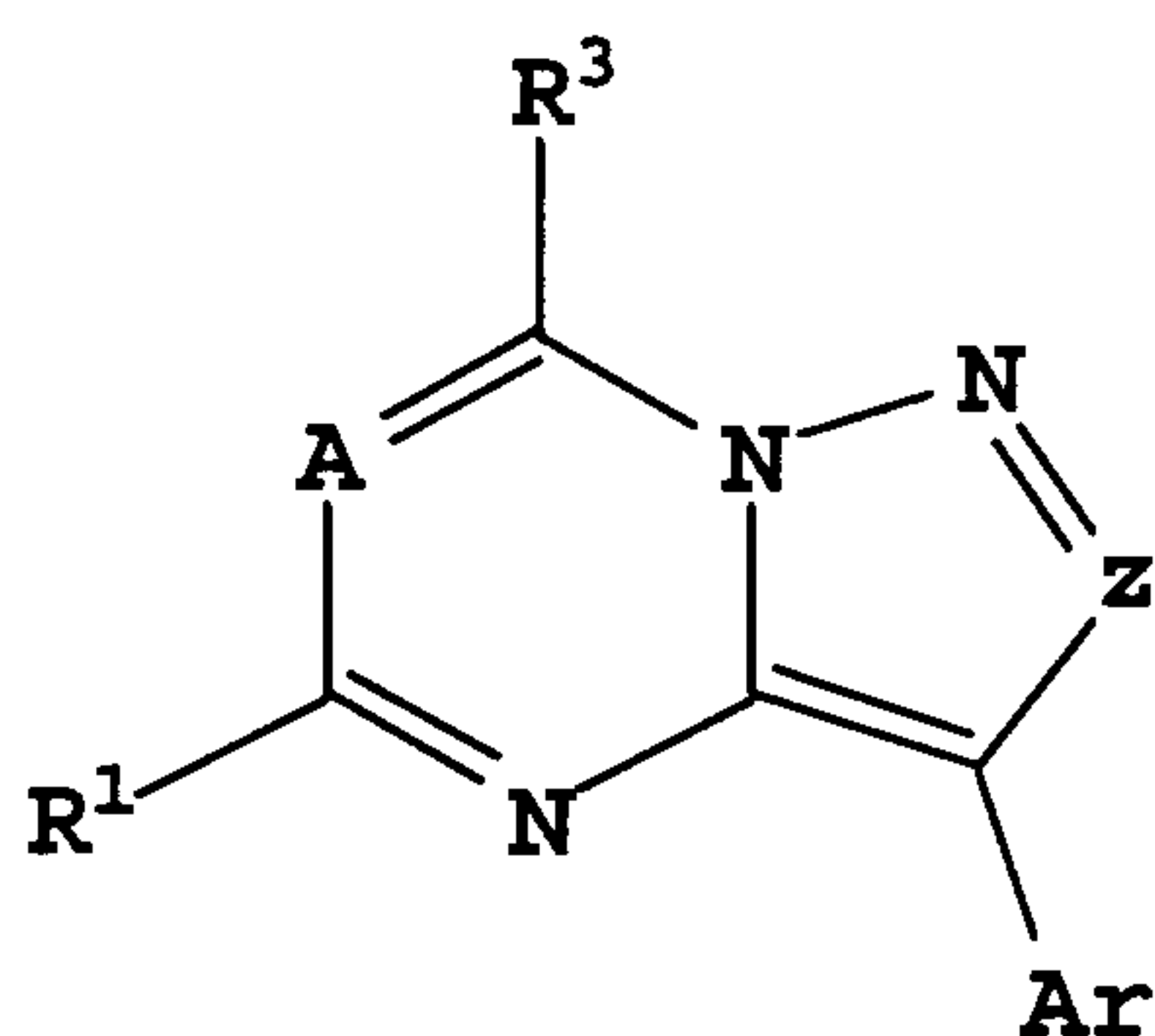
TITLE

AZOLO PYRIMIDINES

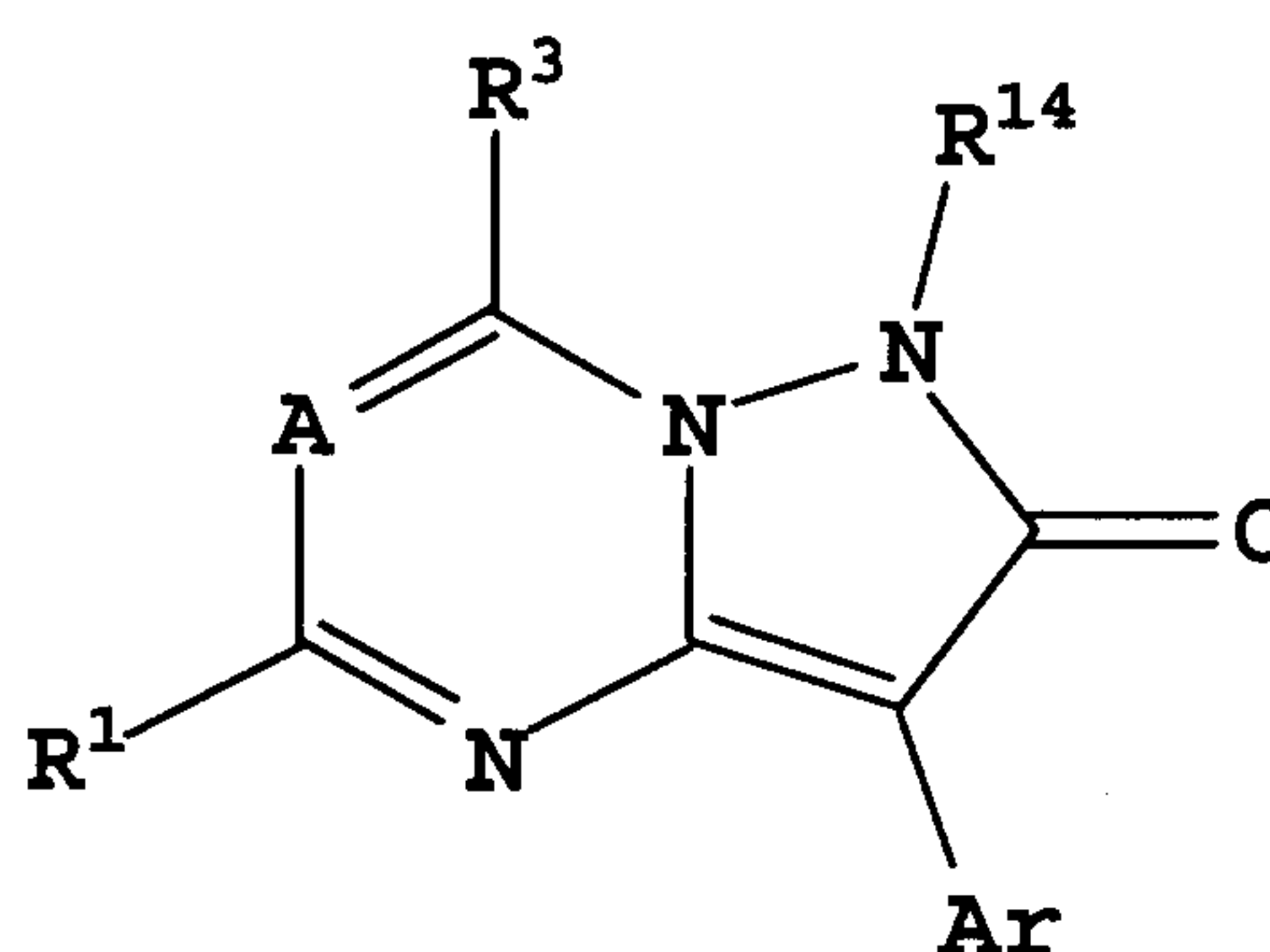
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ABSTRACT OF THE DISCLOSURE

Corticotropin releasing factor (CRF)
antagonists of formula I or II:



(I)



(II)

10

wherein A is CR, and their use in treating anxiety,
depression, and other psychiatric, neurological
disorders as well as treatment of immunological,
15 cardiovascular or heart-related diseases and colonic
hypersensitivity associated with psychopathological
disturbance and stress.

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
10 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
15 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
25 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
30 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.*
35 *Prog. Horm. Res.* 39:245 (1983); G.F. Koob, *Persp.*
Behav. Med. 2:39 (1985); E.B. De Souza et al., *J.*

Neurosci. 5:3189 (1985)). There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

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

hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)].

There is preliminary evidence that tricyclic
5 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
10 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
15 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
20 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
25 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
30 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
35 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)].

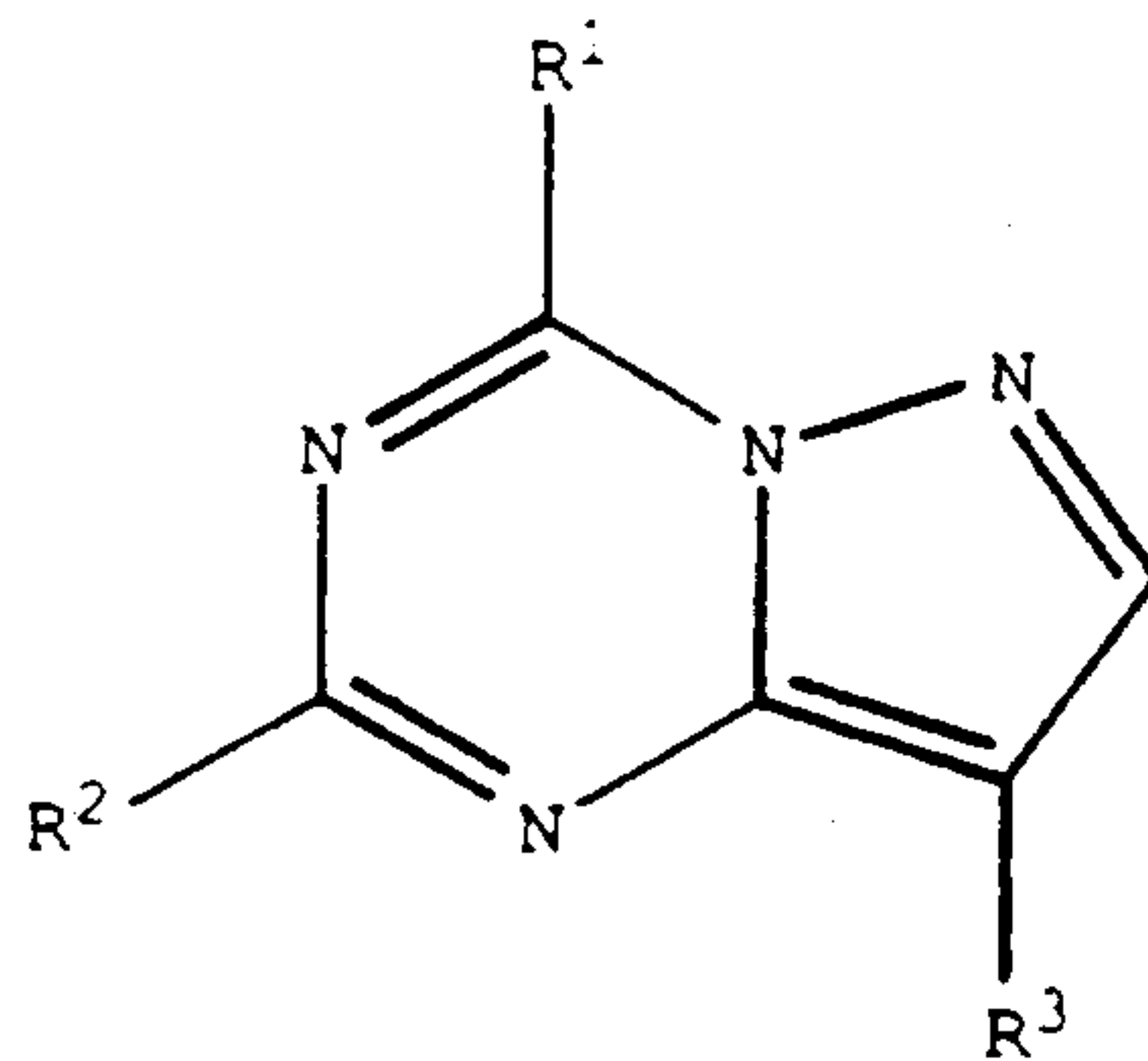
Several publications describe corticotropin releasing factor antagonist compounds and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application WO 95/10506, Pfizer WO 95/33750, Pfizer WO 95/34563, Pfizer WO 95/33727 and Pfizer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

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

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

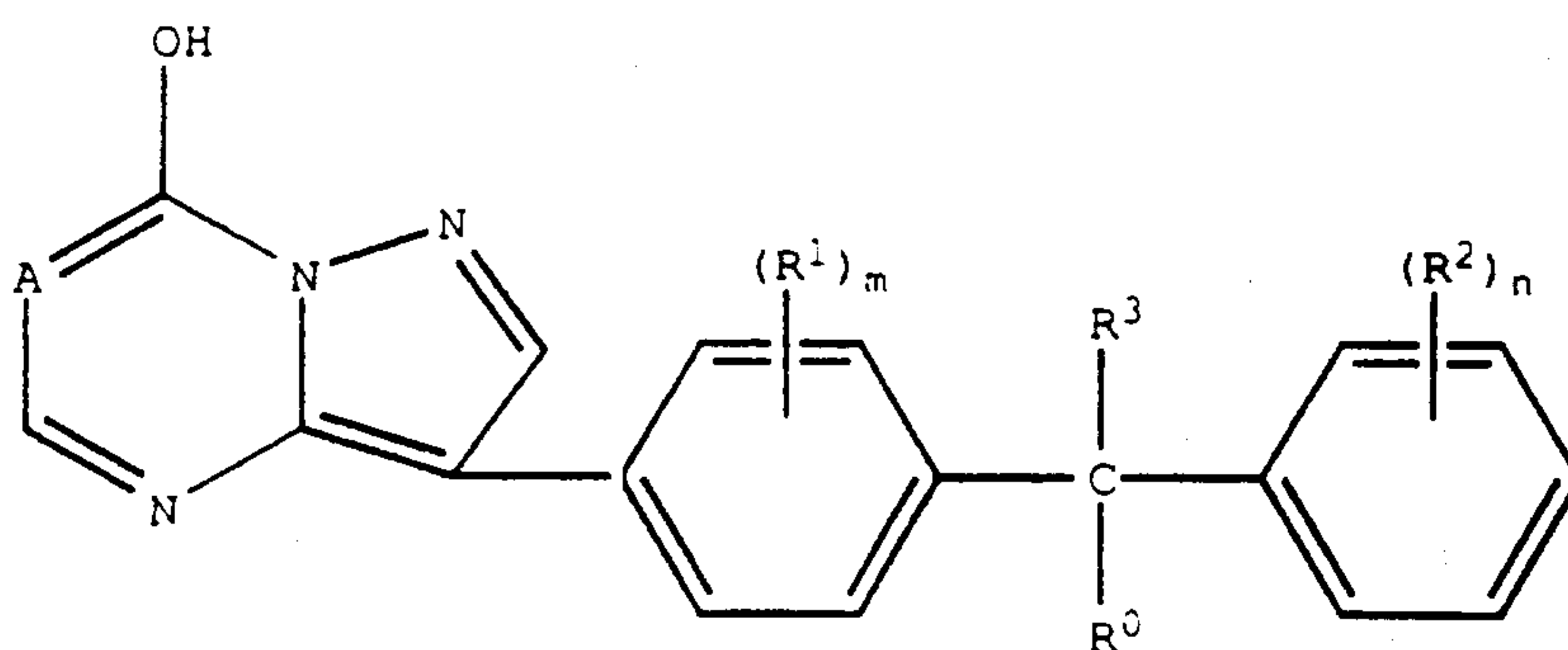
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where R^1 is OH or alkanoyl, R^2 is H, OH, or SH, and R^3 is
 5 an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

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

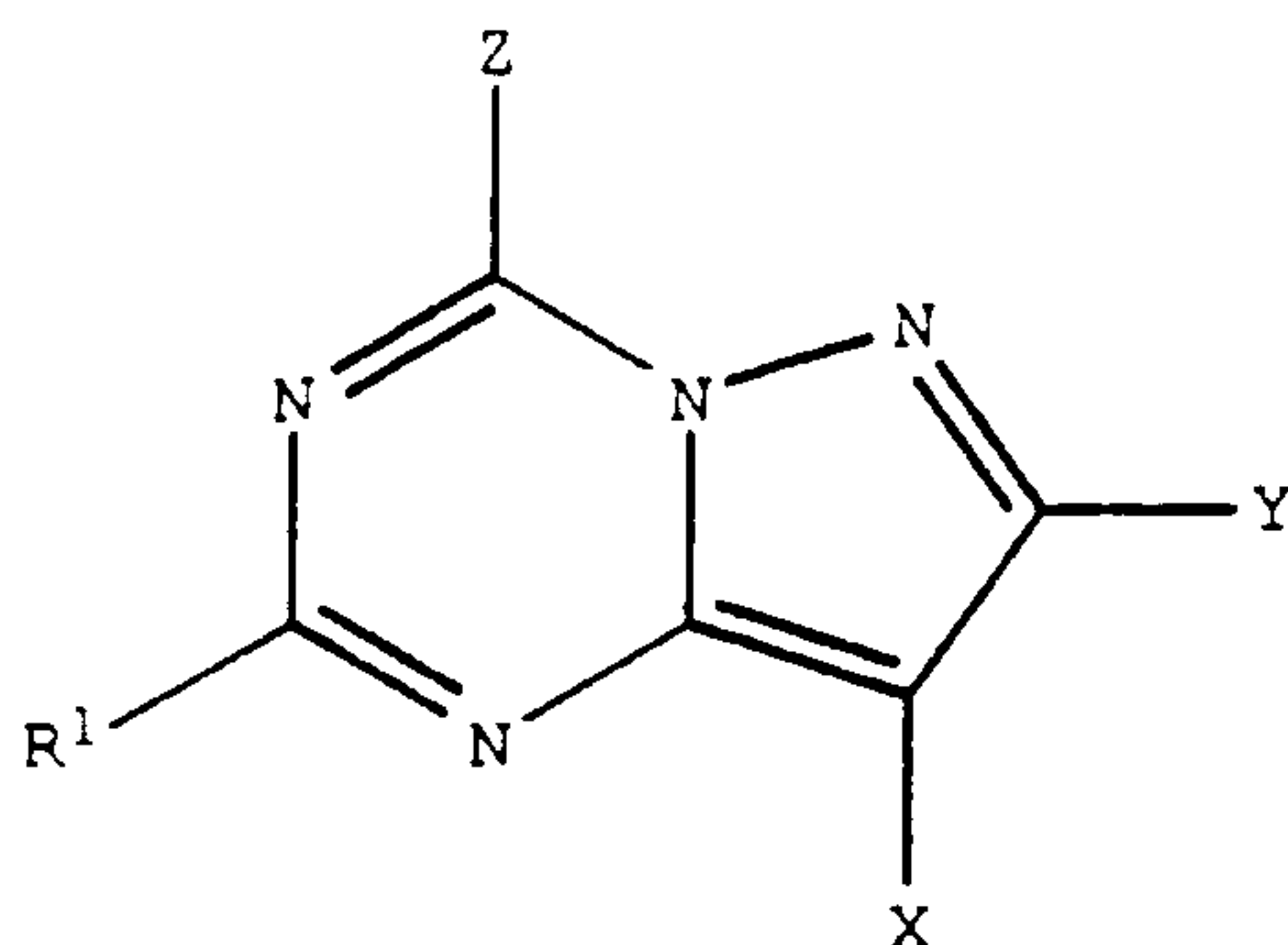


15 where A is CH or N, R^0 and R^3 are H or alkyl, and R^1 and R^2 are H, alkyl, alkoxyl, alkylthio, nitro, etc., and states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and
 20 prostatic carcinoma.

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

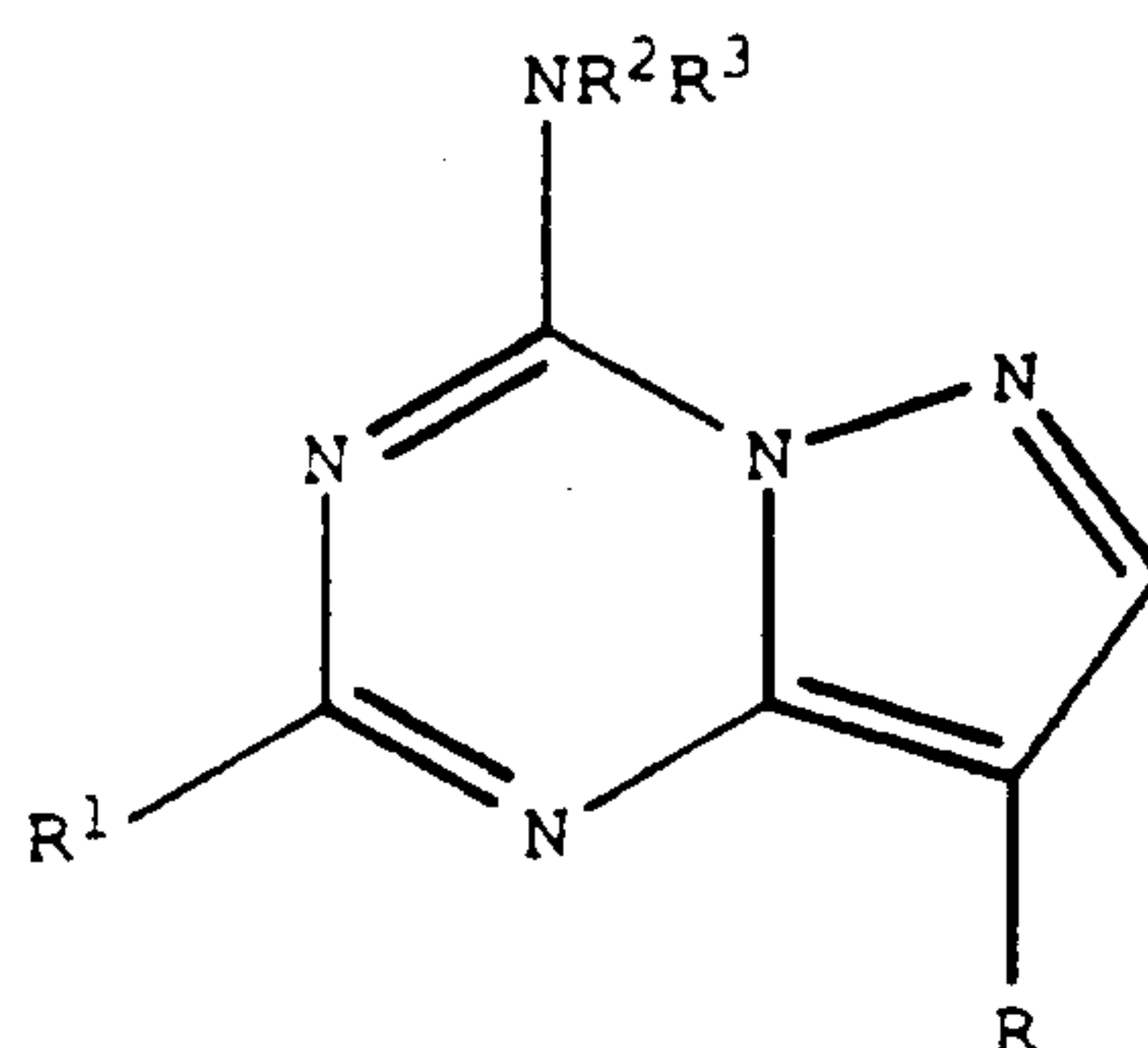
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where R¹ is CH₃, C₂H₅ or C₆H₅, X is H, C₆H₅, m-CH₃C₆H₄, CN, COOEt, Cl, I or Br, Y is H, C₆H₅, o-CH₃C₆H₄, or p-CH₃C₆H₄, and Z is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇, SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

10 US 3,995,039 discloses pyrazolotriazines of the formula:

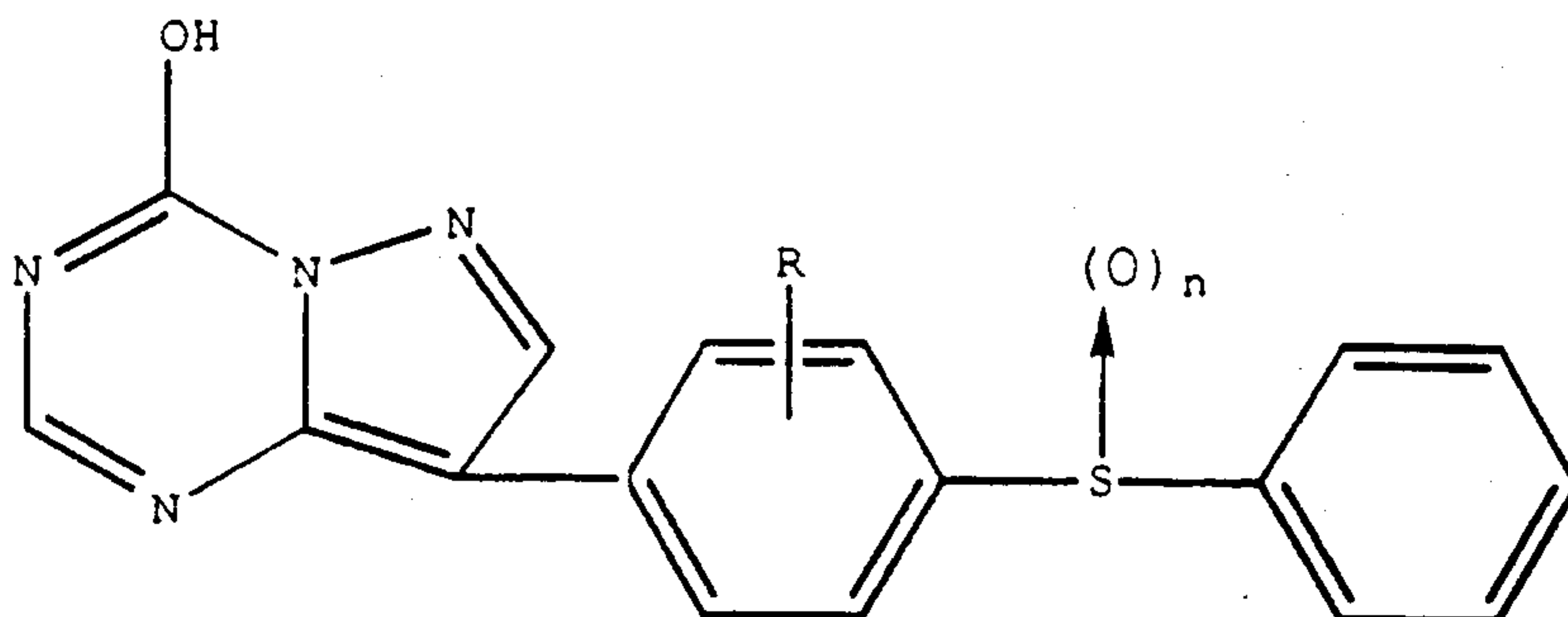


15 where R¹ is H or alkyl, R² is H or alkyl, R³ is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

20 US 5,137,887 discloses pyrazolotriazines of the formula

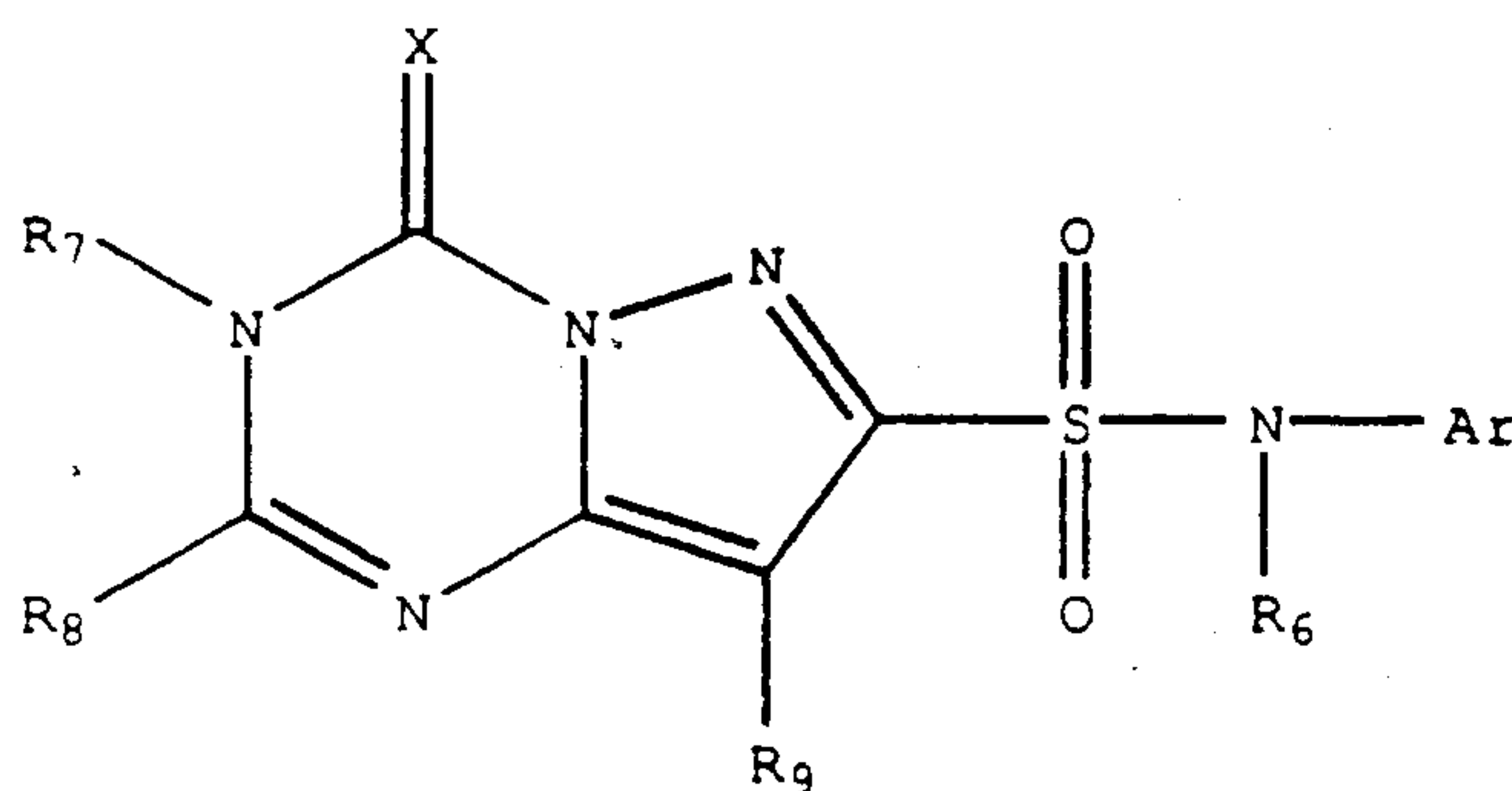
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where R is lower alkoxy, and teaches that the compounds
are xanthine oxidase inhibitors and are useful for
5 treatment of gout.

US 4,892,576 discloses pyrazolotriazines of the
formula



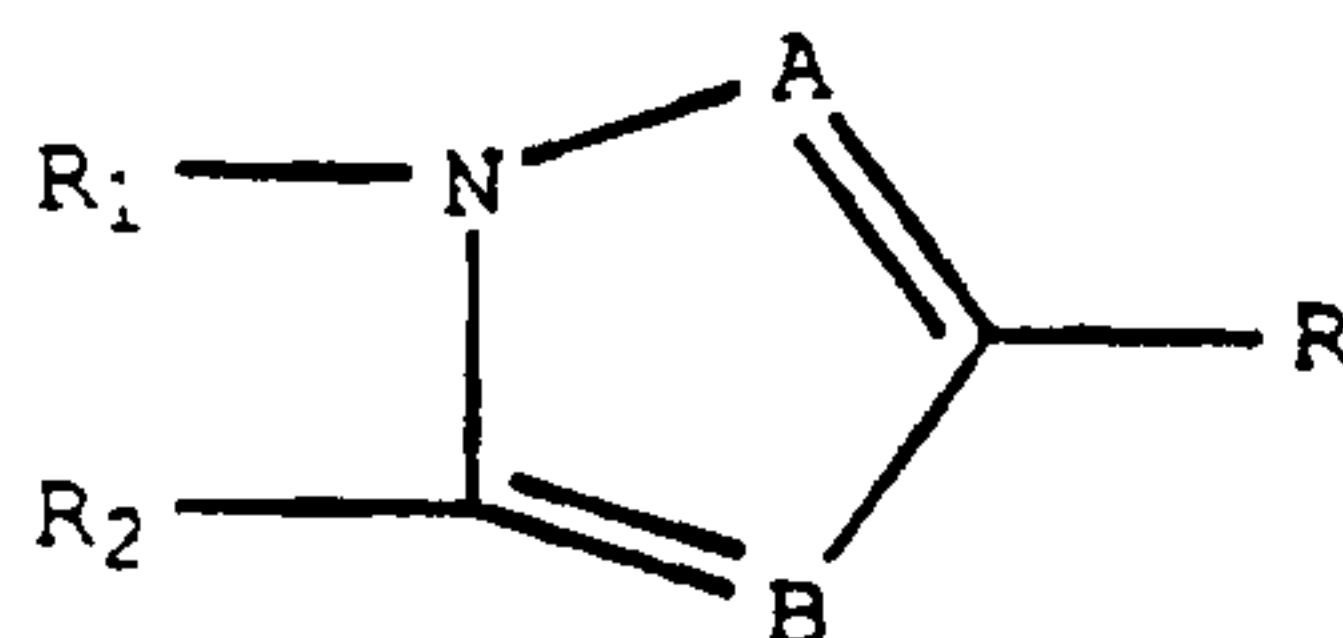
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where X is O or S, Ar is a phenyl, naphthyl, pyridyl or
thienyl group, R₆-R₈ are H, alkyl, etc., and R₉ is H,
alkyl, phenyl, etc. The patent states that the
15 compounds are useful as herbicides and plant growth
regulants.

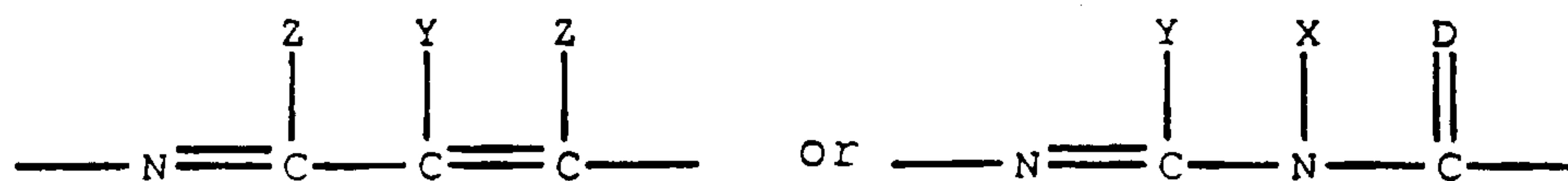
US 5,484,760 and WO 92/10098 discloses
herbicidal compositions containing, among other things,
20 a herbicidal compound of the formula

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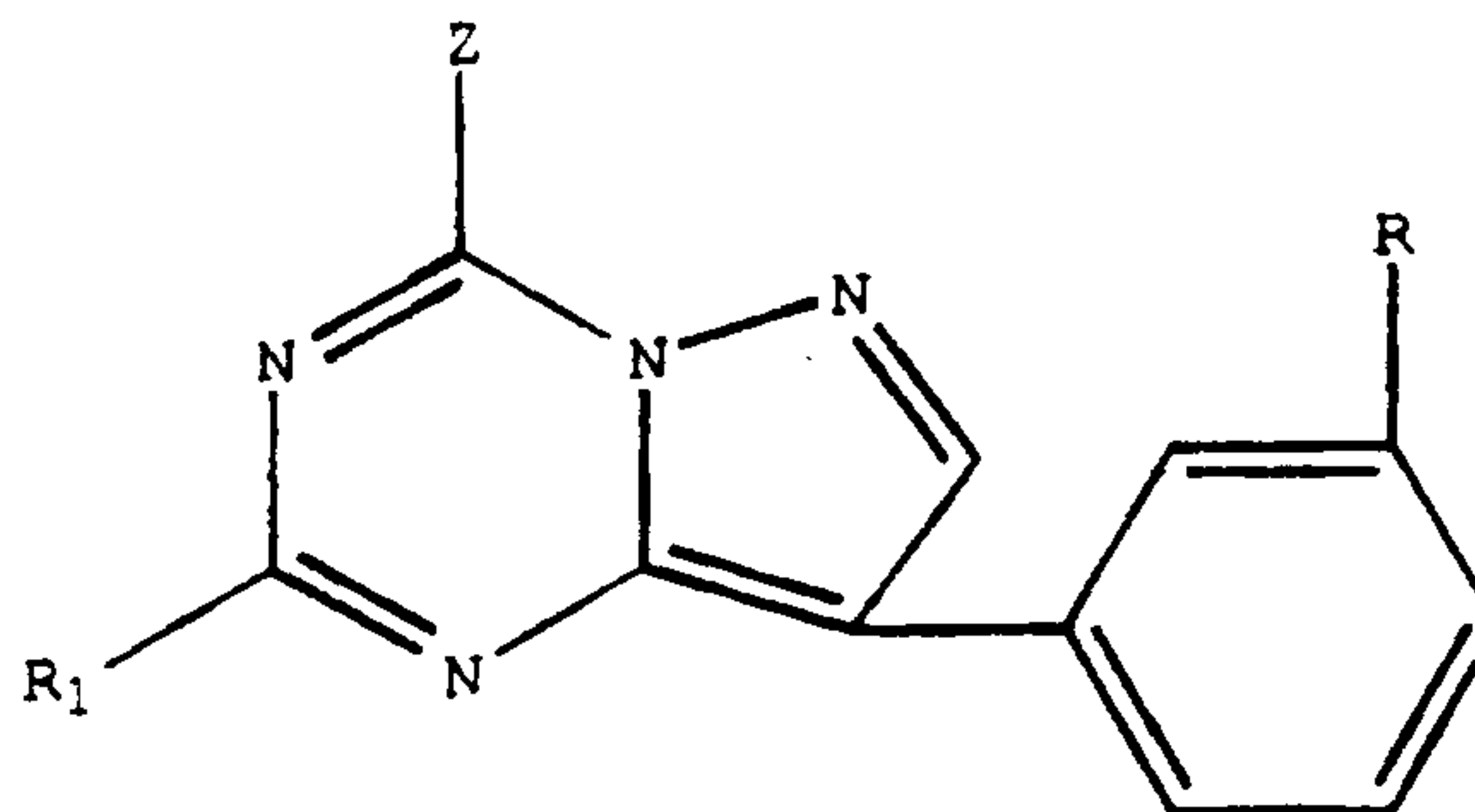


where A can be N, B can be CR₃, R₃ can be phenyl or substituted phenyl, etc., R is -N(R₄)SO₂R₅ or -SO₂N(R₆)R₇
 5 and R₁ and R₂ can be taken together to form



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

US 3,910,907 and Senga et al., J. Med. Chem.,
 1982, 25, 243-249, disclose triazolotriazines cAMP
 phosphodiesterase inhibitors of the formula



where Z is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇, iso-C₃H₇, SH,
 SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, R is H or CH₃, and R₁ is
 20 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.

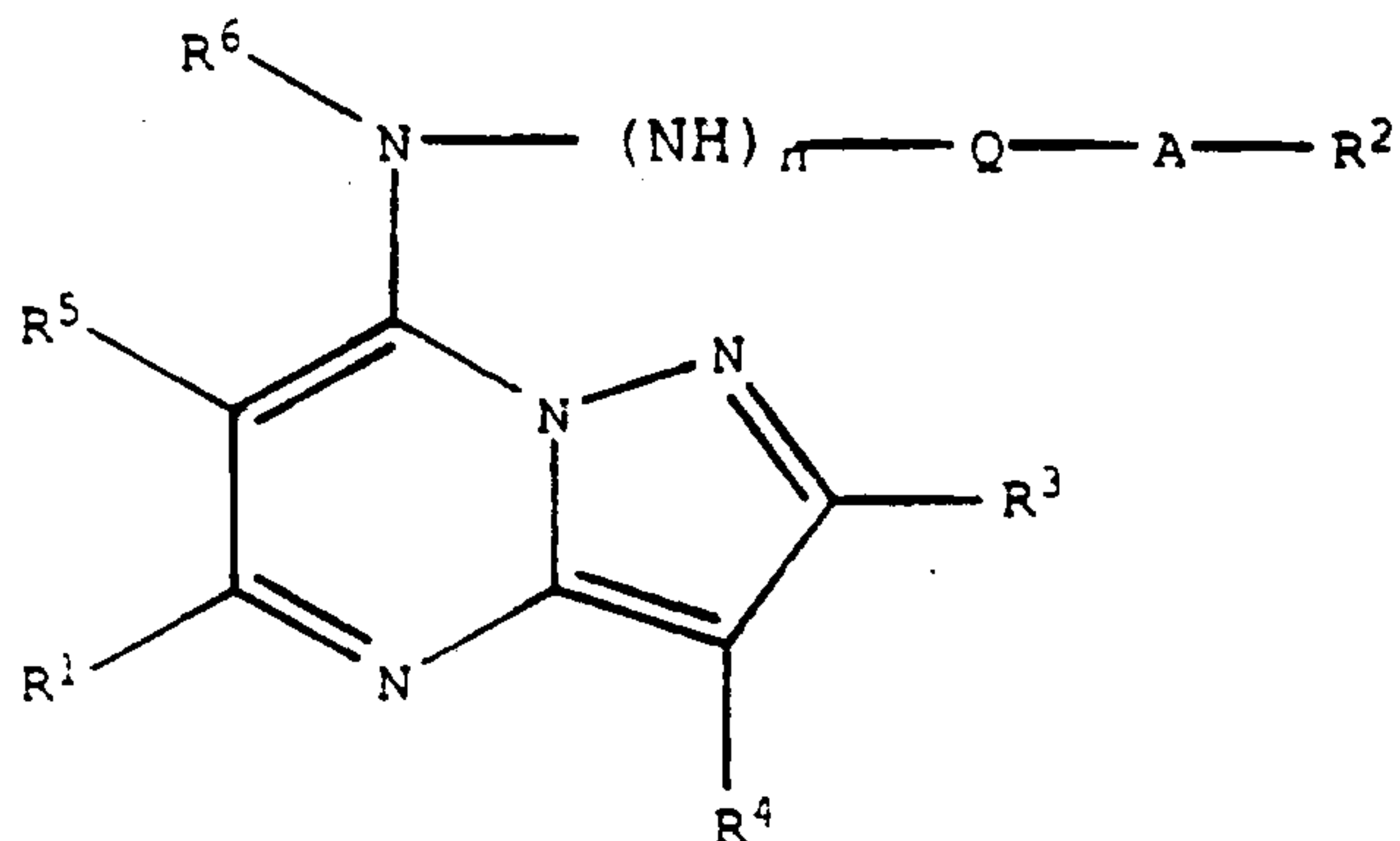
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WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula

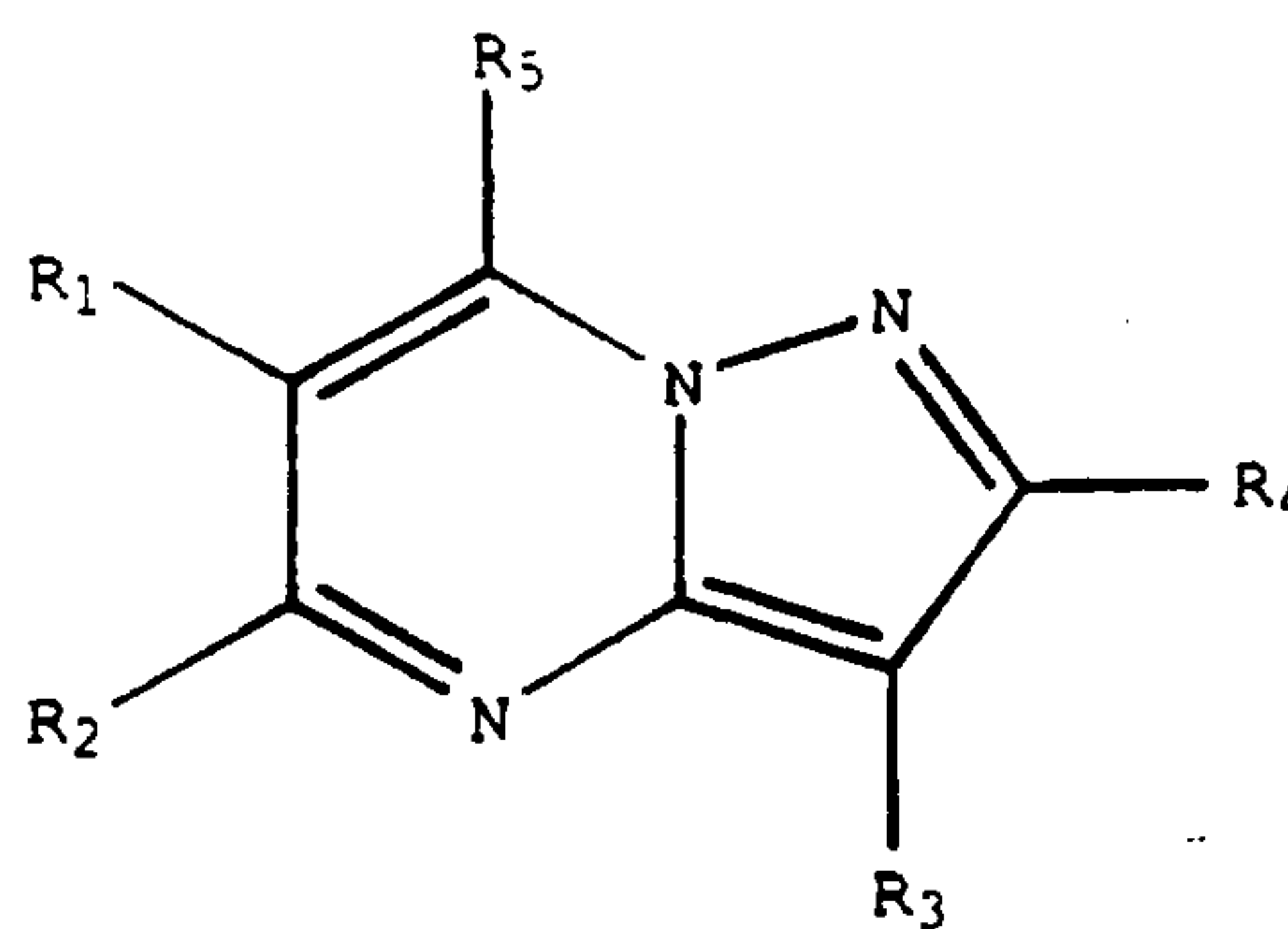
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where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R¹ is H, alkyl, etc., R² is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R³ is H, alkyl or phenyl, R⁴ is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R⁵ and R⁶ are H or alkyl.

15

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



20

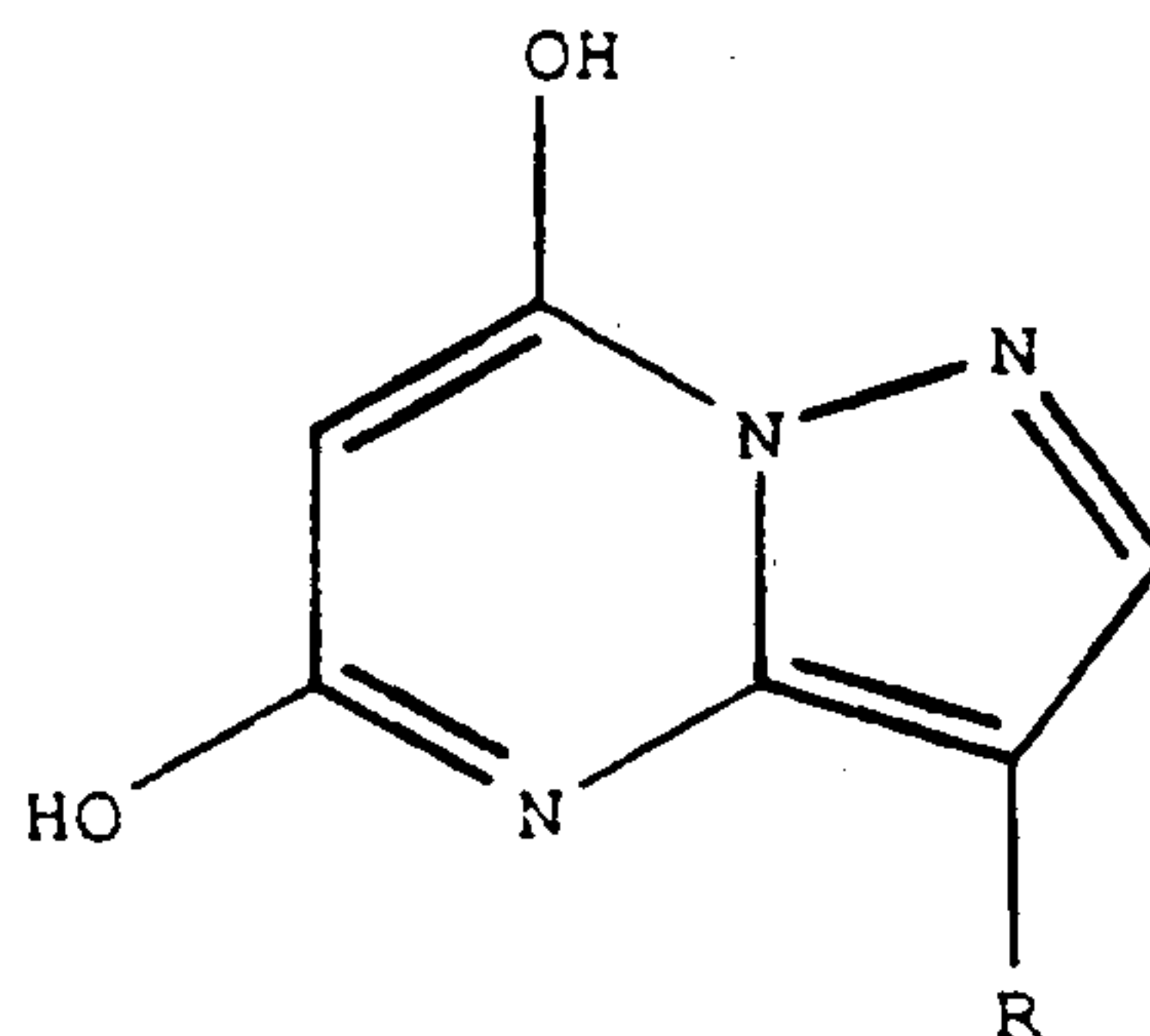
where R₁, R₂, R₃ and R₄ are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R₅

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is SR_6 or NR_7R_8 , R_6 is pyridyl or optionally substituted phenyl, and R_7 and R_8 are H or optionally substituted phenyl.

- 5 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

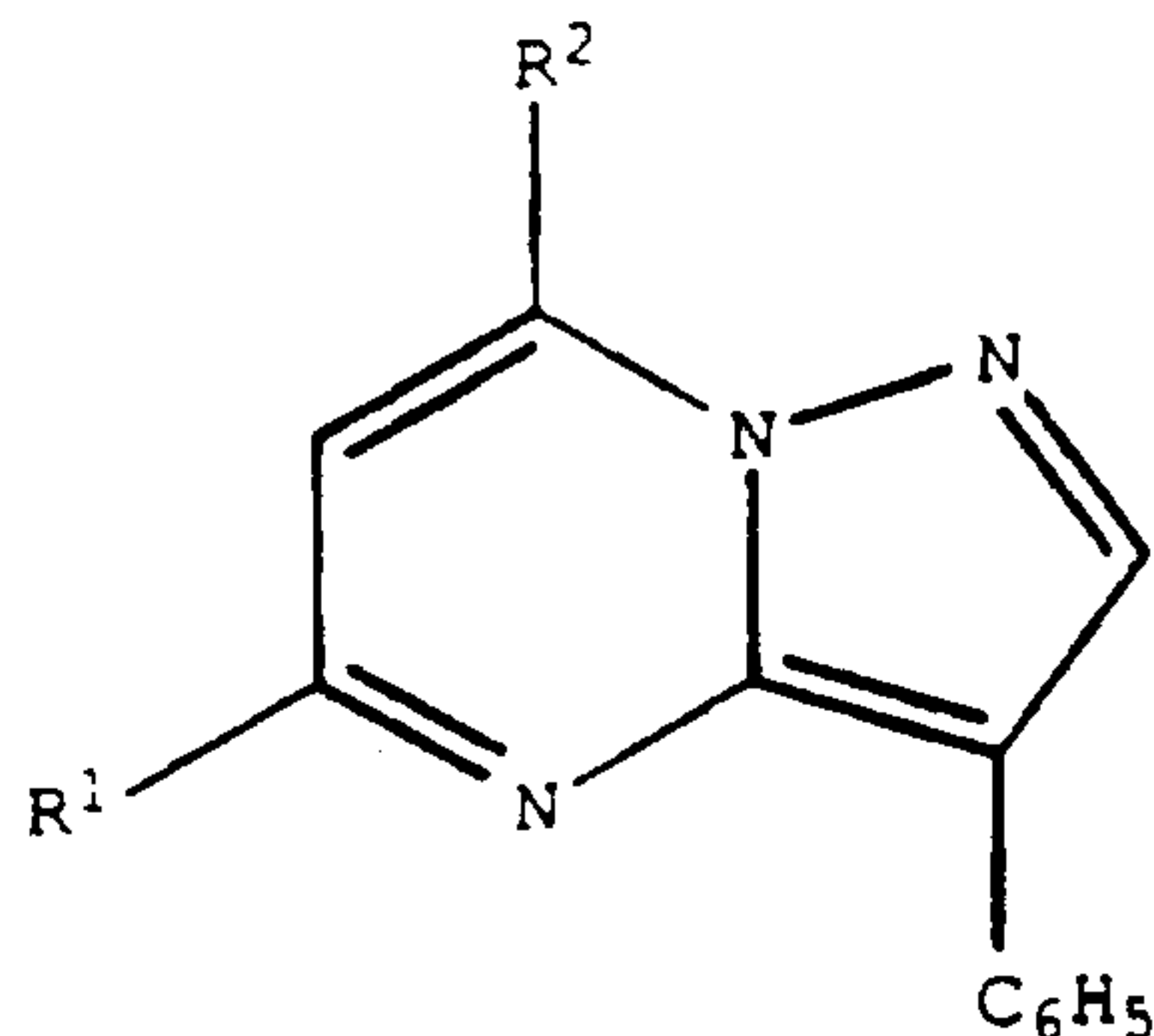


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where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

15

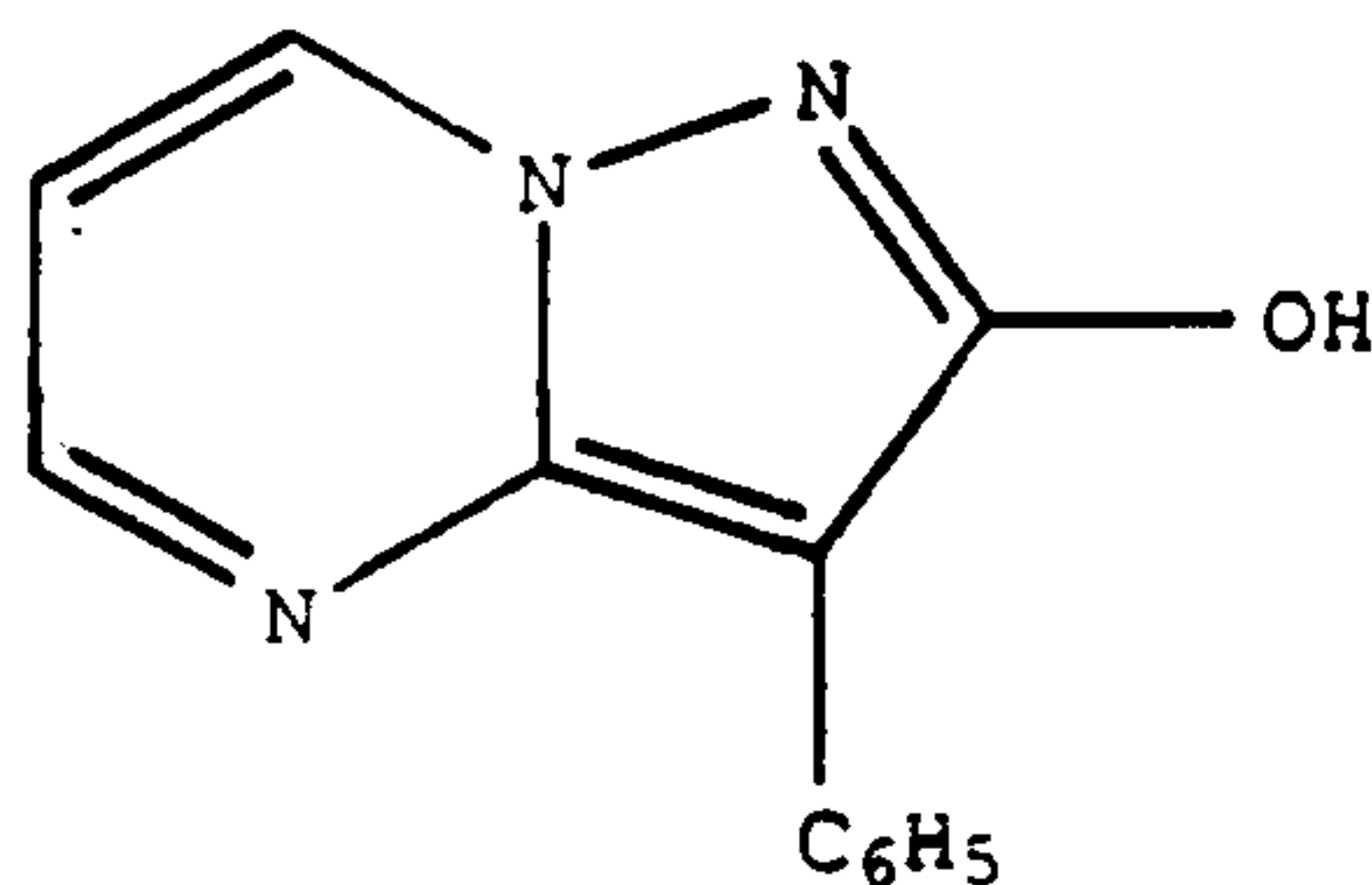
Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula



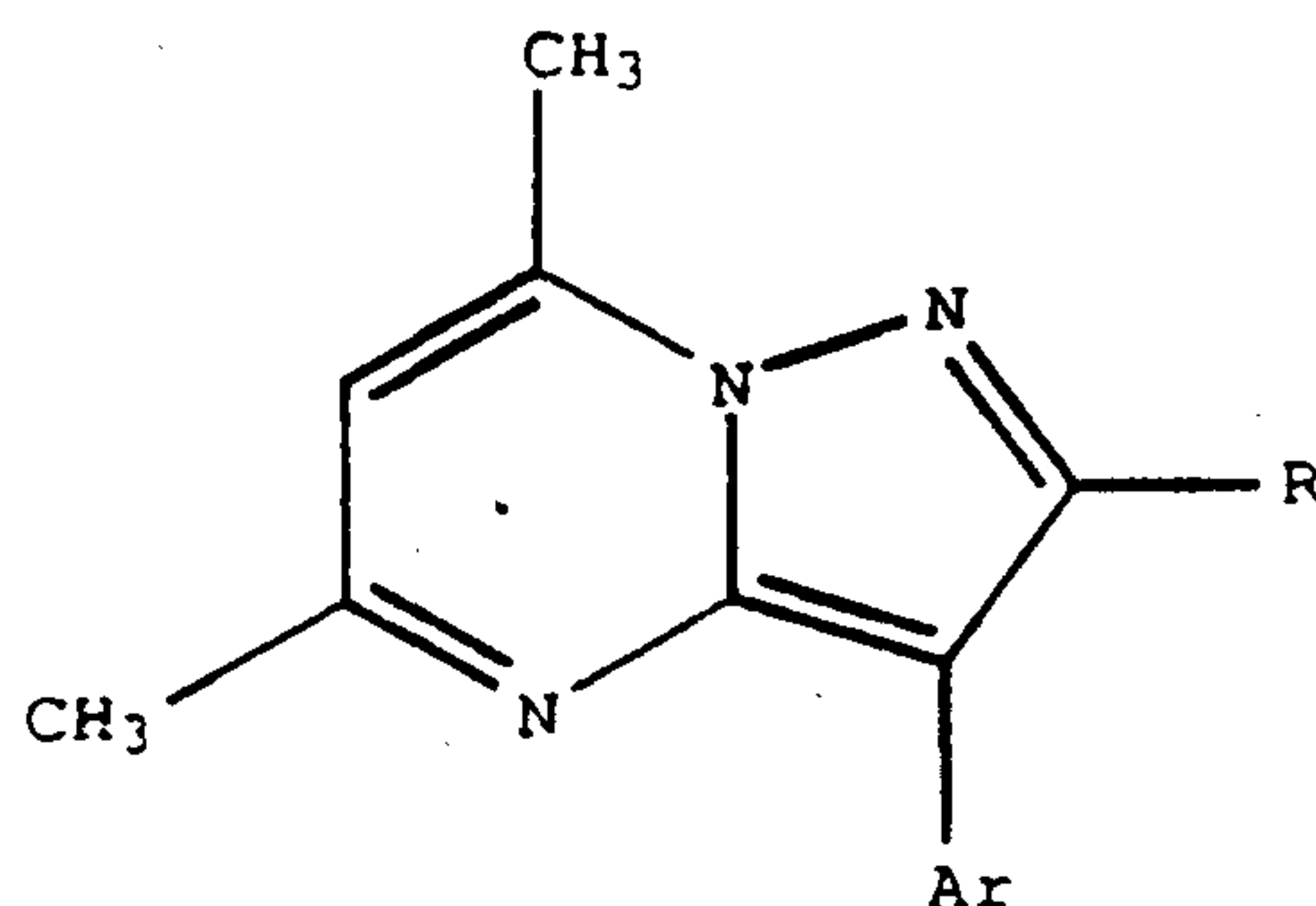
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where R^1 is CF_3 , C_2F_5 , or C_6H_4F , and R^2 is CH_3 , C_2H_5 , CF_3 , or C_6H_4F .

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



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



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

15

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

25

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 ileus and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress;

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

The present invention provides novel compounds
25 which bind to corticotropin releasing factor 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
30 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
35 stress in a mammal.

According to another aspect, the present invention provides novel compounds of Formulae (1) and (2) (described below) which are useful as antagonists of the corticotropin releasing factor.

5 The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds

10 of Formulae (1) and (2), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect of the 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 comprises a method of treating affective disorder, anxiety, depression,

25 headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms,

30 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

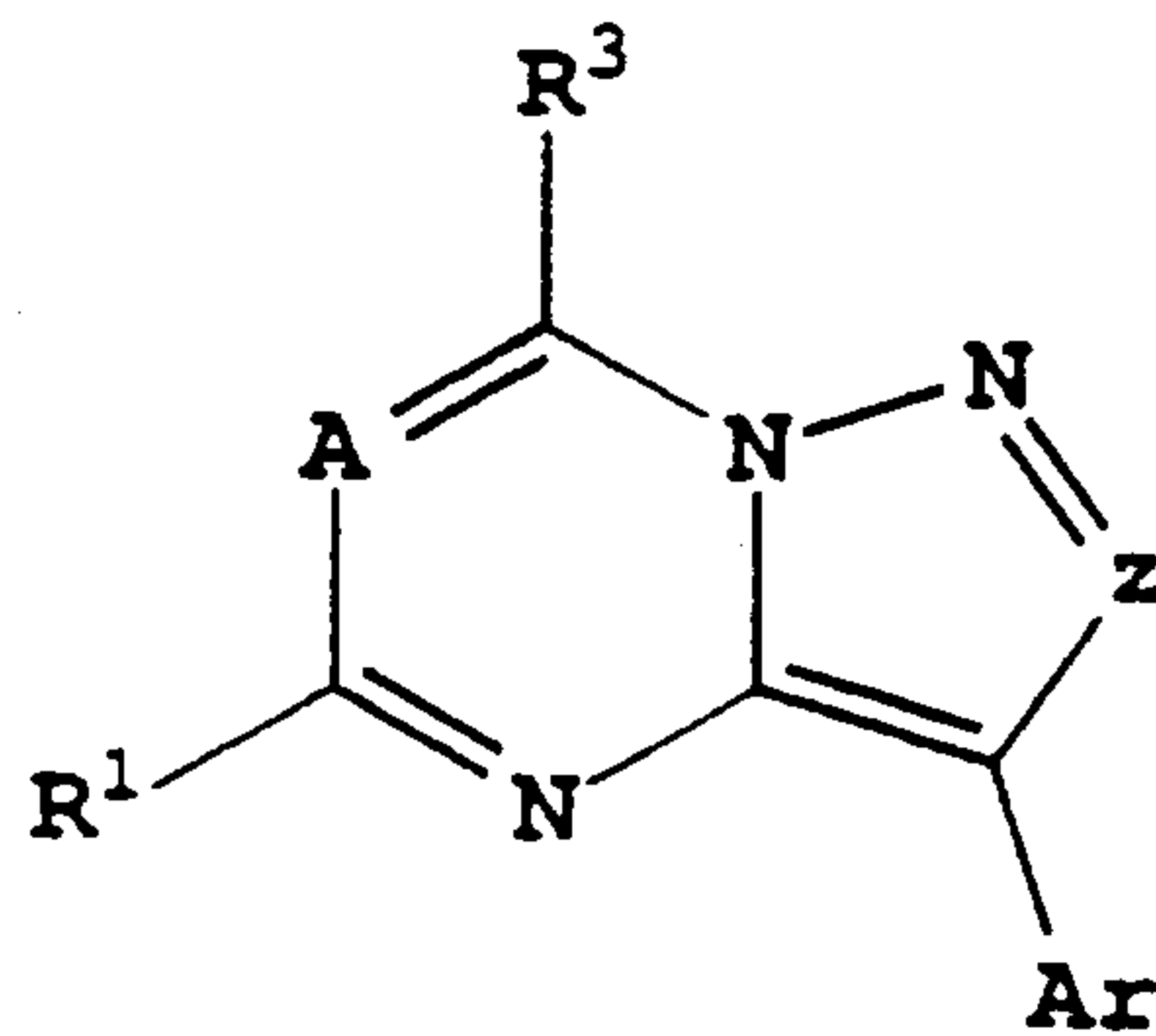
35 lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by

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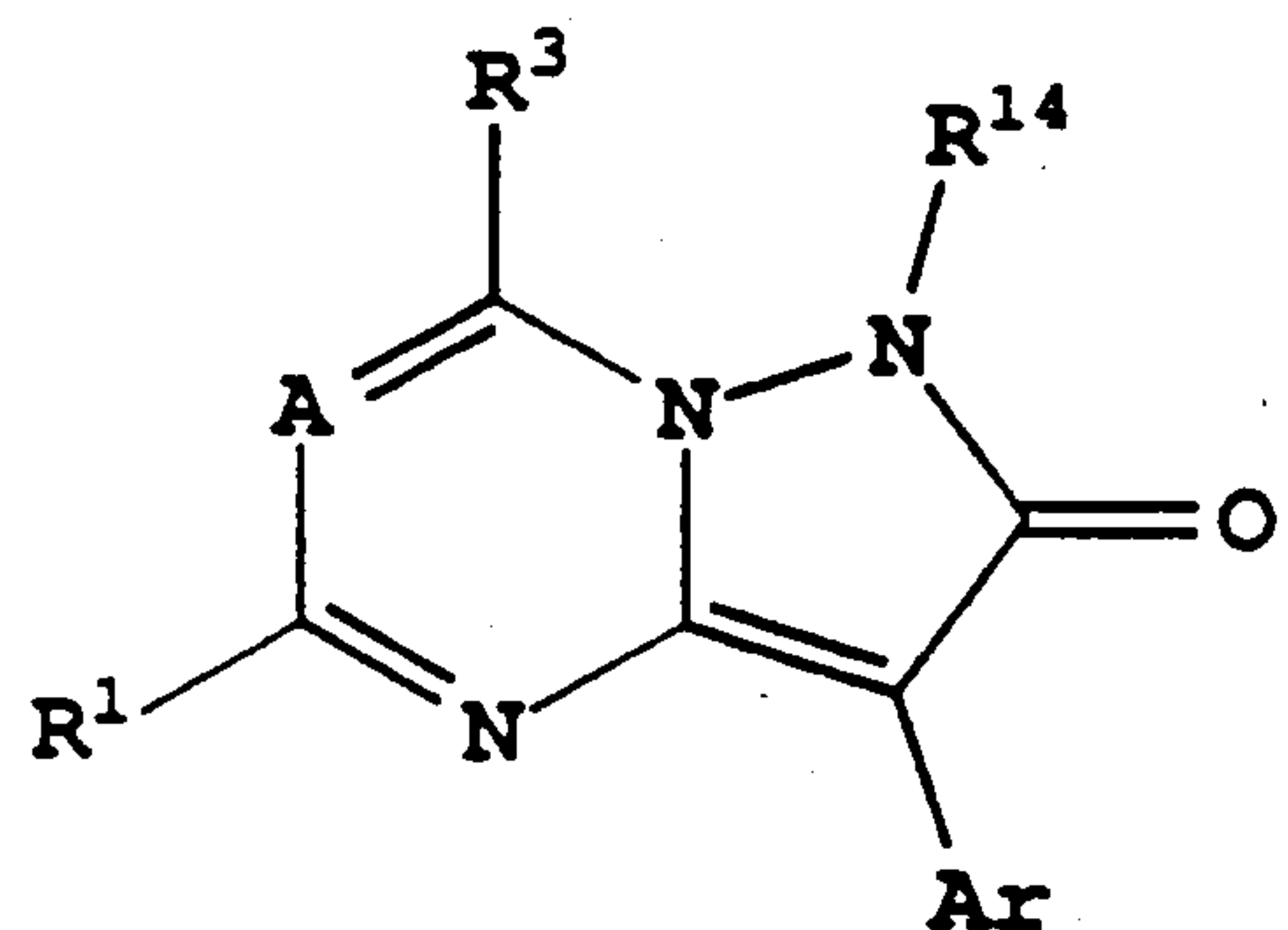
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antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of

5 Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

10

A is N or CR;

15

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is

20

25 attached to an unsaturated carbon atom;

R is independently selected at each occurrence from
H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo,
CN, C₁-C₄ haloalkyl;

5

R¹ is independently selected at each occurrence from
H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
10 cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
15 cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
-NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-
C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

R³ is selected from:
20 -H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
CONR⁶R⁷, aryl, heteroaryl and heterocyclyl,
or
25 -C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
C₁₂ cycloalkylalkyl or C₆-C₁₀
cycloalkenylalkyl, each optionally
substituted with 1 to 3 substituents
30 independently selected at each occurrence
from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
35 heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from:
 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 5 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,
 or S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-
 C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl
 and C₄-C₁₂ cycloalkylalkyl are optionally
 10 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷,
 or S(O)_nR⁷;

15 R^6 and R^7 , R^{6a} and R^{7a} are independently selected at
 each occurrence from:
 -H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 20 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 25 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 30 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

35

alternatively, NR^6R^7 and $\text{NR}^{6a}\text{R}^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups;

5

R^8 is independently selected at each occurrence from H or C₁-C₄ alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl;

10

R^{11} is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

15

R^{12} is C₁-C₄ alkyl or C₁-C₄ haloalkyl;

R^{13} is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;

20

R^{14} is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR^{15} , SH, $\text{S(O)}_n\text{R}^{15}$, COR^{15} , CO_2R^{15} , OC(O)R^{15} , $\text{NR}^8\text{COR}^{15}$, $\text{N(COR}^{15})_2$, $\text{NR}^8\text{CONR}^{16}\text{R}^{15}$, $\text{NR}^8\text{CO}_2\text{R}^{15}$, $\text{NR}^{16}\text{R}^{15}$, $\text{CONR}^{16}\text{R}^{15}$, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;

25

30

R^{15} and R^{16} are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀

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cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;

aryl is phenyl or naphthyl, each optionally
 5 substituted with 1 to 5 substituents
 independently selected at
 each occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano,
 OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵,
 10 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵,
 NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heteroaryl is pyridyl, pyrimidinyl, triazinyl,
 furanyl, pyranyl, quinolinyl, isoquinolinyl,
 15 thienyl, imidazolyl, thiazolyl, indolyl,
 pyrrolyl, oxazolyl, benzofuranyl, benzothienyl,
 benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-
 dihydrobenzothienyl or 2,3-dihydrobenzofuranyl,
 each being optionally substituted with 1 to 5
 20 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and
 25 CONR¹⁶R¹⁵;

heterocyclyl is saturated or partially saturated
 heteroaryl, optionally substituted with 1 to 5
 substituents independently selected at each
 30 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
 CONR¹⁶R¹⁵;

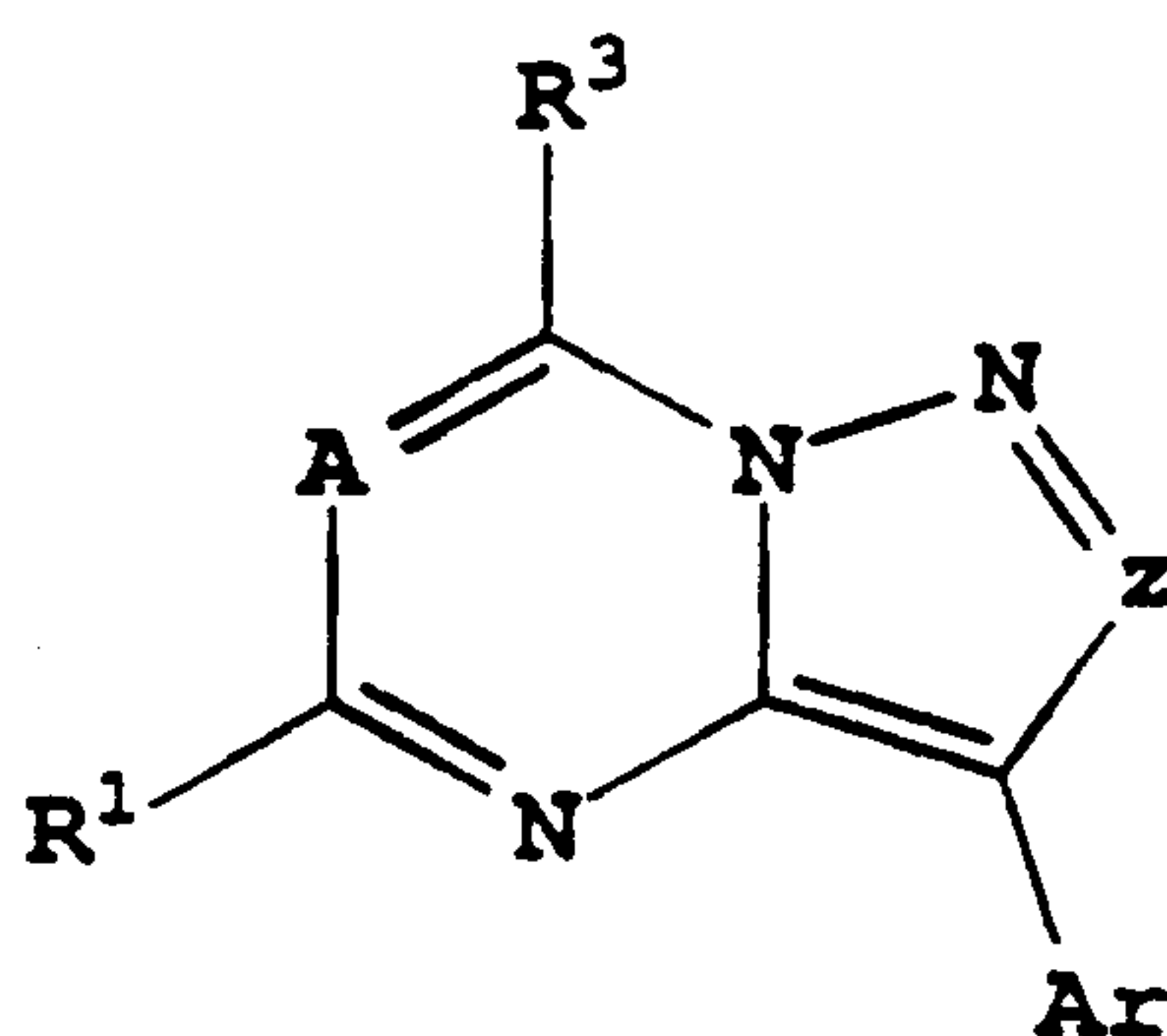
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n is independently at each occurrence 0, 1 or 2,

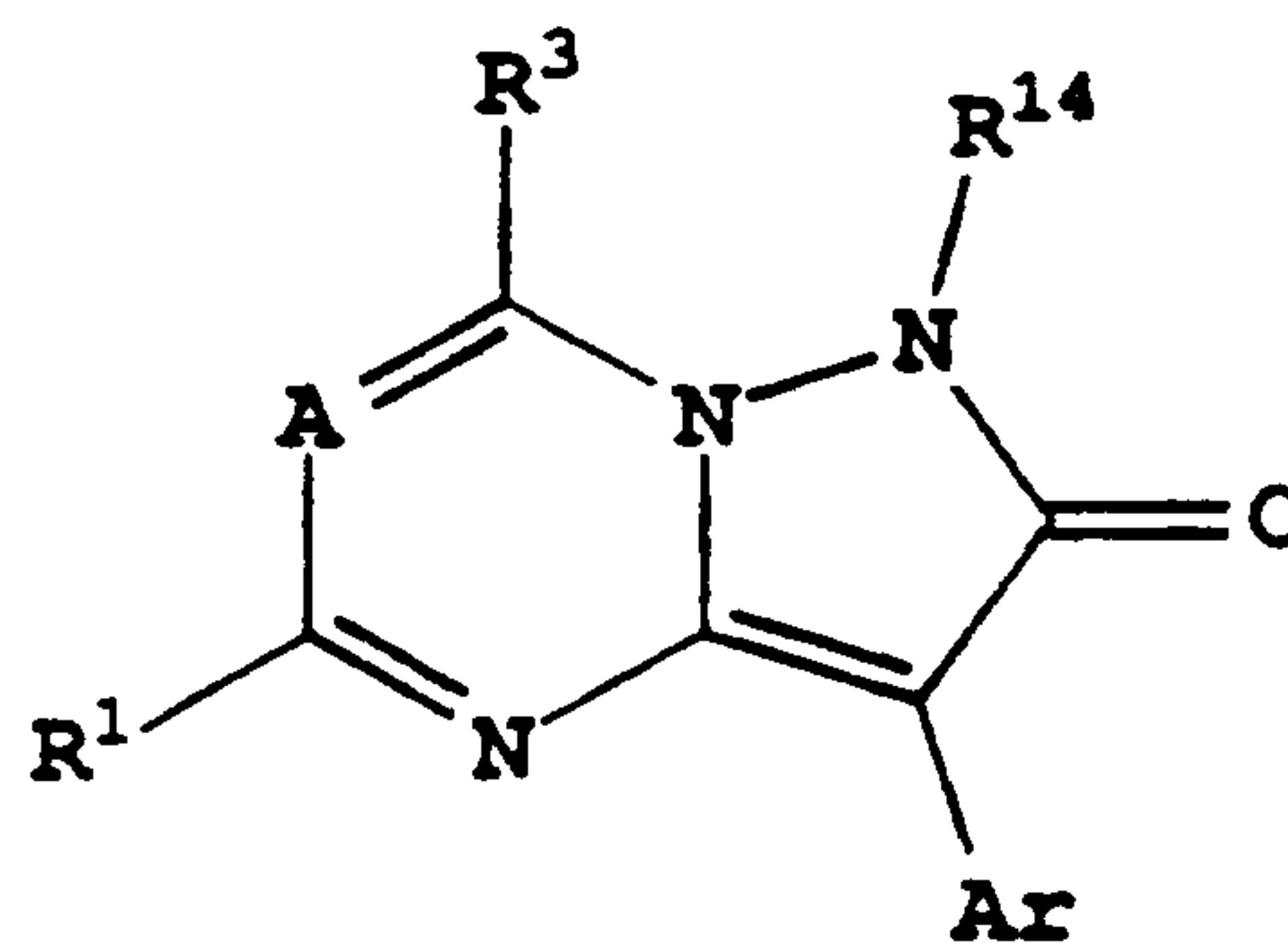
[2] Preferred methods of the present invention are methods in wherein in the compound of Formulae (1) or
 5 (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

[3] Further preferred methods of the above invention
 10 are methods wherein, in the compound of Formulae (1) or (2), A is N, Z is CR^2 , Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3 , and R^3 is $NR^{6a}R^{7a}$.

15 [4] The present invention comprises compounds of Formulae (1) or (2):



(1)



(2)

20

and isomers thereof, stereoisomeric forms thereof, or
 mixtures of stereoisomeric forms thereof, and
 pharmaceutically acceptable salt or pro-drug forms
 25 thereof wherein:

A is N or CR;

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl,
 5 pyrimidinyl, triazinyl, furanyl, thienyl,
 benzothienyl, benzofuranyl, 2,3-
 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl,
 indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-
 benzopyranyl, tetralinyl, each Ar optionally
 10 substituted with 1 to 5 R⁴ groups and each Ar is
 attached to an unsaturated carbon atom;

R is independently selected at each occurrence from
 H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 15 C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo,
 CN, C₁-C₄ haloalkyl;

R¹ is independently selected at each occurrence from
 H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 20 halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
 C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
 cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
 C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

25 R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
 C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
 cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
 -NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-
 C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

30

R³ is selected from:

-H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
 OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
 NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
 35 CONR⁶R⁷, aryl, heteroaryl and
 heterocyclyl, or

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-C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
 C₁₂ cycloalkylalkyl or C₆-C₁₀
 cycloalkenylalkyl, each optionally
 5 substituted with 1 to 3 substituents
 independently selected at each occurrence
 from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
 10 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl and heterocyclyl;

R⁴ is independently selected at each occurrence from:
 15 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,
 or S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-
 20 C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl
 and C₄-C₁₂ cycloalkylalkyl are optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷,
 25 NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷,
 or S(O)_nR⁷;

R⁶ and R⁷, R^{6a} and R^{7a} are independently selected at
 each occurrence from:
 30 -H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 35 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3

- substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 5 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 10 heterocyclyl(C₁-C₄ alkyl), alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups;
 15 R⁸ is independently selected at each occurrence from H or C₁-C₄ alkyl;
 R⁹ and R¹⁰ are independently selected at each
 20 occurrence from H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl;
 R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;
 25 R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;
 R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 30 C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;
 R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-
 35 C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected

at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;

R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

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heterocyclyl is saturated or partially saturated
heteroaryl, optionally substituted with 1 to 5
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
5 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
CONR¹⁶R¹⁵;

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

with the provisos that:

- 15 (1) when A is N, Z is CR², R² is H, R³ is -OR⁷ or
-OCOR¹³, and R⁷ is H, then R¹ is not H, OH or
SH;
- 20 (2) when A is N, Z is CR², R¹ is CH₃ or C₂H₅, R² is H,
and R³ is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇,
SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, then Ar is not
phenyl or m-CH₃-phenyl;
- 25 (3) when A is N, Z is CR², R² is H, and Ar is
pyridyl, pyrimidinyl or pyrazinyl, and R³ is
NR^{6a}R^{7a}, then R^{6a} and R^{7a} are not H or alkyl;
- (4) when A is N, Z is CR², and R² is SO₂NR⁶R⁷, then R³
is not OH or SH;
- 30 (5) when A is CR and Z is CR², then R² is not-NR⁶SO₂R⁷
or -SO₂NR⁶R⁷;
- (6) when A is N, Z is CR² and R² is -NR⁶SO₂R⁷ or
-SO₂NR⁶R⁷, then R³ is not OH or SH;
- 35 (7) when A is N, Z is CR², R¹ is methyl or ethyl, R²
is H, and R³ is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇,

iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, then Ar is not unsubstituted phenyl or m-methylphenyl;

- 5 (8) when A is CR, Z is CR², R² is H, phenyl or alkyl, R³ is NR⁸COR⁷ and Ar is phenyl or phenyl substituted with phenylthio, then R⁷ is not aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocycl(C₁-C₄ alkyl);
- 10 (9) when A is CR, Z is CR², R² is H or alkyl, Ar is phenyl, and R³ is SR¹³ or NR^{6a}R^{7a}, then R¹³ is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or
- 15 (10) when A is CH, Z is CR², R¹ is OR¹¹, R² is H, R³ is OR⁷, and R⁷ and R¹¹ are both H, then Ar is not phenyl, p-Br-phenyl, p-Cl-phenyl, p-NHCOCH₃-phenyl, p-CH₃-phenyl, pyridyl or naphthyl;
- 20 (11) when A is CH, Z is CR², R² is H, Ar is unsubstituted phenyl, and R³ is CH₃, C₂H₅, CF₃ or C₆H₄F, then R₁ is not CF₃ or C₂F₅;
- 25 (12) when A is CR, R is H, Z is CR², R² is OH, and R¹ and R³ are H, then Ar is not phenyl;
- (13) when A is CR, R is H, Z is CR², R² is OH or NH₂, R¹ and R³ are CH₃, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

30

[5] Preferred compounds of the above invention are compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R¹ is H, C₁-C₄ alkyl, halo, CN, C₁-C₁₂ hydroxyalkyl, C₁-C₄

alkoxyalkyl or $\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, R^3 is $\text{NR}^{6a}\text{R}^{7a}$ and R^{6a} is unsubstituted $\text{C}_1\text{-C}_4$ alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or $\text{C}_3\text{-C}_6$ cycloalkyl; and (2) A is N, R^1 is H, $\text{C}_1\text{-C}_4$ alkyl, halo, CN, $\text{C}_1\text{-C}_{12}$ hydroxyalkyl, $\text{C}_1\text{-C}_4$ alkoxyalkyl or $\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, R^3 is $\text{NR}^{6a}\text{R}^{7a}$ and R^{7a} is unsubstituted $\text{C}_1\text{-C}_4$ alkyl, then R^{6a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or $\text{C}_3\text{-C}_6$ cycloalkyl.

[6] Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

[7]. Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR^2 , Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3 , and R^3 is $\text{NR}^{6a}\text{R}^{7a}$.

[11] More preferred compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N.

[12] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[13] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[14] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is NR^6aR^7a or OR^7 .

[15] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is NR^6aR^7a or OR^7 .

[16] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2 .

- [17] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.
- 10 [18] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is
- 15 NR^{6a}R^{7a} or OR⁷.

- [19] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:
- 20

- H,
- C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
- 25 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3
- 30 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
- 35 heteroaryl or heterocyclyl,

-aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-; and

R^{7a} is independently selected at each occurrence from:

- 5 -H,
 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 10 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 15 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 20 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

- alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
 piperidine, pyrrolidine, piperazine, N-
 25 methypiperazine, morpholine or thiomorpholine, each
 optionally substituted with 1-3 C₁-C₄ alkyl groups.

- [20] More preferred compounds of the above invention
 also include compounds and isomers thereof,
 30 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein R^{6a}
 and R^{7a} are identical and are selected from:
 -C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally
 35 substituted with 1 to 3 substituents
 independently selected at each occurrence from

C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 5 aryl, heteroaryl or heterocyclyl, and
 -aryl or heteroaryl.

[21] More preferred compounds of the above invention
 also include compounds and isomers thereof,
 10 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} is selected from:

-H,
 15 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 20 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 25 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 30 heterocyclyl(C₁-C₄ alkyl);

R^{7a} is selected from:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is
 substituted with 1-3 substituents
 independently selected at each occurrence from
 35 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,

CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl.

5 [22] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
10 one of R^{6a} and R^{7a} is selected from:

-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
optionally substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
15 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl,

-aryl,

20 -heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
alkyl.

25 [23] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
30 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
each such C₁-C₁₀ alkyl optionally substituted with
1 to 3 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³,
35 COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,

$R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[24] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is NR^6aR^7a or OR^7 .

[25] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR^{15} , SH, $S(O)_nR^{13}$, COR^{15} , CO_2R^{15} , $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);

R^{7a} is independently selected at each occurrence from:

- H,
-C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
5 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
10 occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
15 heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl),
- 20 alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
piperidine, pyrrolidine, piperazine, N-
methylpiperazine, morpholine or thiomorpholine, each
optionally substituted with 1-3 C₁-C₄ alkyl groups.
- 25 [26] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein R^{6a}
30 and R^{7a} are identical and are selected from:
-C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally
substituted with 1 to 3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
35 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵,

CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl, and
 -aryl or heteroaryl.

5

[27] More preferred compounds of the above invention
 also include compounds and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 10 acceptable salt or pro-drug forms thereof wherein R^{6a}
 and R^{7a} are identical and are

-C₁-C₄ alkyl, each such C₁-C₄ alkyl

optionally substituted with 1 to 3

15 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵,
 CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

20

[28] More preferred compounds of the above invention
 also include compounds and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 25 acceptable salt or pro-drug forms thereof wherein
 R^{6a} is selected from:

-H,

-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,

30 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-

C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,

or C₆-C₁₄ cycloalkenylalkyl, each

optionally substituted with 1 to 3

35 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-

C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,

cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 5 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

R^{7a} is:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is
 10 substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 15 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl.

[29] More preferred compounds of the above invention
 also include compounds and isomers thereof,
 20 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein one of
 R^{6a} and R^{7a} is selected from:

-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
 25 optionally substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 30 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl,
 -aryl,
 -heteroaryl or
 -heterocyclyl,
 35 and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
 alkyl.

[30] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, each such C₁-C₁₀ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

[31] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

- Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents,
- R³ is NR^{6a}R^{7a} or OR⁷ and
- R¹ and R² are independently selected from H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl.

[32] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

5 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
10 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-
15 C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄
alkyl);
R^{7a} is independently selected at each occurrence from:
-H,
-C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
20 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
25 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
30 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl),
35

alternatively, NR^6R^7 and $\text{NR}^{6a}\text{R}^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 $\text{C}_1\text{-C}_4$ alkyl groups.

5

[33] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

- $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, halo, $\text{C}_1\text{-C}_4$ haloalkyl, cyano, OR^{15} , SH, $\text{S(O)}_n\text{R}^{13}$, $-\text{COR}^{15}$, CO_2R^{15} , $\text{OC(O)}\text{R}^{13}$, $\text{NR}^8\text{COR}^{15}$, $\text{N(COR}^{15})_2$, $\text{NR}^8\text{CONR}^{16}\text{R}^{15}$, $\text{NR}^8\text{CO}_2\text{R}^{13}$, $\text{NR}^{16}\text{R}^{15}$, $\text{CONR}^{16}\text{R}^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

[34] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

- $\text{C}_1\text{-C}_4$ alkyl, each such $\text{C}_1\text{-C}_4$ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, halo, $\text{C}_1\text{-C}_4$ haloalkyl, cyano, OR^{15} , SH, $\text{S(O)}_n\text{R}^{13}$, $-\text{COR}^{15}$, CO_2R^{15} , $\text{OC(O)}\text{R}^{13}$, $\text{NR}^8\text{COR}^{15}$, $\text{N(COR}^{15})_2$, $\text{NR}^8\text{CONR}^{16}\text{R}^{15}$, $\text{NR}^8\text{CO}_2\text{R}^{13}$, $\text{NR}^{16}\text{R}^{15}$, $\text{CONR}^{16}\text{R}^{15}$, aryl, heteroaryl or heterocyclyl.

[35] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

- H,
 - C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 - C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl,
 - aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);
- R^{7a} is:
- C₁-C₄ alkyl and each such C₁-C₄ alkyl is substituted with 1-3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

[36] More preferred compounds of the above invention also include compounds and isomers thereof,

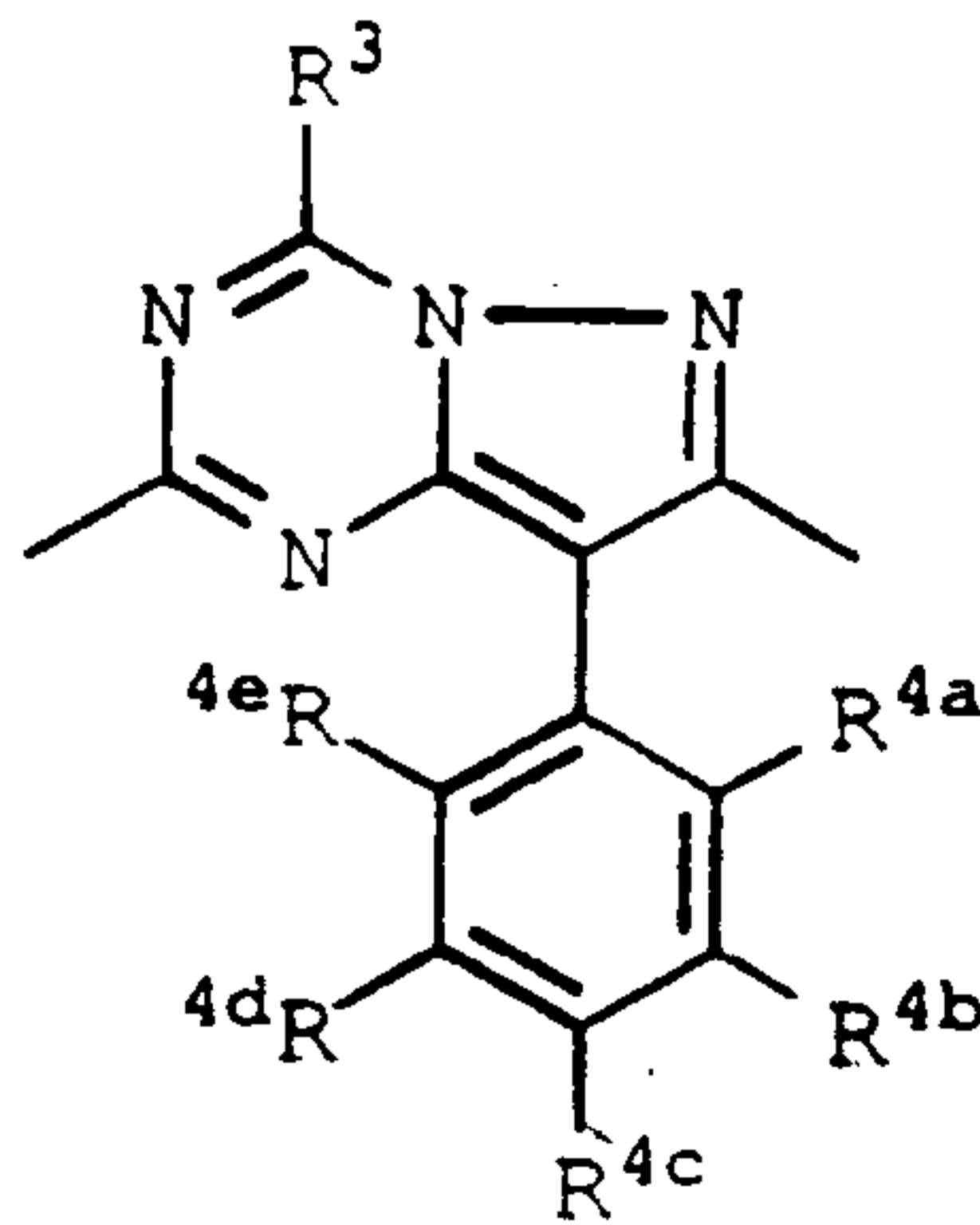
stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

- 5 -C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
 optionally substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
 10 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl,
 -aryl,
 -heteroaryl or
 15 -heterocyclyl,
 and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
 alkyl.

- [37] More preferred compounds of the above invention
 20 also include compounds and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
 25 each such C₁-C₁₀ alkyl optionally substituted with
 1 to 3 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³,
 COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 30 R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl.

[38] Specifically preferred compounds of the above invention are compounds of Formula (50)

35



FORMULA (50)

- 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, selected from the group consisting of:
- 10 a compound of Formula (50) wherein R³ is -NHCH(n-Pr)₂, 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 (50) wherein R³ is -N(Et)(n-Bu), 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 (50) wherein R³ is -(n-Pr)(CH₂CPr), 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 (50) wherein 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 (50) wherein R³ is -NHCH(Et)(n-Bu), 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 (50) wherein 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;

- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, 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 (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, 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 (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(Me)(Ph)$, 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 (50) wherein R^3 is $-N(n-Pr)_2$, 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 (50) wherein R^3 is $-NHCH(Et)(n-Pr)$, 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 (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 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 Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-OEt$, 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 (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, 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 (50) wherein R^3 is $-NHCH(Me)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-OCH(Et)(CH_2OMe)$, 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 (50) wherein R^3 is $-N(n-Pr)(CH_2cPr)$, 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 (50) wherein R^3 is $-NHCH(Me)(CH_2N(Me)_2)$, 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 (50) wherein R^3 is $-N(cPr)(CH_2CH_2CN)$, 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 (50) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(n-Bu)(CH_2CN)$, 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 (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 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 Me, R^{4d} is H and R^{4e} is Me;
- 45

- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, 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 (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, 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 R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 20 a compound of Formula (50) wherein R^3 is morpholino, 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 (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 H and R^{4e} is H;
- 25 is H;
- 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 H and R^{4e} is H;
- 30 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 H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NH(c-Pr)$, 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 (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, 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 $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 45 a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

- 5 a compound of Formula (50) wherein R^3 is
-NHCH(CH₂OMe)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c}
is Br, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 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(CH₂CH₂OMe)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(Et)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 -N(Et)₂, 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(CH₂OMe)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 (50) wherein R^3 is
-NHCH(Et)(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 (50) wherein R^3 is -N(c-
Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d}
is Me and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is -N(c-
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 (50) wherein R^3 is (S)-
 $\text{NHCH}(\text{CH}_2\text{OMe})(\text{CH}_2\text{CH}_2\text{OMe})$, 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 R^3 is
 $-\text{NHCH}(\text{CH}_2\text{OMe})(\text{CH}_2\text{CH}_2\text{OMe})$, 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 (50) wherein R^3 is $-\text{NHCH}(\text{Et})_2$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is
 H;
- 15 a compound of Formula (50) wherein R^3 is
 $-\text{NH}(\text{CH}_2\text{OMe})(\text{CH}_2\text{-iPr})$, 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 (50) wherein R^3 is $-\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is
 H;
- a compound of Formula (50) wherein R^3 is $-\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e}
 is H;
- 25 a compound of Formula (50) wherein R^3 is
 $-\text{NHCH}(\text{CH}_2\text{OMe})(\text{n-Pr})$, 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 (50) wherein R^3 is
 $-\text{NHCH}(\text{CH}_2\text{OEt})(\text{Et})$, 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 (50) wherein R^3 is
 $-\text{NHCH}(\text{CH}_2\text{OMe})(\text{CH}_2\text{CH}_2\text{OMe})$, R^{4a} is Me, R^{4b} is H, R^{4c}
 is NMe_2 , R^{4d} is H and R^{4e} is H;
- 40 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 Cl, R^{4d} is H and R^{4e} is H;
- 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 Cl, R^{4d} is H and R^{4e} is H;
- 45

- 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 Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H 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 Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e} is H;
- 20 H;
- a compound of Formula (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, 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 (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, 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 (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45 H;

- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, 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 (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H 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 Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-N(CH_2c-Pr)(n-Pr)$, 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 (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, 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 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 $-N(Et)_2$, 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 $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, 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 $-N(c-Pr)(CH_2CH_2CN)$, 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 $-NHCH(CH_2OH)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and
- 5 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 H.
- 10 [39] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and
- 15 pharmaceutically acceptable salt or pro-drug forms thereof.
- [40] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.
- 25
- [41] More preferred are compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is CR.
- 30
- [42] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.
- 35

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[43] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

10 [44] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

15 [45] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.

25 [46] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR².

30 [47] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is

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phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

[48] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

10

[49] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.

[50] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

[51] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of

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stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl,
and each Ar is optionally substituted with 1
5 to 4 R⁴ substituents,

-R³ is NR^{6a}R^{7a} or OR⁷ and

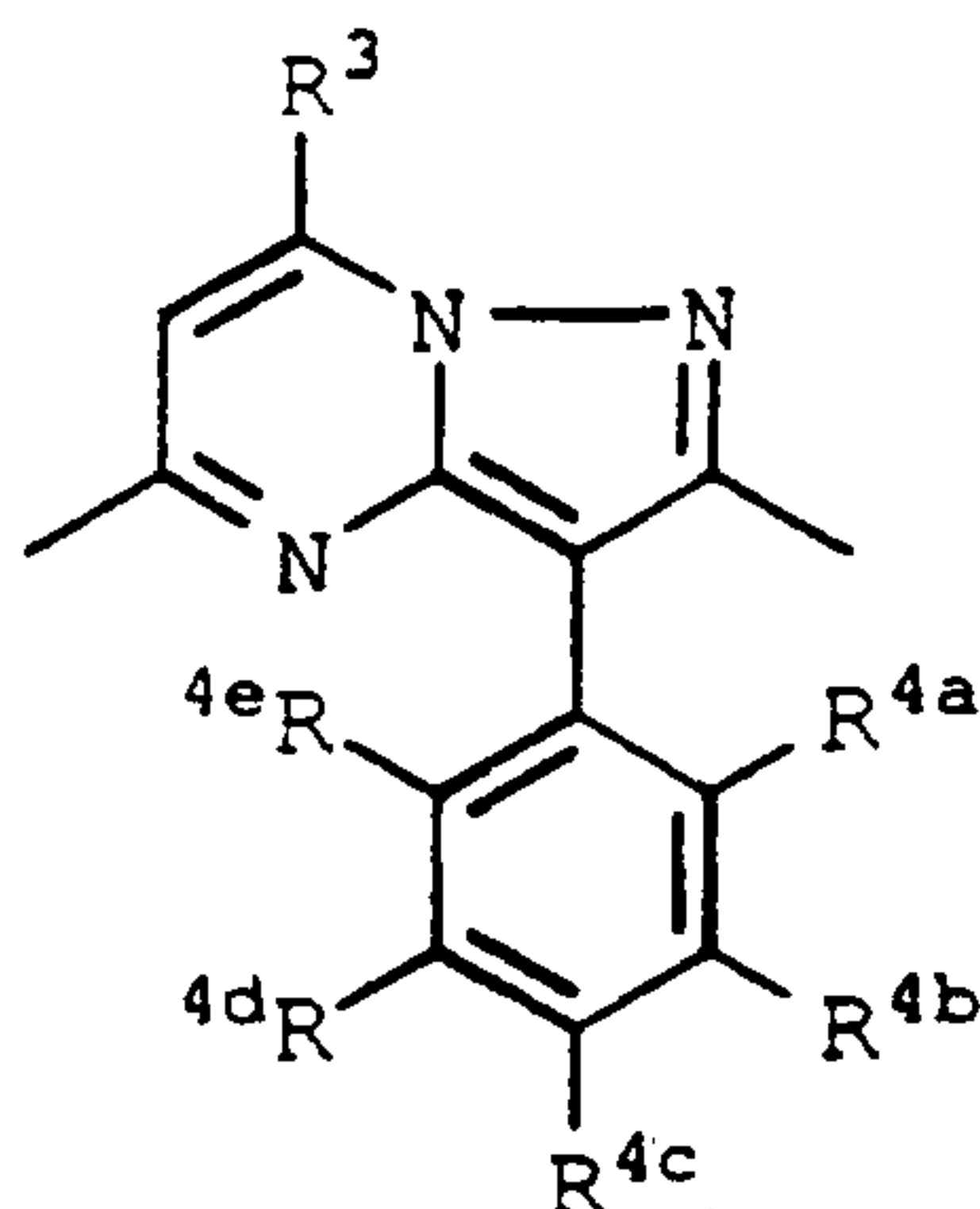
-R¹ and R² are independently selected from H, C₁-C₄
alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀
cycloalkylalkyl.

10

[52] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

15 acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-
20 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

25 [53] Specifically preferred compounds of the above invention are compounds of Formula (51)



FORMULA (51)

- 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:
- 10 a compound of Formula (51) wherein R^3 is $-\text{NHCH}(\text{n-Pr})_2$, 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 (51) wherein R^3 is $-\text{NHCH}(\text{CH}_2\text{OMe})_2$, 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 (51) wherein R^3 is $-\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$, 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 (51) wherein R^3 is $-\text{N}(\text{c-Pr})(\text{CH}_2\text{CH}_2\text{CN})$, 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 (51) wherein R^3 is $-\text{NHCH}(\text{CH}_2\text{OMe})_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

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- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(n-Bu)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) 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 H;
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is (S) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NH(Et)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

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- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is (S) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is (S) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 45

- 5 a compound of Formula (51) 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;
- 10 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) 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;
- 35 a compound of Formula (51) 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;
- 40 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 50 a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 55 a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 60 a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 and
- a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.
- 20

[54] More specifically preferred is 7-(3-pentylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

25

[55] More specifically preferred is 7-(Diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

30

[56] More specifically preferred is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and

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pharmaceutically acceptable salt or pro-drug forms thereof.

The present invention also provides
5 pharmaceutical compositions comprising compounds of
Formulae (1) and (2) and a pharmaceutically
acceptable carrier.

Many compounds of this invention have one or more
10 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
15 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
20 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.

25 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
30 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-
35 carbon bonds which may occur in any stable point
along the chain, such as ethenyl, propenyl, and the

like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

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

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

The term "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis,

Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing

Company, Easton, PA, 1985, p. 1418.

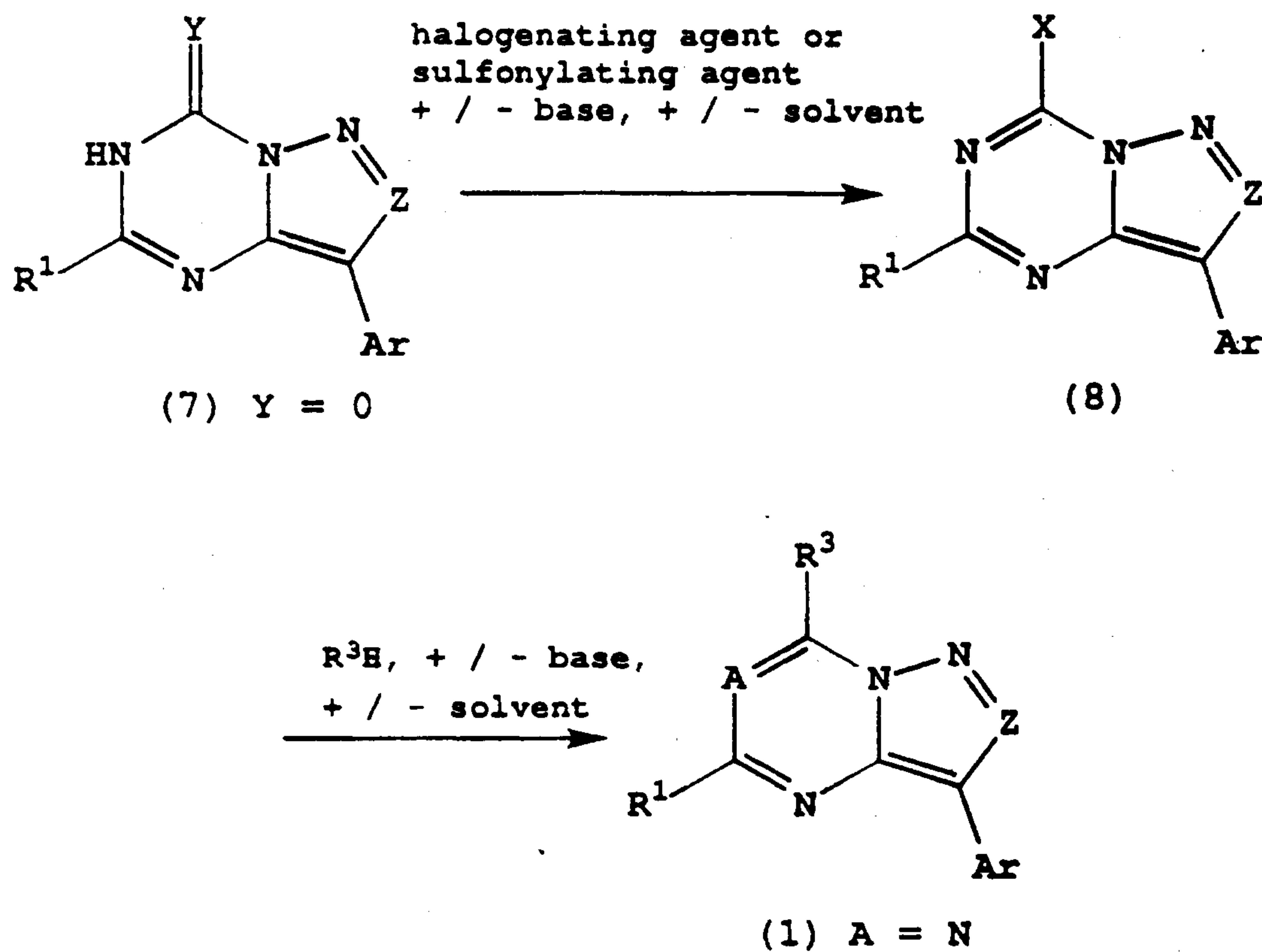
"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds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

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

Syntheses

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

SCHEME 1



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, arylsulfonyloxy or haloalkane-sulfonyloxy). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3 , PCl_5 , $POBr_3$, PBr_3 or PBr_5 . Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal

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

Compounds of Formula (8) may be reacted with compounds of Formula R^3H (where R^3 is defined as above except R^3 is not SH, COR^7 , CO_2R^7 , aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80 to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

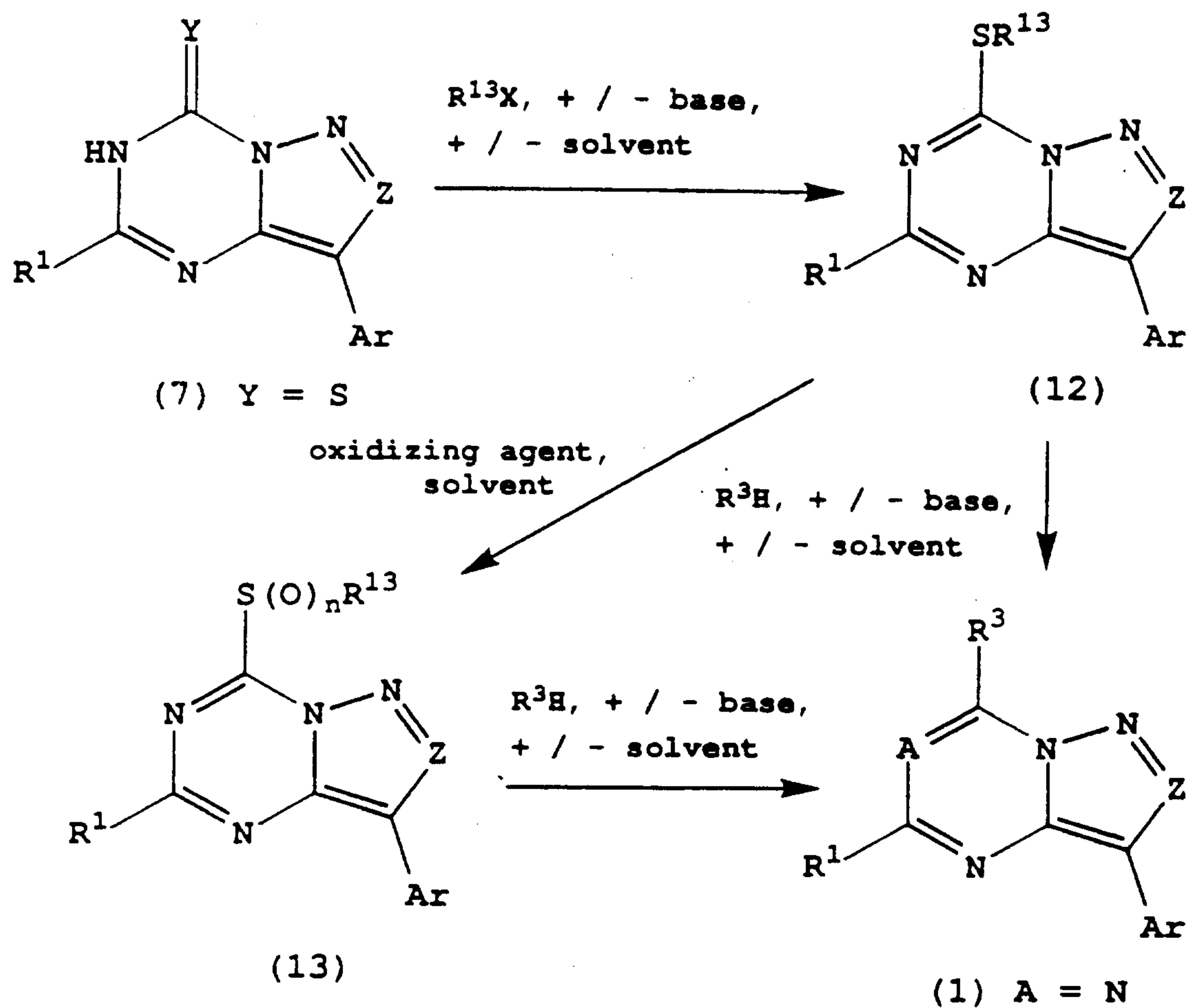
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N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile),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

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

SCHEME 2



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

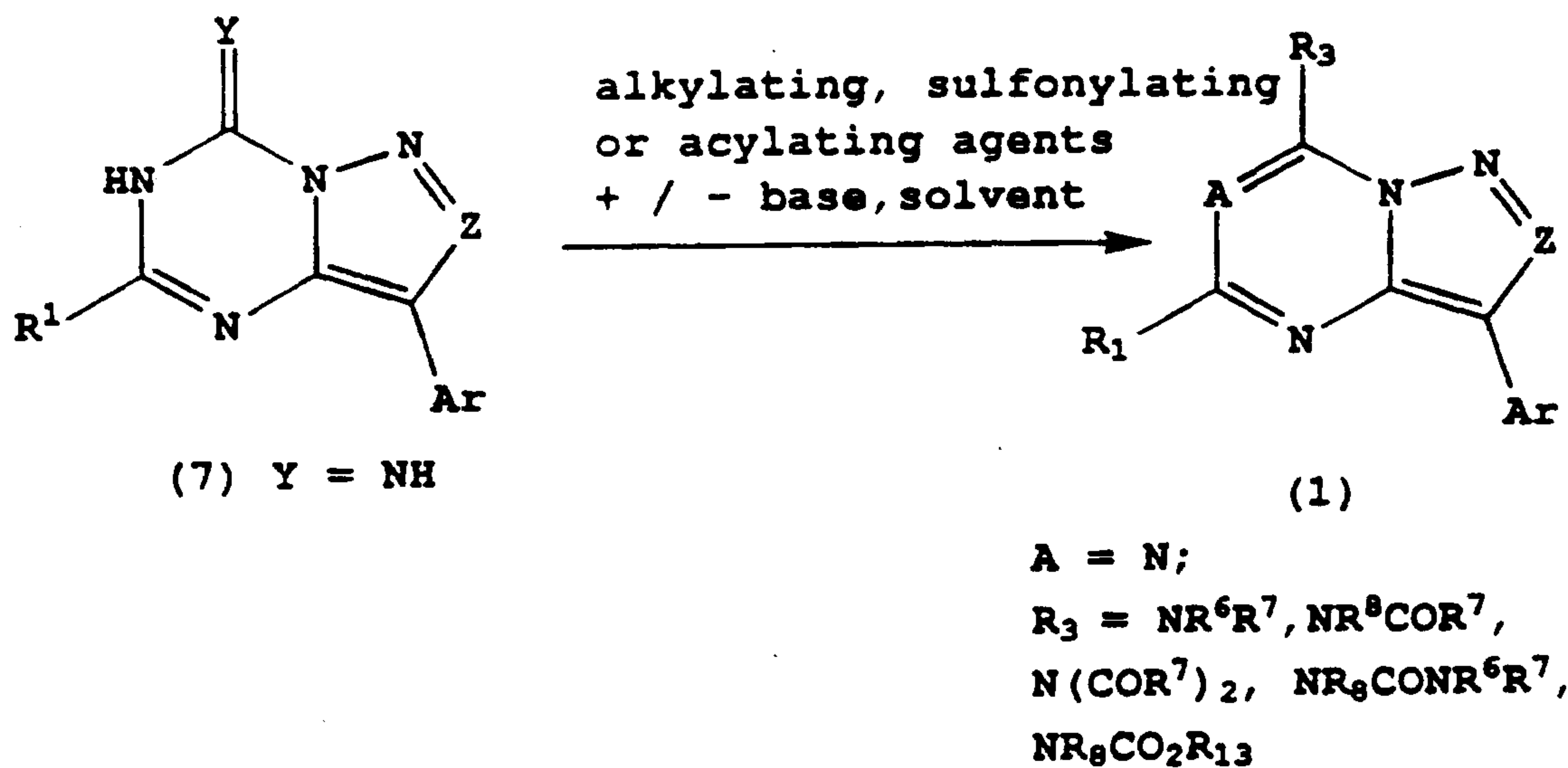
bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons,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

Compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme 1 above. Alternatively, compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may be oxidized to compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) by treatment with an oxidizing agent in the presence of an inert solvent at temperatures ranging from -80°C to 250°C. Oxidizing agents include, but are not limited to, hydrogen peroxide, alkane or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid), dioxirane, oxone, or sodium periodate. Inert solvents may include, but are not limited to, alkanones (3 to 10 carbons, preferably acetone), water, alkyl alcohols (1 to 6 carbons), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens

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

Compounds of Formula (1), where R^3 may be $-\text{NR}^8\text{COR}^7$,
 15 $-\text{N}(\text{COR}^7)_2$, $-\text{NR}^8\text{CONR}^6\text{R}^7$, $-\text{NR}^8\text{CO}_2\text{R}^{13}$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^8\text{SO}_2\text{R}^7$, may be prepared from compounds of Formula (7), where Y is NH , by the procedures depicted in Scheme 3.

SCHEME 3



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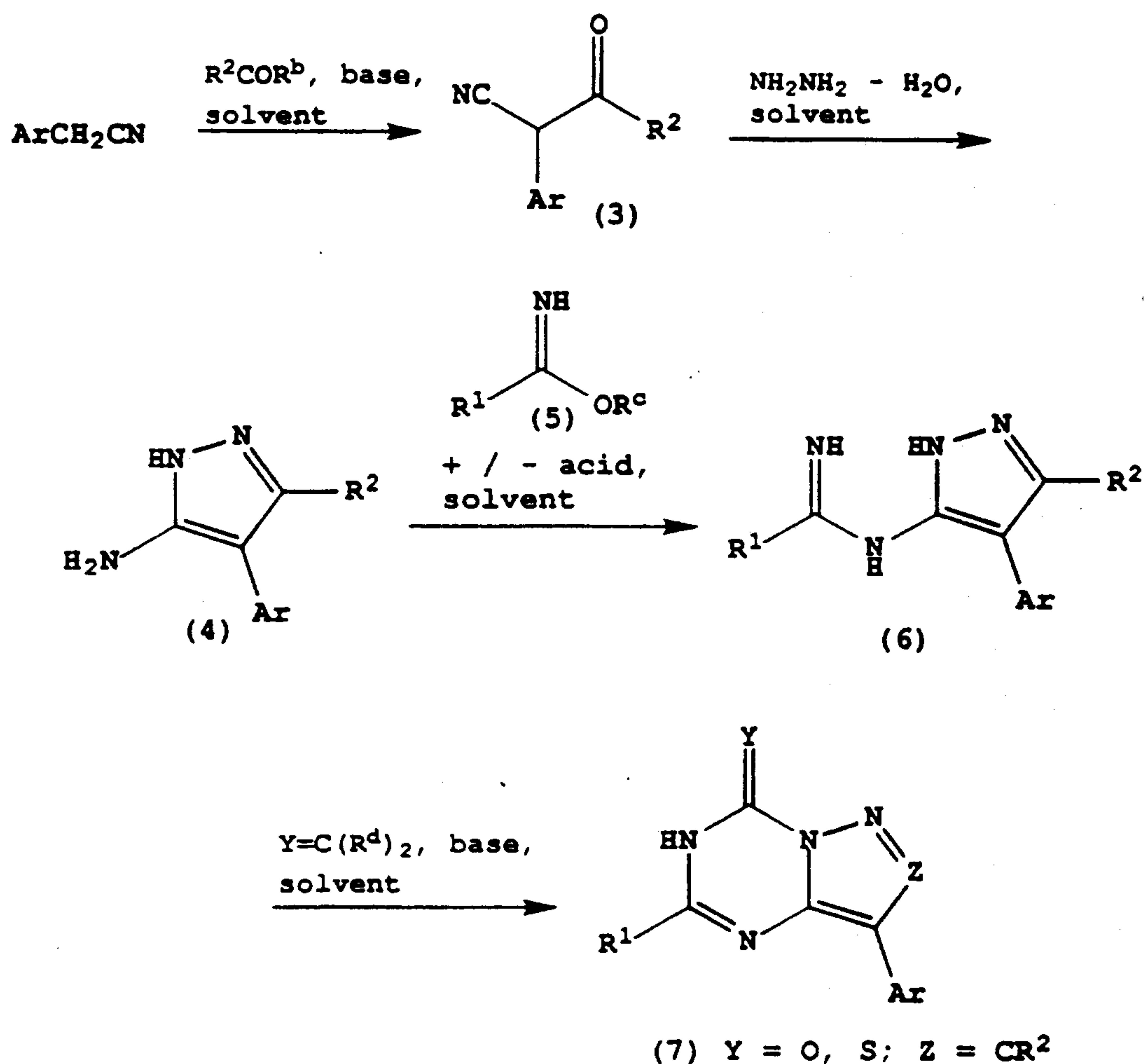
Reaction of compounds of Formula (7), where Y is NH , with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with

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 $-\text{NR}^8\text{COR}^7$, $-\text{N}(\text{COR}^7)_2$,
5 $-\text{NR}^8\text{CONR}^6\text{R}^7$, $-\text{NR}^8\text{CO}_2\text{R}^{13}$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^8\text{SO}_2\text{R}^7$. 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)-
10 halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C_1 - C_4 alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C_1 - C_{10} alkanoyl halides or anhydrides, C_1 - C_{10} haloalkanoyl halides or anhydrides
20 with 1 - 10 halogens, C_2 - C_8 alkoxyalkanoyl halides or anhydrides, C_3 - C_6 cycloalkanoyl halides or anhydrides, C_4 - C_{12} cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C_1 - C_4) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides,
25 heteroaryl(C_1 - C_4) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C_1 - C_4) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C_1 - C_{10} alkylsulfonyl halides or anhydrides, C_1 - C_{10}
30 haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C_2 - C_8 alkoxyalkylsulfonyl halides or anhydrides, C_3 - C_6 cycloalkylsulfonyl halides or anhydrides, C_4 - C_{12} cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C_1 - C_4 alkyl)-, heteroarylsulfonyl halides or anhydrides,
35 heteroaryl(C_1 - C_4 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
5 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
10 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
15 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
20 (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
25 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

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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

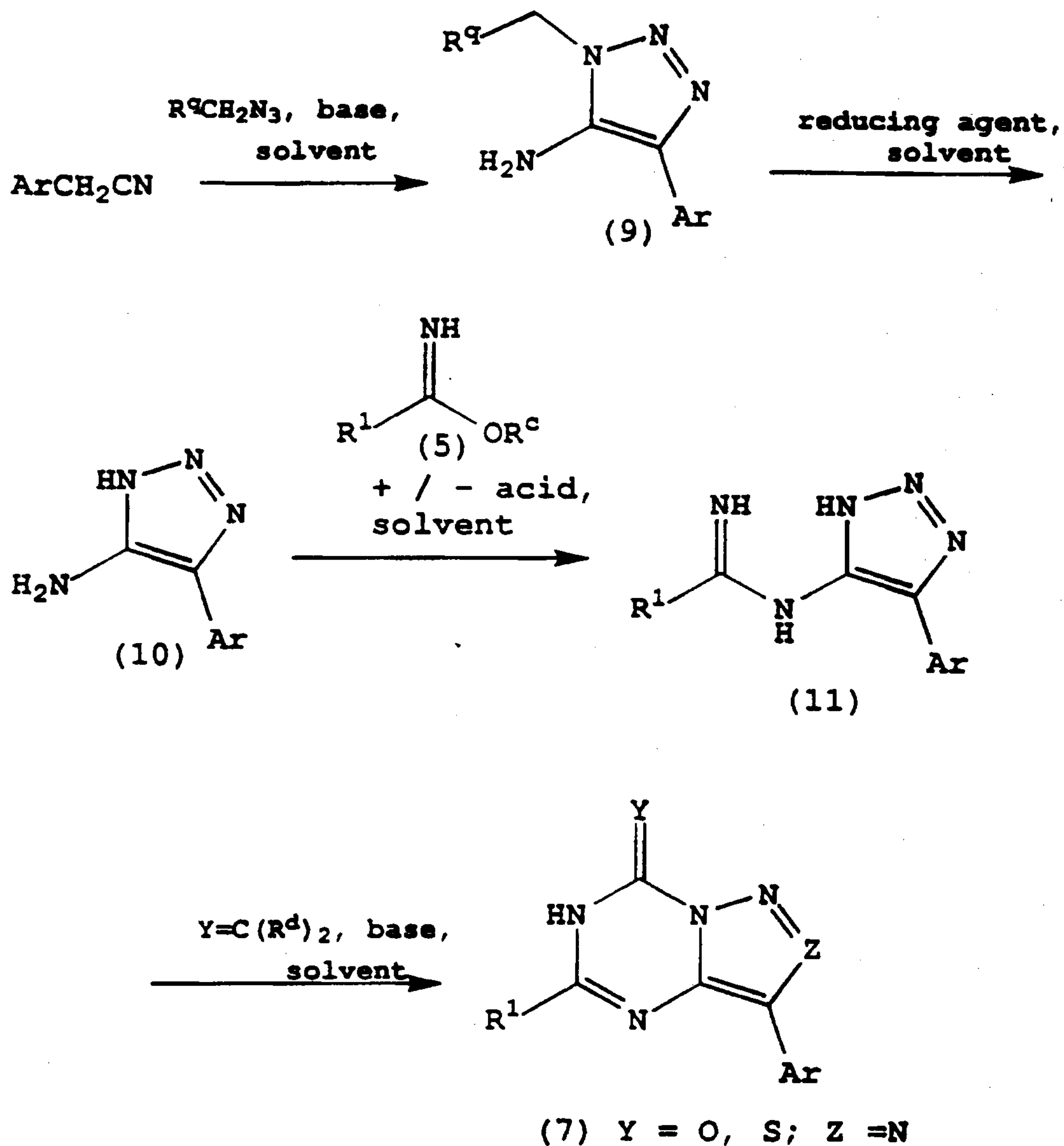
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dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred temperatures 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



Compounds of ArCH_2CN are reacted with compounds of Formula $\text{R}^9\text{CH}_2\text{N}_3$ (where R^9 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).

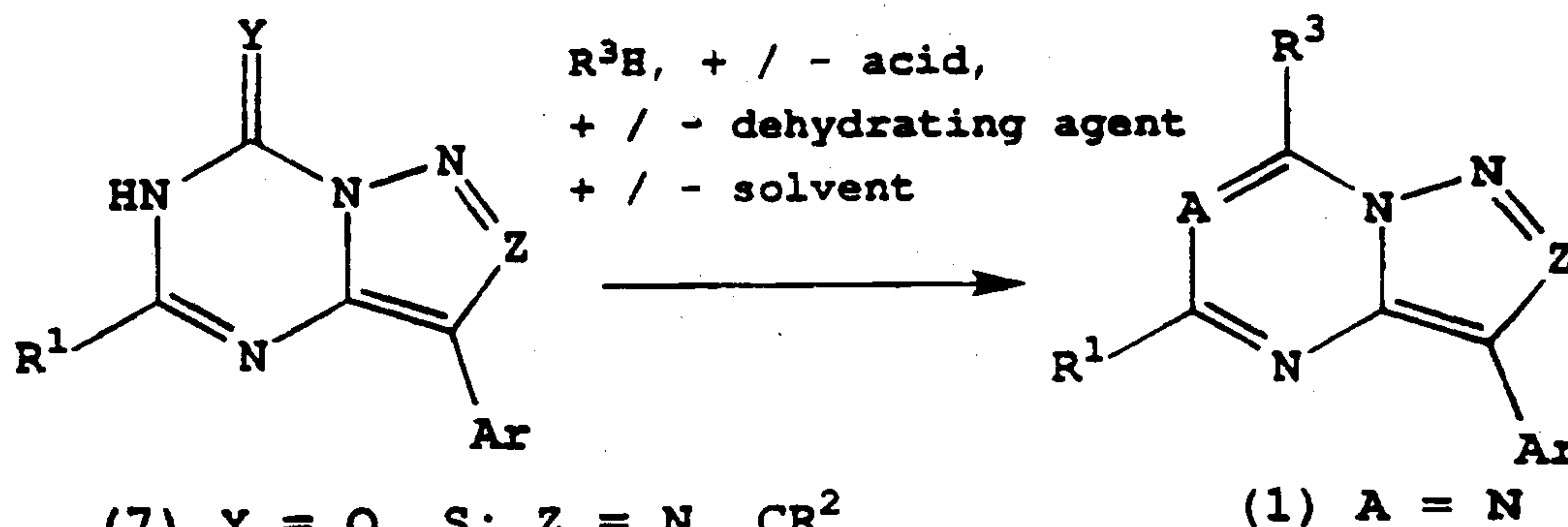
10 Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (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

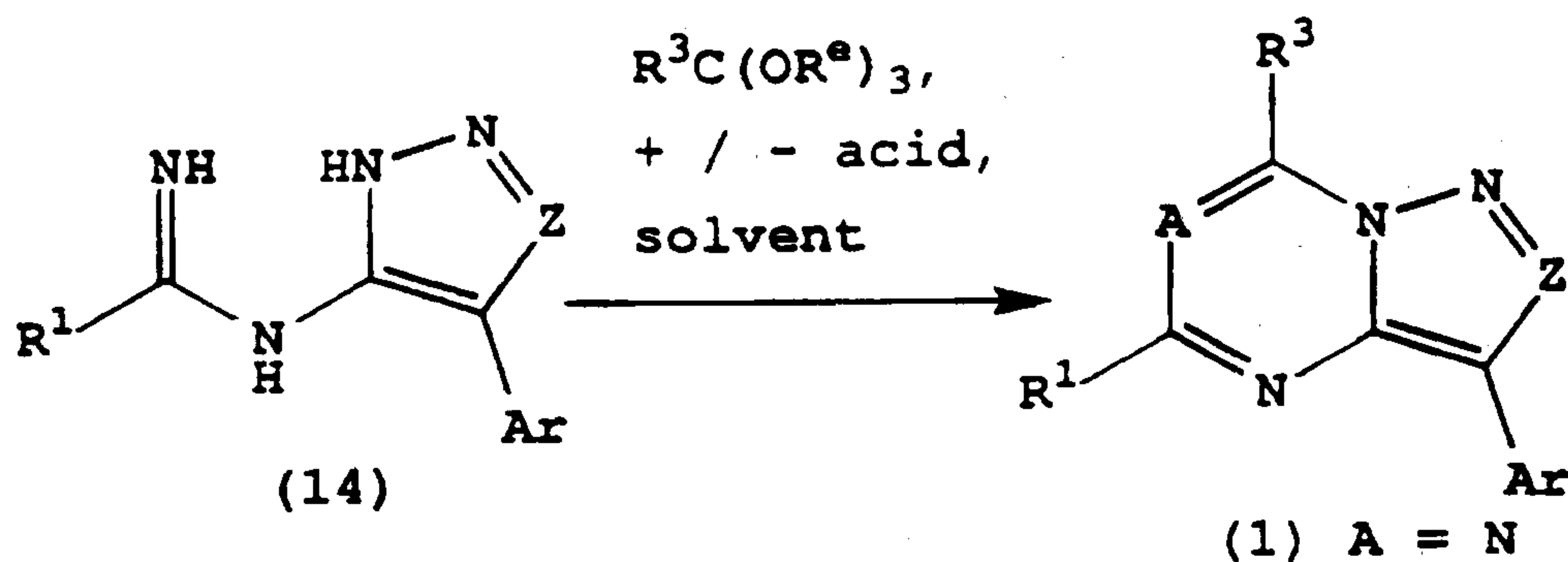


Compounds of Formula (7) may be reacted with compounds of Formula R³H in the presence of a dehydrating agent in an inert solvent at reaction temperatures ranging from 0°C to 250°C. Dehydrating agents include, but are not limited to, P₂O₅, molecular sieves or inorganic or organic acids. Acids may include,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

alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably glyme or diglyme), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or halocarbons of 1 to 10 carbons and 1 to 10 halogens (preferably chloroform). Preferred reaction temperatures range from ambient temperature to 150°C.

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

SCHEME 7

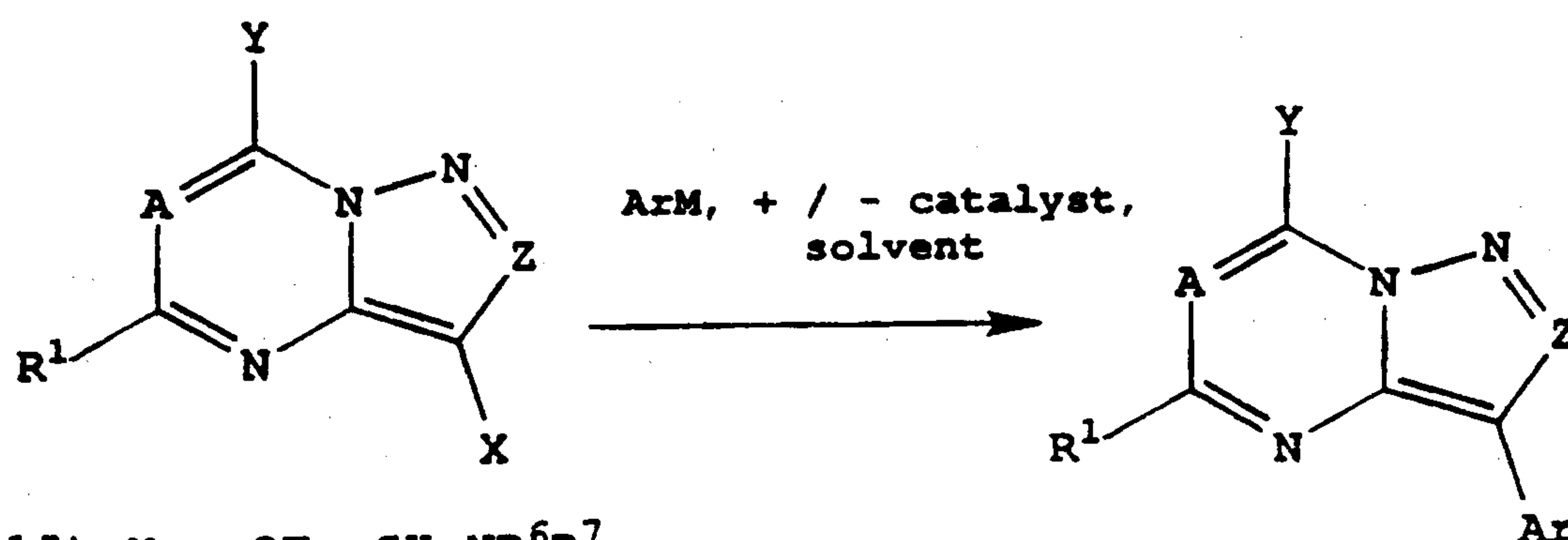


Intermediate compounds of Formula (14), where Z is defined above, may be reacted with compounds of Formula R³C(OR^e)₃, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to 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



(15) $Y = \text{OH, SH, NR}^6\text{R}^7$;
 $Z = \text{N, CR}^2$,
 $X = \text{Br, Cl, I, B(OR}^{\text{'''}}\text{)}_2$

(7) $A = \text{N}$

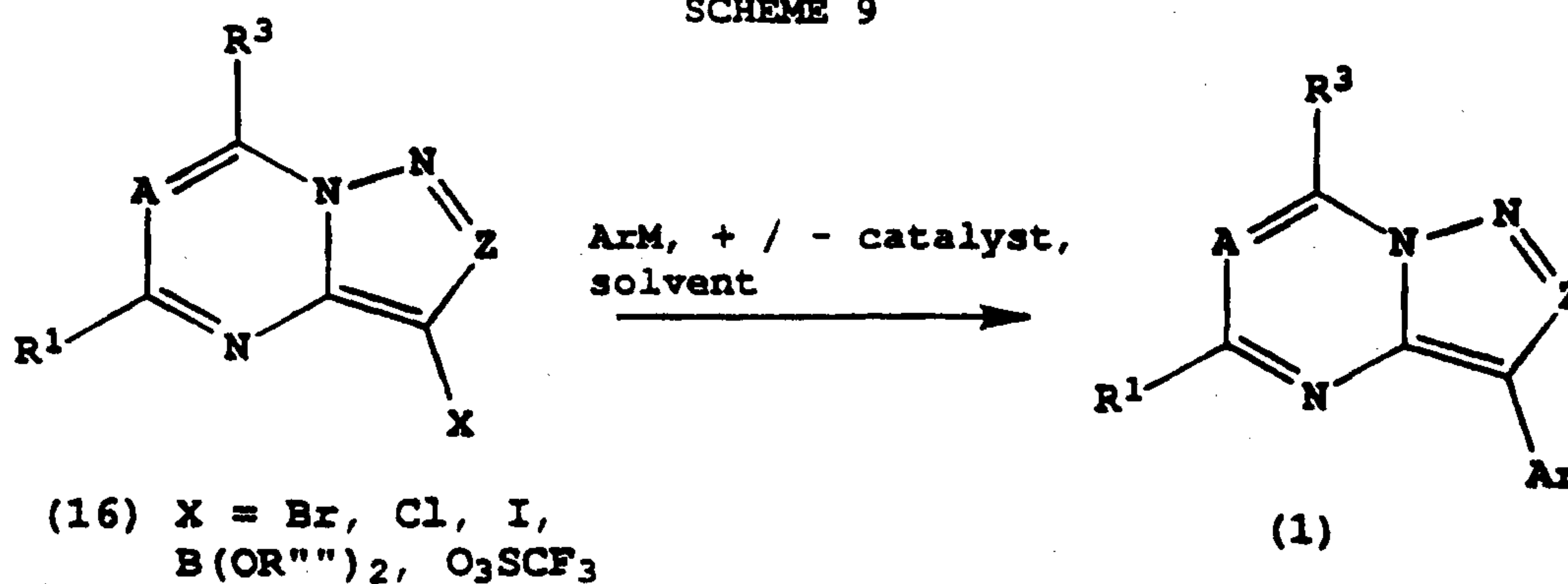
Compounds of Formula (15), (where Y is OH, SH, NR^6R^7 ; Z is defined above, X is Br, Cl, I, O_3SCF_3 or $\text{B(OR}^{\text{'''}}\text{)}_2$ and $\text{R}^{\text{'''}}$ is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl_2 , CeBr_2 or copper halides) in the presence or absence of an

organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ. Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as Pd(PPh₃)₄), palladium halides or alkanoates (such as PdCl₂(PPh₃)₂ or Pd(OAc)₂) or nickel complexes (such as NiCl₂(PPh₃)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 sp² Carbon Centers, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 3, 481-520).

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

SCHEME 9

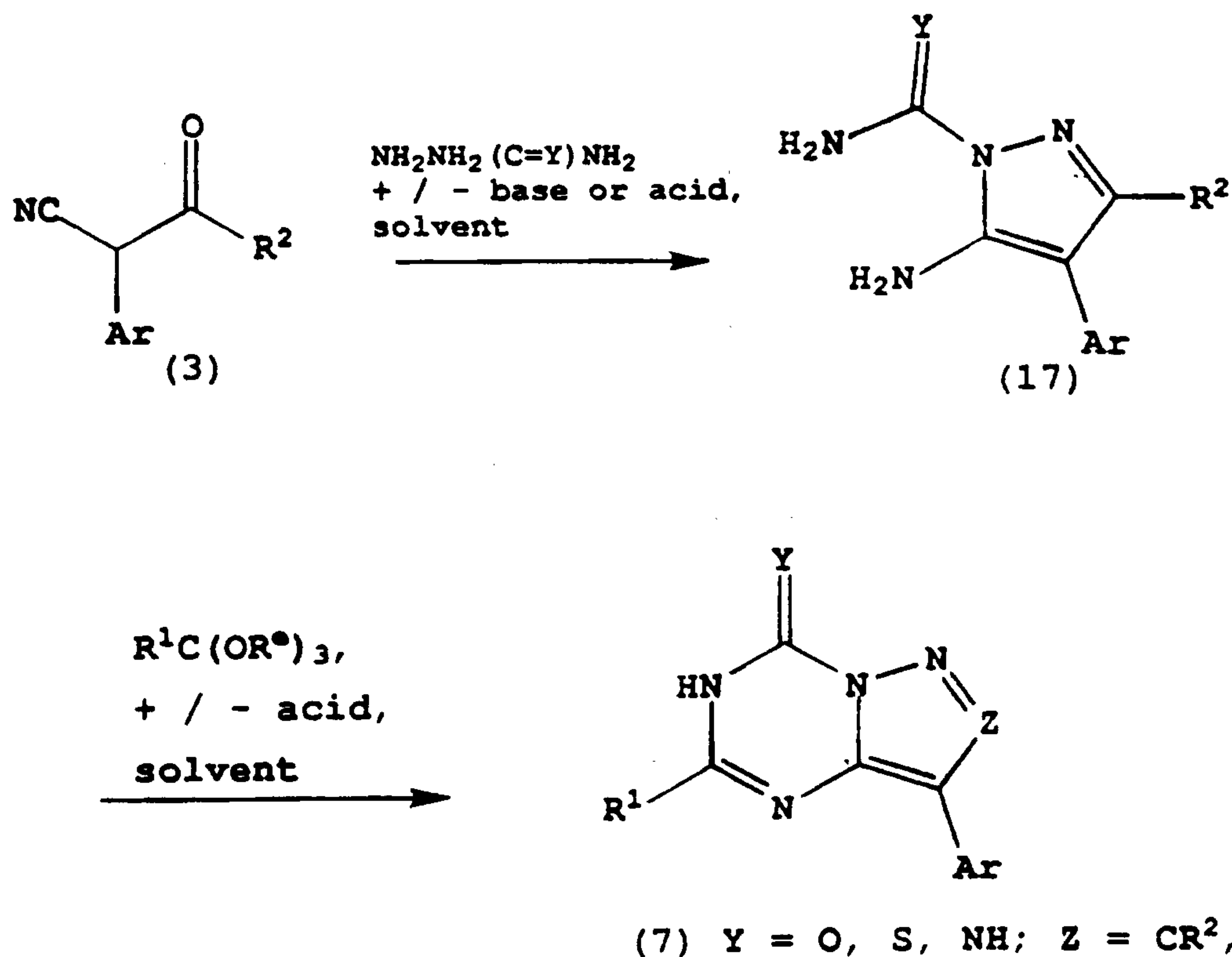


Compounds of Formula (16), where A, Z, R¹ and R³ are defined above and X is Br, Cl, I, O₃SCF₃ or B(OR^{'''})₂ and R^{'''} is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl₂, CeBr₂ or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ (see the above references in Comprehensive Organic Synthesis). Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as Pd(PPh₃)₄), palladium halides or alkanoates (such as PdCl₂(PPh₃)₂ or Pd(OAc)₂) or nickel complexes (such as NiCl₂(PPh₃)₂). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably

benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C .

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

SCHEME 10



Compounds of Formula (3) may be reacted with compounds of Formula $\text{H}_2\text{NNH}(\text{C}=\text{Y})\text{NH}_2$, where Y is O, S or NH, in the presence or absence of a base or acid in an inert solvent at temperatures from 0°C to 250°C to produce compounds of Formula (17). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts

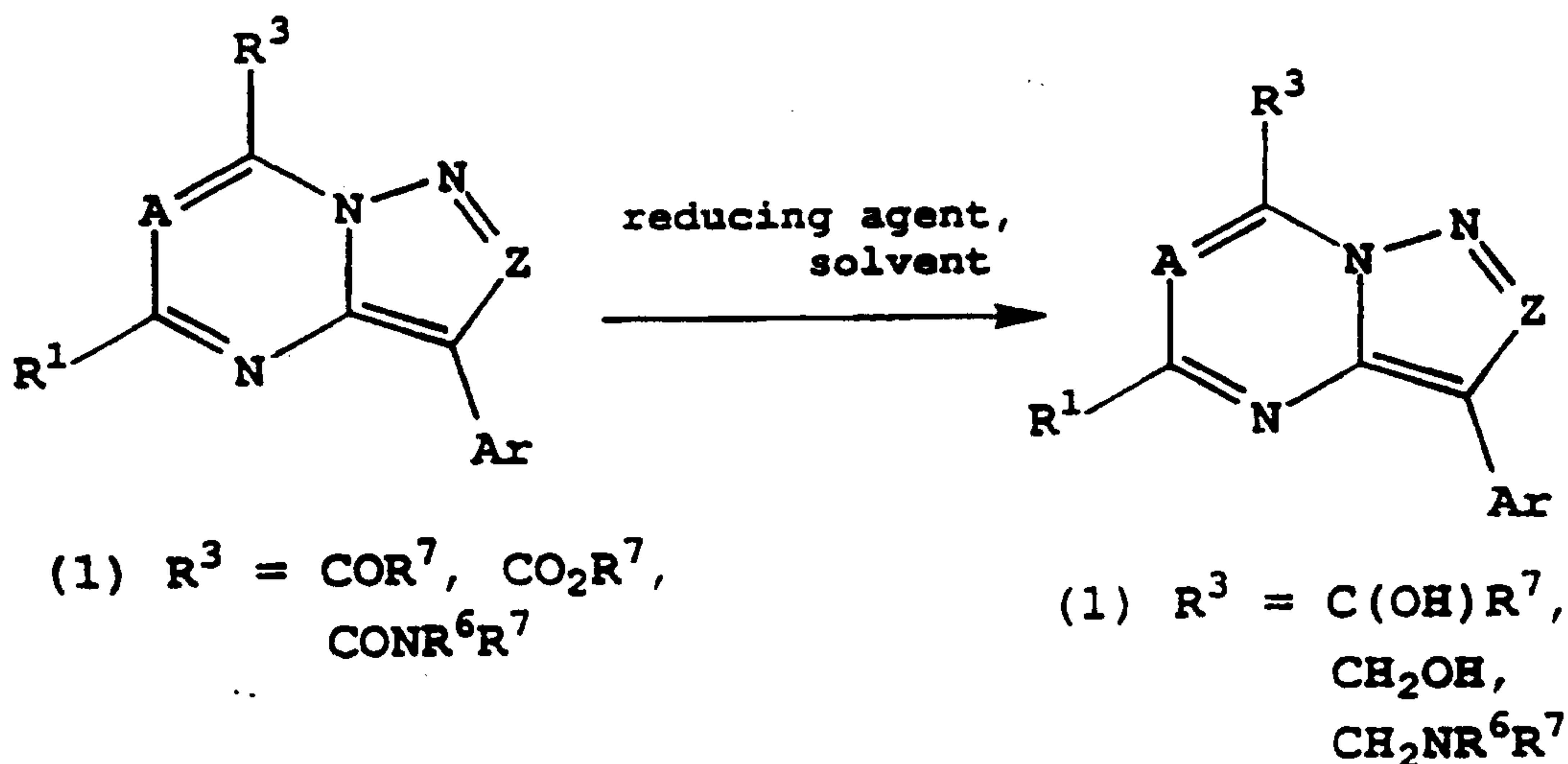
of such acids may be used. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane).

Preferred reaction temperatures range from 0°C to 150°C. Compounds of Formula (17) may then be reacted with compounds of Formula $R^3C(OR^e)_3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to 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

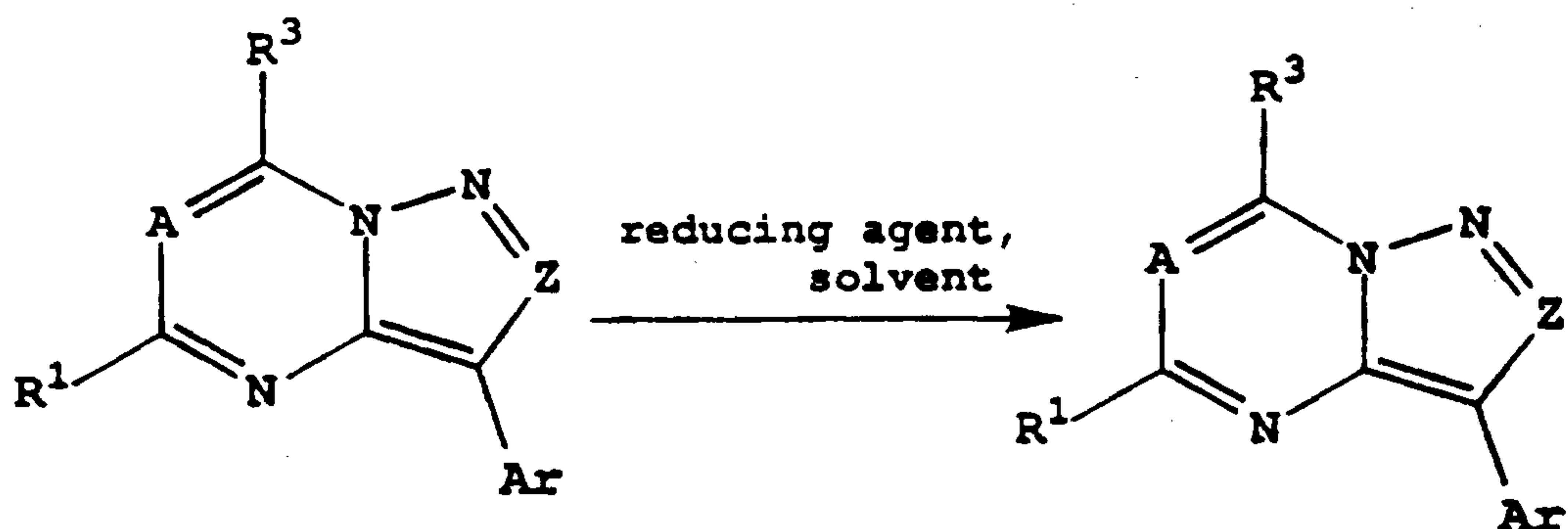


- Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides, 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 $C(OH)(R^7)_2$ by treatment with a reagent of Formula R^7M in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 12



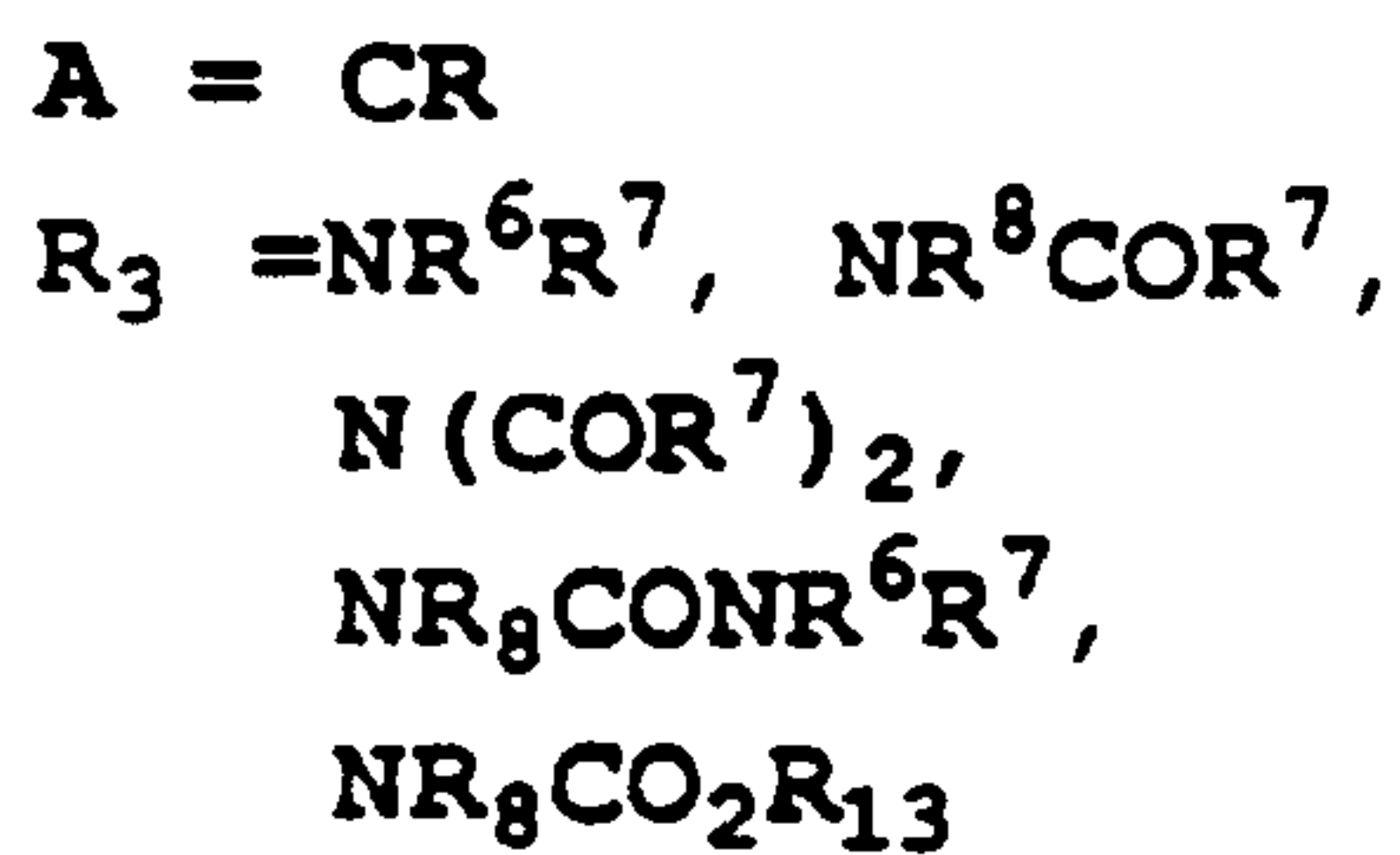
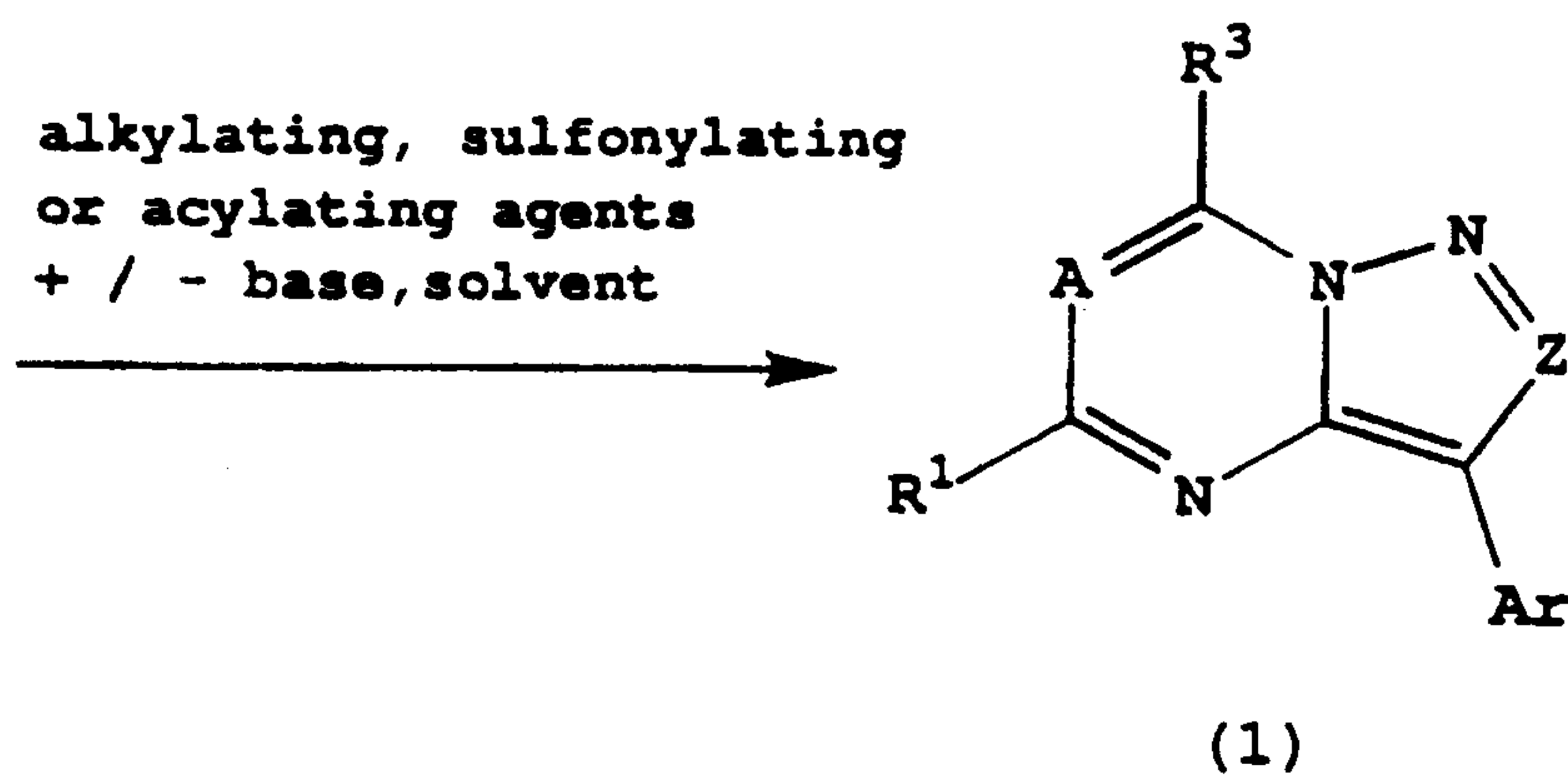
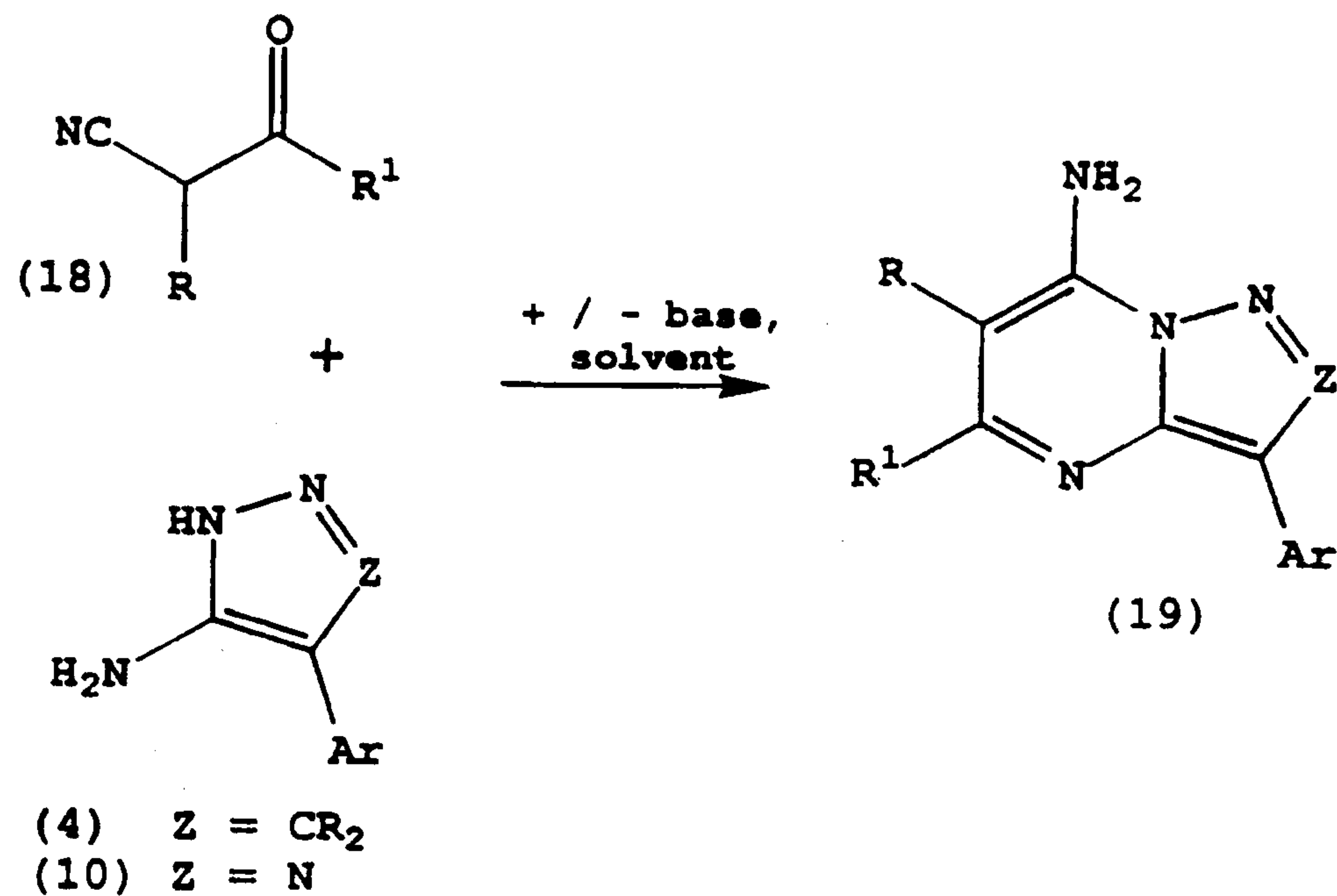
(1) $R^3 = COR^7, CO_2R^7,$

(1) $R^3 = C(OH)(R^7)_2$

M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl₂, CeBr₂ or copper halides. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

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

SCHEME 13



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

ranging from -50°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (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 -triflates; aryl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates; or

5 heterocyclyl(C₁-C₄ 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

10 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,

15 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

20 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,

25 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

30 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

35 bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably

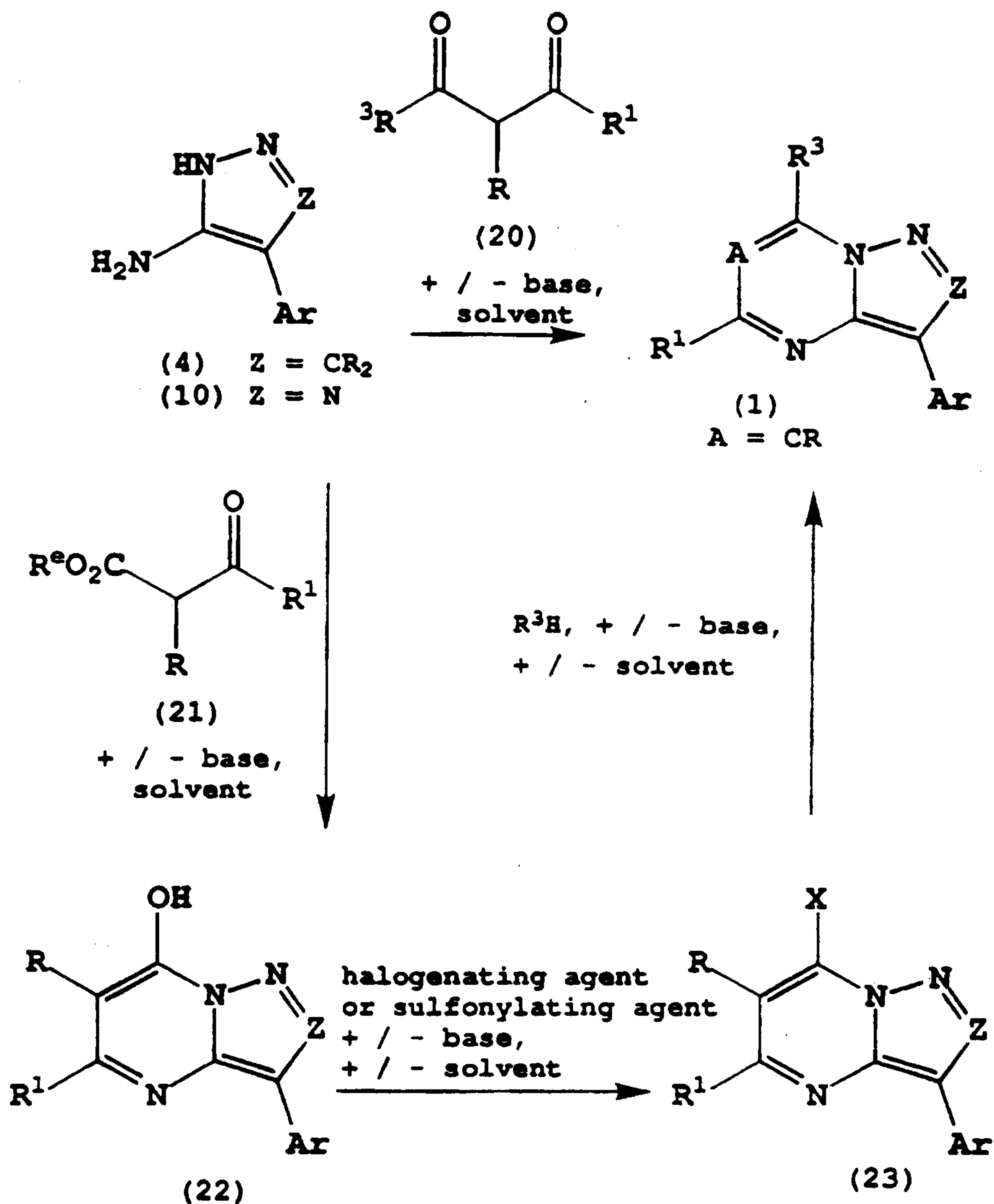
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pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

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

SCHEME 14



5 Compounds of Formula (4) or (10) may be treated with compounds of Formula (20), where R^1 and R^3 are defined above in the presence or absence of base in an inert solvent at temperatures ranging from $0^\circ C$ 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
metal hydrides, alkali metal dialkylamides (preferably
5 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
10 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
15 (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
20 temperatures range from 0°C to 100°C. Alternatively,
compounds of Formula (1) where A is CR and R is defined
above, may be synthesized through intermediates (22) and
(23).

Compounds of Formula (4) or (10) may be treated
25 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
(1), where A is CR and R is defined above. 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 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 (22) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (23) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkane-sulfonyloxy). Halogenating agents include, but are not limited to, 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 p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trimethylsilyl)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
5 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-
10 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
15 100°C.

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
20 absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably
25 sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal
bis(trialkylsilyl)amides (preferably sodium
30 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
35 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably

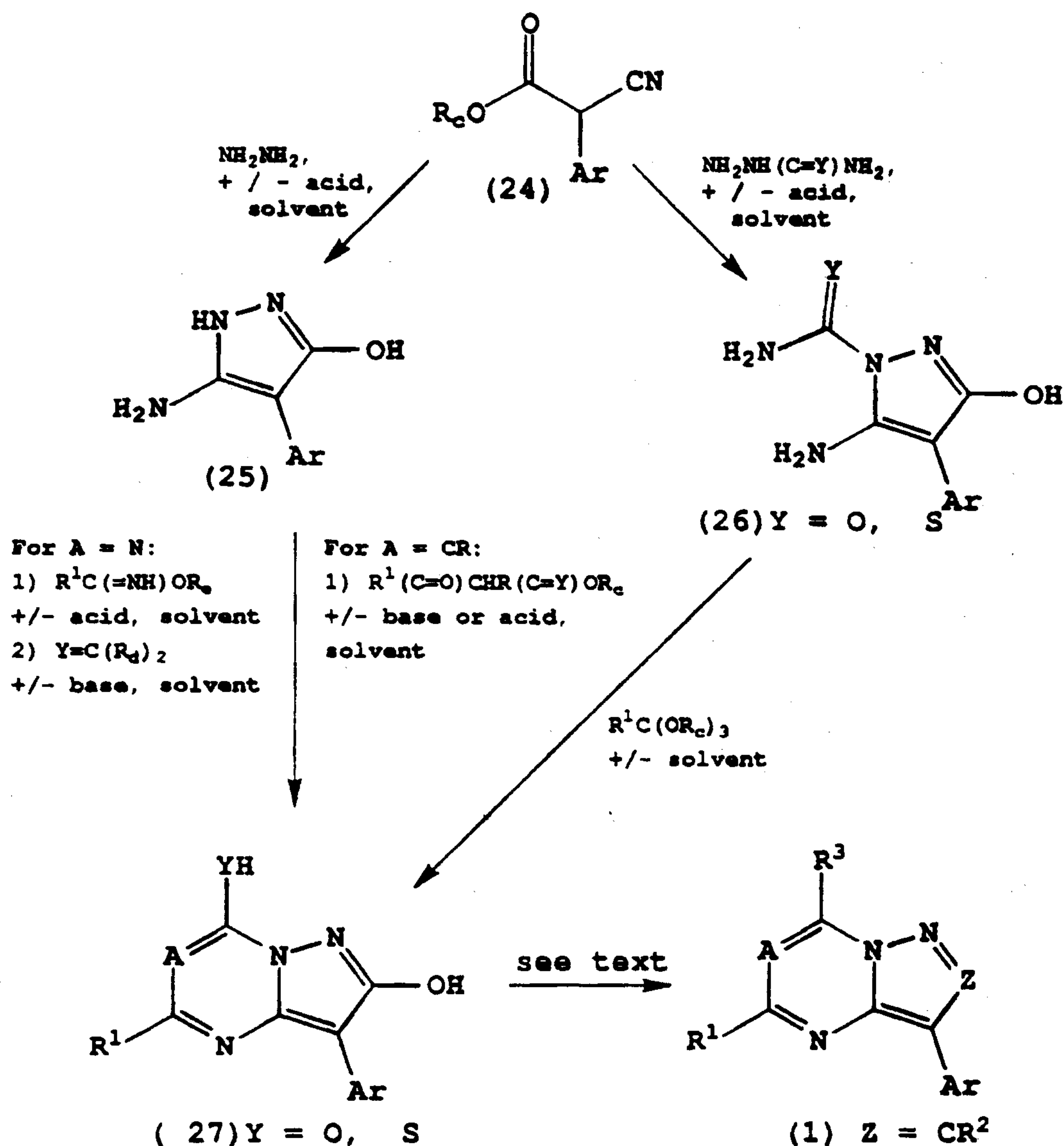
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tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

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

SCHEME 15



- A compound of Formula (24) (R_e is a lower alkyl group and Ar is defined as above) may be reacted with
- 5 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.
- 10 Compounds of Formula (25), where A is N, may be reacted with reagents of the formula $\text{R}^1\text{C}(=\text{NH})\text{OR}_e$, 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

5 (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
10 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
15 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
20 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).

25 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
30 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
35 compounds of Formula (1). The reaction conditions and reagents used for these conversions are similar to the

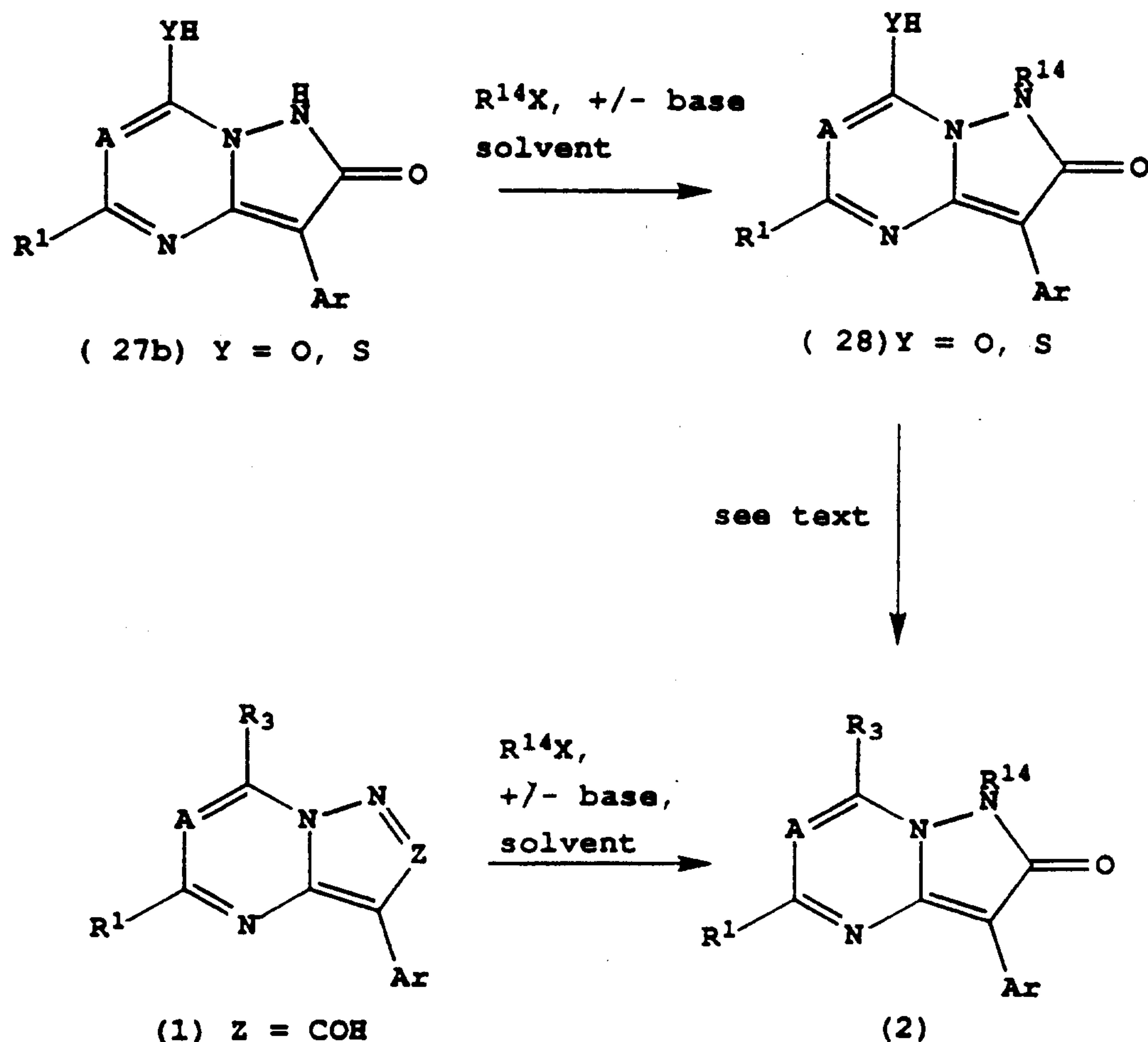
ones employed for the conversion of intermediate compounds of Formulae (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1
5 (where A is N).

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

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

Some compounds of Formula (2) may be prepared by
30 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 (2) by treatment with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H in the presence or absence of a base in an inert solvent to give compounds of Formula (2). The reaction conditions used for these conversions are similar to the

ones employed for the conversion of intermediate compounds (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N).

- 5 Alternatively, compounds of Formula (28) (Y is S) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or
10 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
15 (13)) to compounds of Formula (1) in Scheme 2.

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

- For Scheme 16, the terms "base" and "inert solvent" may have the meanings given below. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1
30 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
35 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.

15

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). Chromatography was

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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.

5

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
10 illustrate and not to limit the invention.

EXAMPLE 1

Preparation of

15 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]
-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)

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

Sodium pellets (9.8g, 0.43 mol) were added portionwise to a solution of 2,4-dimethylphenylacetonitrile (48 g, 0.33 mol) in ethyl acetate (150 mL) at ambient temperature. The reaction
25 mixture was heated to reflux temperature and stirred for 16 hours. The resulting suspension was cooled to room temperature and filtered. The collected precipitate was washed with copious amounts of ether and then air-dried. The solid was dissolved in water and a 1N HCl solution
30 was added until the pH = 5-6. The mixture was extracted with ethyl acetate (3 X 200 mL); the combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to afford a white solid (45.7g, 74% yield): NMR (CDCl₃, 300 MHz):; CI-MS: 188 (M + H).

35

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

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A mixture of 1-cyano-1-(2,4-dimethylphenyl)propan-2-one (43.8g, 0.23 mol), hydrazine-hydrate (22 mL, 0.46 mol), glacial acetic acid (45 mL, 0.78 mol) and toluene (500 mL) were stirred at reflux temperature for 18 hours in an apparatus fitted with a Dean-Stark trap. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. The residue was dissolved in 6N HCl and the resulting solution was extracted with ether three times. A concentrated ammonium hydroxide solution was added to the aqueous layer until pH = 11. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a pale brown viscous oil (34.6g, 75% yield): NMR (CDCl₃, 300 MHz): 7.10 (s, 1H), 7.05 (d, 2H, J=1), 2.37 (s, 3H), 2.10 (s, 3H); CI-MS: 202 (M + H).

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

Ethyl acetamidate hydrochloride (60g, 0.48 mol) was added quickly to a rapidly stirred mixture of potassium carbonate (69.5g, 0.50 mol), dichloromethane (120 mL) and water (350 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 120 mL). The combined organic layers were dried over MgSO₄ 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

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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 mixture 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

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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
5 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,
10 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-
15 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
20 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 MgSO₄ and filtered. Solvent was removed
25 in vacuo to give a yellow solid (520 mg), which was homogeneous by thin layer chromatography (ethyl acetate):

NMR (CDCl₃, 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).

30

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

A mixture of 4-(2,4,6-trimethylphenyl)-5-aminotriazole (400 mg, 1.98 mmol), ethyl acetamidate (
35 261 mg, 3 mmol) and glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (6 mL) was stirred at ambient

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temperature for 4 hours. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. Drying in vacuo afforded a white solid (490 mg, 82% yield): NMR (DMSO-d₆, 300 MHz): 7.90-7.70 (br s, 0.5H), 7.50-7.20 (br. s, 0.5H), 6.90 (s, 2H), 6.90 (s, 2H), 3.50-3.10 (br s, 3H), 2.30-2.20 (br s, 3H), 2.05 (d, 1H, J = 7), 1.96 (s, 6H), 1.87 (s, 6H); CI-MS: 244 (M + H).

- 10 D. 5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(4H)-one
- Sodium (368 mg, 16.2 mmol) was added with stirring to ethanol (10 mL) at room temperature. After the sodium had reacted, 4-(2,4,6-trimethylphenyl)-5-
- 15 acetamidino-triazole, acetic acid salt (490 mg, 1.6 mmol) and diethyl carbonate (1.6 mL, 13 mmol) were added. The reaction mixture was stirred at reflux temperature for 5 hours, then cooled to room temperature. The reaction mixture was diluted with
- 20 water; a 1N HCl solution was added until pH = 5-6 and three extractions with ethyl acetate were performed. The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a yellow residue. Trituration with ether and filtration afforded
- 25 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

- 30 Preparation of 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine
- (Formula 1, where R³ is CH(CHCO₂CH₃)₂, R₁ is CH₃, Z is C-CH₃, Ar is 2,4-dimethylphenyl)

35

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]

5 -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-
10 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
15 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-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

Sodium hydride (60% in oil, 80 mg, 2 mmol) was washed with hexanes twice, decanted after each washing
25 and taken up in anhydrous tetrahydrofuran (THF, 1 mL). A solution of diethyl malonate (0.32g, 2 mmol) in THF (2 mL) was added dropwise over 5 min, during which time vigorous gas evolution ensued. A solution of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-
30 pyrazolotriazine (0.5g, 1.75 mmol) in THF (2 mL) was added and the reaction mixture was then stirred under a nitrogen atmosphere for 48 hours. The resulting suspension was poured onto water and extracted three times with ethyl acetate. The combined organic layers
35 were washed once with brine, dried over MgSO₄ and filtered. Solvent was removed *in vacuo* to give a brown

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oil. Column chromatography (ethyl acetate:hexanes::1:9) afforded, after removal of solvent in vacuo, a pale yellow solid ($R_f = 0.2$, 250 mg, 35% yield): mp 50-52°C; NMR ($CDCl_3$, 300 MHz): 12.35 (br.s, 1H, 7.15-7.00 (m, 3H), 4.40 (q, 2H, $J = 7$), 4.30 (q, 2H, $J = 7$), 2.4, 2.35, 2.3, 2.2, 2.1 (5 s, 12H), 1.4 (t, 3H, $J = 7$), 1.35-1.25 (m, 3H); CI-HRMS: Calcd: 411.2032, Found: 411.2023.

10

EXAMPLE 6

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

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

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

20 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
25 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
30 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 ($CDCl_3$, 300 MHz): 7.55 (d, 1H, $J = 1$), 7.38 (dd, 1H, $J = 7, 1$), 7.30 (d, 1H, $J = 7$),
35 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

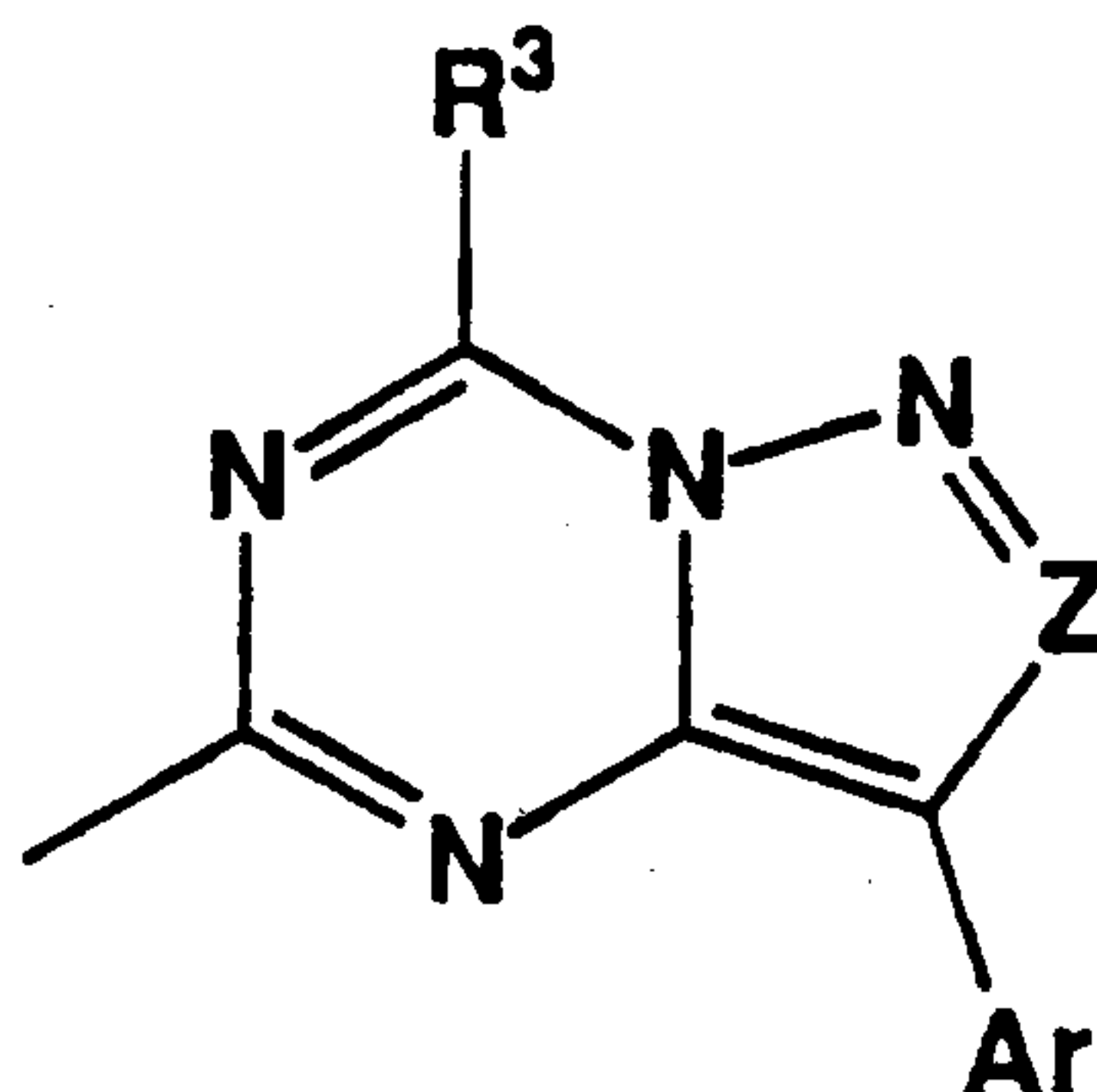
B. 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

A mixture of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Part A, 570 mg, 1.74 mmol), 1,3-dimethoxypropyl-2-aminopropane (25mg, 2.08 mmol) and ethanol (10 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was poured onto water (25 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over 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), 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



5	Ex.	Z	R ₃	Ar	mp (°C)
	6 ^a	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	118-120
	7 ^b	C-Me	NHCHPr ₂	2,4-Cl ₂ -Ph	114-116
	8 ^c	C-Me	NEtBu	2,4-Cl ₂ -Ph	oil
	9 ^d	C-Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Cl ₂ -Ph	oil
10	10 ^e	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	oil
	11 ^f	C-Me	NH-3-heptyl	2,4-Cl ₂ -Ph	90-92
	12 ^g	C-Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	179-181
	13 ^h	C-Me	NEt ₂	2,4-Cl ₂ -Ph	133-134
	14 ⁱ	C-Me	NHCH(CH ₂ OEt) ₂	2,4-Cl ₂ -Ph	oil
15	15 ^j	C-Me	NH-3-pentyl	2,4-Cl ₂ -Ph	139-140
	16 ^k	C-Me	NMePh	2,4-Cl ₂ -Ph	60-62
	17 ^l	C-Me	NPr ₂	2,4-Cl ₂ -Ph	oil
	18 ^m	C-Me	NH-3-hexyl	2,4-Cl ₂ -Ph	130-132
	19	C-Me	morpholino	2,4-Cl ₂ -Ph	
20	20	C-Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Cl ₂ -Ph	
	21	C-Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Cl ₂ -Ph	
	22	C-Me	NH-4-tetrahydropyranyl	2,4-Cl ₂ -Ph	
	23	C-Me	NH-cyclopentyl	2,4-Cl ₂ -Ph	
	24	C-Me	1,2,3,4-tetrahydro- isoquinolinyl	2,4-Cl ₂ -Ph	
25	25	C-Me	CH ₂ -(1,2,3,4-tetrahydro- isoquinolinyl)	2,4-Cl ₂ -Ph	
	26 ⁿ	C-Me	OEt	2,4-Cl ₂ -Ph	141-143
	27	C-Me	OCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	

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	28	C-Me	OCH ₂ Ph	2,4-Cl ₂ -Ph	
	29	C-Me	O-3-pentyl	2,4-Cl ₂ -Ph	
	30	C-Me	SEt	2,4-Cl ₂ -Ph	
	31	C-Me	S(O)Et	2,4-Cl ₂ -Ph	
5	32	C-Me	SO ₂ Et	2,4-Cl ₂ -Ph	
	33	C-Me	CH(CO ₂ Et) ₂	2,4-Cl ₂ -Ph	
	34	C-Me	C(Et)(CO ₂ Et) ₂	2,4-Cl ₂ -Ph	
	35	C-Me	CH(Et)CH ₂ OH	2,4-Cl ₂ -Ph	
	36	C-Me	CH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	
10	37	C-Me	CONMe ₂	2,4-Cl ₂ -Ph	
	38	C-Me	COCH ₃	2,4-Cl ₂ -Ph	
	39	C-Me	CH(OH)CH ₃	2,4-Cl ₂ -Ph	
	40	C-Me	C(OH)Ph-3-pyridyl	2,4-Cl ₂ -Ph	
	41	C-Me	Ph	2,4-Cl ₂ -Ph	
15	42	C-Me	2-CF ₃ -Ph	2,4-Cl ₂ -Ph	
	43	C-Me	2-Ph-Ph	2,4-Cl ₂ -Ph	
	44	C-Me	3-pentyl	2,4-Cl ₂ -Ph	
	45	C-Me	cyclobutyl	2,4-Cl ₂ -Ph	
	46	C-Me	3-pyridyl	2,4-Cl ₂ -Ph	
20	47	C-Me	CH(Et)CH ₂ CONMe ₂	2,4-Cl ₂ -Ph	
	48	C-Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Cl ₂ -Ph	
	49 ^o	C-Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph	125-127
	50	C-Me	NHCHPr ₂	2,4,6-Me ₃ -Ph	
	51	C-Me	NEtBu	2,4,6-Me ₃ -Ph	
25	52	C-Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4,6-Me ₃ -Ph	
	53 ^{ae}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph	123-124
	54	C-Me	NH-3-heptyl	2,4,6-Me ₃ -Ph	
	55 ^{ac}	C-Me	NHCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph	145-146
	56 ^{ah}	C-Me	NEt ₂	2,4,6-Me ₃ -Ph	88-90
30	57 ^{ai}	C-Me	NHCH(CH ₂ OEt) ₂	2,4,6-Me ₃ -Ph	132-134
	58 ^{ad}	C-Me	NH-3-pentyl	2,4,6-Me ₃ -Ph	134-135
	59	C-Me	NMePh	2,4,6-Me ₃ -Ph	
	60	C-Me	NPr ₂	2,4,6-Me ₃ -Ph	
	61	C-Me	NH-3-hexyl	2,4,6-Me ₃ -Ph	
35	62	C-Me	morpholino	2,4,6-Me ₃ -Ph	
	63	C-Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4,6-Me ₃ -Ph	

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	64	C-Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4,6-Me ₃ -Ph	
	65	C-Me	NH-4-tetrahydropyranyl	2,4,6-Me ₃ -Ph	
	66	C-Me	NH-cyclopentyl	2,4,6-Me ₃ -Ph	
	67	C-Me	1,2,3,4-tetrahydro-	2,4,6-Me ₃ -Ph	
5			isoquinolinyl		
	68	C-Me	CH ₂ -(1,2,3,4-tetrahydro-	2,4,6-Me ₃ -Ph	
			isoquinolinyl)		
	69	C-Me	OEt	2,4,6-Me ₃ -Ph	
	70	C-Me	OCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph	
10	71	C-Me	OCH ₂ Ph	2,4,6-Me ₃ -Ph	
	72	C-Me	O-3-pentyl	2,4,6-Me ₃ -Ph	
	73	C-Me	SEt	2,4,6-Me ₃ -Ph	
	74	C-Me	S(O)Et	2,4,6-Me ₃ -Ph	
	75	C-Me	SO ₂ Et	2,4,6-Me ₃ -Ph	
15	76	C-Me	CH(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph	
	77	C-Me	C(Et)(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph	
	78	C-Me	CH(Et)CH ₂ OH	2,4,6-Me ₃ -Ph	
	79	C-Me	CH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph	
	80	C-Me	CONMe ₂	2,4,6-Me ₃ -Ph	
20	81	C-Me	COCH ₃	2,4,6-Me ₃ -Ph	
	82	C-Me	CH(OH)CH ₃	2,4,6-Me ₃ -Ph	
	83	C-Me	C(OH)Ph-3-pyridyl	2,4,6-Me ₃ -Ph	
	84	C-Me	Ph	2,4,6-Me ₃ -Ph	
	85	C-Me	2-CF ₃ -Ph	2,4,6-Me ₃ -Ph	
25	86	C-Me	2-Ph-Ph	2,4,6-Me ₃ -Ph	
	87	C-Me	3-pentyl	2,4,6-Me ₃ -Ph	
	88	C-Me	cyclobutyl	2,4,6-Me ₃ -Ph	
	89	C-Me	3-pyridyl	2,4,6-Me ₃ -Ph	
	90	C-Me	CH(Et)CH ₂ CONMe ₂	2,4,6-Me ₃ -Ph	
30	91	C-Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4,6-Me ₃ -Ph	
	92 ^P	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	44-45
	93 ^Q	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	oil
	94 ^R	C-Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	102-104
	95 ^S	C-Me	NH-3-pentyl	2,4-Me ₂ -Ph	102-104
35	96 ^t	C-Me	NEt ₂	2,4-Me ₂ -Ph	oil
	97 ^u	C-Me	N(CH ₂ CN) ₂	2,4-Me ₂ -Ph	148-150

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	98 ^v	C-Me	NHCH(Me)CH ₂ OMe	2,4-Me ₂ -Ph	102-104
	99 ^w	C-Me	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	oil
	100 ^x	C-Me	NPr-c-C ₃ H ₅	2,4-Me ₂ -Ph	oil
	101 ^y	C-Me	NHCH(Me)CH ₂ NMe ₂	2,4-Me ₂ -Ph	47-48
5	102 ^z	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	117-118
	103 ^{aa}	C-Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	oil
	104 ^{ab}	C-Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	oil
	105	C-Me	NHCHPr ₂	2,4-Me ₂ -Ph	
	106	C-Me	NEtBu	2,4-Me ₂ -Ph	
10	107	C-Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Me ₂ -Ph	
	108	C-Me	NH-3-heptyl	2,4-Me ₂ -Ph	
	109	C-Me	NEt ₂	2,4-Me ₂ -Ph	
	110	C-Me	NHCH(CH ₂ OEt) ₂	2,4-Me ₂ -Ph	
	111	C-Me	NH-3-pentyl	2,4-Me ₂ -Ph	
15	112	C-Me	NMePh	2,4-Me ₂ -Ph	
	113	C-Me	NPr ₂	2,4-Me ₂ -Ph	
	114	C-Me	NH-3-hexyl	2,4-Me ₂ -Ph	
	115	C-Me	morpholino	2,4-Me ₂ -Ph	
	116	C-Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Me ₂ -Ph	
20	117	C-Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Me ₂ -Ph	
	118	C-Me	NH-4-tetrahydropyranyl	2,4-Me ₂ -Ph	
	119	C-Me	NH-cyclopentyl	2,4-Me ₂ -Ph	
	120	C-Me	1,2,3,4-tetrahydro- isoquinolinyl	2,4-Me ₂ -Ph	
25	121	C-Me	CH ₂ -(1,2,3,4-tetrahydro- isoquinolinyl)	2,4-Me ₂ -Ph	
	122	C-Me	OEt	2,4-Me ₂ -Ph	
	123	C-Me	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	
	124	C-Me	OCH ₂ Ph	2,4-Me ₂ -Ph	
30	125	C-Me	O-3-pentyl	2,4-Me ₂ -Ph	
	126	C-Me	SEt	2,4-Me ₂ -Ph	
	127	C-Me	S(O)Et	2,4-Me ₂ -Ph	
	128	C-Me	SO ₂ Et	2,4-Me ₂ -Ph	
3		C-Me	CH(CO ₂ Et) ₂	2,4-Me ₂ -Ph	50-52
35	129	C-Me	C(Et)(CO ₂ Et) ₂	2,4-Me ₂ -Ph	

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	130	C-Me	CH(Et)CH ₂ OH	2,4-Me ₂ -Ph	
	131	C-Me	CH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	
	132	C-Me	CH(Et)CH ₂ OEt	2,4-Me ₂ -Ph	
	133	C-Me	CONMe ₂	2,4-Me ₂ -Ph	
5	134	C-Me	COCH ₃	2,4-Me ₂ -Ph	
	135	C-Me	CH(OH)CH ₃	2,4-Me ₂ -Ph	
	136	C-Me	C(OH)Ph-3-pyridyl	2,4-Me ₂ -Ph	
	137	C-Me	Ph	2,4-Me ₂ -Ph	
	138	C-Me	2-CF ₃ -Ph	2,4-Me ₂ -Ph	
10	139	C-Me	2-Ph-Ph	2,4-Me ₂ -Ph	
	140	C-Me	3-pentyl	2,4-Me ₂ -Ph	
	141	C-Me	cyclobutyl	2,4-Me ₂ -Ph	
	142	C-Me	3-pyridyl	2,4-Me ₂ -Ph	
	143	C-Me	CH(Et)CH ₂ CONMe ₂	2,4-Me ₂ -Ph	
15	144	C-Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Me ₂ -Ph	
	145 ^{bc}	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4-MeO-Ph	45-46
	146 ^{bd}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-MeO-Ph	oil
	147 ^{be}	C-Me	NHCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph	86-88
	148 ^{bf}	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-MeO-Ph	oil
20	149	C-Me	OCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph	
	150 ^{af}	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-MeO-Ph	88-90
	151 ^{al}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-MeO-Ph	oil
	152 ^{ag}	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph	95-97
	153	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-MeO-Ph	
25	154	C-Me	OCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph	
	155	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph	
	156	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph	oil
	157	C-Me	NHCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph	
	158	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-NMe ₂ -Ph	
30	159	C-Me	OCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph	
	160	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph	
	161	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph	
	162	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph	
	163	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-NMe ₂ -Ph	
35	164	C-Me	OCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph	
	165	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph	

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	166	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph	
	167	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph	
	168	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-i-Pr-Ph	
	169	C-Me	OCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph	
5	170	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-Me-Ph	
	171	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-Me-Ph	
	172	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4-Me-Ph	
	173	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-Me-Ph	
	174	C-Me	OCH(Et)CH ₂ OMe	2-Br-4-Me-Ph	
10	175 ^{ar}	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4-Br-Ph	108-109
	176	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-Br-Ph	
	177	C-Me	NHCH(Et)CH ₂ OMe	2-Me-4-Br-Ph	
	178	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-Br-Ph	
	179	C-Me	OCH(Et)CH ₂ OMe	2-Me-4-Br-Ph	
15	180	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph	
	181	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph	
	182	C-Me	NHCH(CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph	
	183	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph	
	184	C-Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph	
20	185	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph	
	186	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph	
	187	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph	
	188	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph	
	189	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph	
25	190	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph	
	191	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph	
	192	C-Me	NHCH(CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph	
	193	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph	
	194	C-Me	NHCH(CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph	
30	195	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph	
	196	C-Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl	
	197	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl	
	198	C-Me	NHCH(CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph	
	199	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph	
35	200	C-Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph	
	201	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph	

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	202	C-Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	203	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	204	C-Me	NHCH(CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	205	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
5	206	C-Me	NHCH(CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	207	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	208	C-Me	NHCH(CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	209	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	210	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-N(Me) ₂ -6-MeO-Ph
10	211	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-N(Me) ₂ -6-MeO-Ph
	212	C-Me	NHCH(CH ₂ OMe) ₂	2,4-[SMe] ₂ -Ph
	213	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-[SMe] ₂ -Ph
	214	C-Me	NHCH(CH ₂ OMe) ₂	2,4-[SO ₂ Me] ₂ -Ph
	215	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-[SO ₂ Me] ₂ -Ph
15	216	C-Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	217	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	218	C-Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	219	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	220	C-Me	NHCH(CH ₂ OMe) ₂	2-N(Me) ₂ -4-Me-Ph
20	221	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-N(Me) ₂ -4-Me-Ph
	222	C-Me	NHCH(CH ₂ OMe) ₂	2-MeS-4,6-(Me) ₂ -Ph
	223	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeS-4,6-(Me) ₂ -Ph
	224	C-Me	NHCH(CH ₂ OMe) ₂	2-(CH ₃ CO)-4,6-(Me) ₂ -Ph
	225	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-(CH ₃ CO)-4,6-(Me) ₂ -Ph
25	226	H	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	227	H	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	228	CF ₃	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	229	CF ₃	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	230	N	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
30	231	N	NHCHPr ₂	2,4,6-Me ₃ -Ph
	232	N	NEtBu	2,4,6-Me ₃ -Ph
	233	N	NPr(CH ₂ -c-C ₃ H ₅)	2,4,6-Me ₃ -Ph
	234	N	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
	235	N	NH-3-heptyl	2,4,6-Me ₃ -Ph
35	236	N	NHCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	237	N	NEt ₂	2,4,6-Me ₃ -Ph

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	238	N	NHCH(CH ₂ OEt) ₂	2,4,6-Me ₃ -Ph
	239	N	NH-3-pentyl	2,4,6-Me ₃ -Ph
	240	N	NMePh	2,4,6-Me ₃ -Ph
	241	N	NPr ₂	2,4,6-Me ₃ -Ph
5	242	N	NH-3-hexyl	2,4,6-Me ₃ -Ph
	243	N	morpholino	2,4,6-Me ₃ -Ph
	244	N	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4,6-Me ₃ -Ph
	245	N	NHCH(CH ₂ Ph)CH ₂ OMe	2,4,6-Me ₃ -Ph
	246	N	NH-4-tetrahydropyranyl	2,4,6-Me ₃ -Ph
10	247	N	NH-cyclopentyl	2,4,6-Me ₃ -Ph
	248	N	1,2,3,4-tetrahydro- isoquinolinyl	2,4,6-Me ₃ -Ph
	249	N	CH ₂ -(1,2,3,4-tetrahydro- isoquinolinyl)	2,4,6-Me ₃ -Ph
15	250	N	OEt	2,4,6-Me ₃ -Ph
	251	N	OCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	252	N	OCH ₂ Ph	2,4,6-Me ₃ -Ph
	253	N	O-3-pentyl	2,4,6-Me ₃ -Ph
	254	N	SEt	2,4,6-Me ₃ -Ph
20	255	N	S(O)Et	2,4,6-Me ₃ -Ph
	256	N	SO ₂ Et	2,4,6-Me ₃ -Ph
	257	N	CH(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
	258	N	C(Et)(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
	259	N	CH(Et)CH ₂ OH	2,4,6-Me ₃ -Ph
25	260	N	CH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	261	N	CONMe ₂	2,4,6-Me ₃ -Ph
	262	N	COCH ₃	2,4,6-Me ₃ -Ph
	263	N	CH(OH)CH ₃	2,4,6-Me ₃ -Ph
	264	N	C(OH)Ph-3-pyridyl	2,4,6-Me ₃ -Ph
30	265	N	Ph	2,4,6-Me ₃ -Ph
	266	N	2-CF ₃ -Ph	2,4,6-Me ₃ -Ph
	267	N	2-Ph-Ph	2,4,6-Me ₃ -Ph
	268	N	3-pentyl	2,4,6-Me ₃ -Ph
	269	N	cyclobutyl	2,4,6-Me ₃ -Ph
35	270	N	3-pyridyl	2,4,6-Me ₃ -Ph
	271	N	CH(Et)CH ₂ CONMe ₂	2,4,6-Me ₃ -Ph

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	272	N	CH(Et)CH ₂ CH ₂ NMe ₂	2,4,6-Me ₃ -Ph
	273	N	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	274	N	NHCHPr ₂	2,4-Me ₂ -Ph
	275	N	NEtBu	2,4-Me ₂ -Ph
5	276	N	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Me ₂ -Ph
	277	N	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	278	N	NH-3-heptyl	2,4-Me ₂ -Ph
	279	N	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	280	N	NEt ₂	2,4-Me ₂ -Ph
10	281	N	NHCH(CH ₂ OEt) ₂	2,4-Me ₂ -Ph
	282	N	NH-3-pentyl	2,4-Me ₂ -Ph
	283	N	NMePh	2,4-Me ₂ -Ph
	284	N	NPr ₂	2,4-Me ₂ -Ph
	285	N	NH-3-hexyl	2,4-Me ₂ -Ph
15	286	N	morpholino	2,4-Me ₂ -Ph
	287	N	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Me ₂ -Ph
	288	N	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Me ₂ -Ph
	289	N	NH-4-tetrahydropyranyl	2,4-Me ₂ -Ph
	290	N	NH-cyclopentyl	2,4-Me ₂ -Ph
20	291	N	1,2,3,4-tetrahydro- isoquinolinyl	2,4-Me ₂ -Ph
	292	N	CH ₂ -(1,2,3,4-tetrahydro- isoquinolinyl)	2,4-Me ₂ -Ph
	293	N	OEt	2,4-Me ₂ -Ph
25	294	N	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	295	N	OCH ₂ Ph	2,4-Me ₂ -Ph
	296	N	O-3-pentyl	2,4-Me ₂ -Ph
	297	N	SEt	2,4-Me ₂ -Ph
	298	N	S(O)Et	2,4-Me ₂ -Ph
30	299	N	SO ₂ Et	2,4-Me ₂ -Ph
	300	N	CH(CO ₂ Et) ₂	2,4-Me ₂ -Ph
	301	N	C(Et)(CO ₂ Et) ₂	2,4-Me ₂ -Ph
	302	N	CH(Et)CH ₂ OH	2,4-Me ₂ -Ph
	303	N	CH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
35	304	N	CONMe ₂	2,4-Me ₂ -Ph
	305	N	COCH ₃	2,4-Me ₂ -Ph

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	306	N	CH(OH)CH ₃	2,4-Me ₂ -Ph	
	307	N	C(OH)Ph-3-pyridyl	2,4-Me ₂ -Ph	
	308	N	Ph	2,4-Me ₂ -Ph	
	309	N	2-CF ₃ -Ph	2,4-Me ₂ -Ph	
5	310	N	2-Ph-Ph	2,4-Me ₂ -Ph	
	311	N	3-pentyl	2,4-Me ₂ -Ph	
	312	N	cyclobutyl	2,4-Me ₂ -Ph	
	313	N	3-pyridyl	2,4-Me ₂ -Ph	
	314	N	CH(Et)CH ₂ CONMe ₂	2,4-Me ₂ -Ph	
10	315	N	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Me ₂ -Ph	
	316 ^{an}	C-Me	NEt ₂	2-Br-4-MeO-Ph	oil
	317 ^{am}	C-Me	NH-3-pentyl	2-Br-4-MeO-Ph	oil
	318 ^{aj}	C-Me	NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2,4,6-Me ₃ -Ph	101-103
	319 ^{ao}	C-Me	NH(c-C ₃ H ₅)	2,4-Me ₂ -Ph	oil
15	320 ^{ak}	C-Me	morpholino	2,4,6-Me ₃ -Ph	139-141
	321 ^{ap}	C-Me	NHCH(CH ₂ OMe) ₂	2-CN-4-Me-Ph	152-153
	322 ^{aq}	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4,6-Me ₃ -Ph	149-151
	324 ^{as}	C-Me	NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-Br-Ph	115-117
	325 ^{at}	C-Me	NHCH(CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph	55-57
20	326 ^{au}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph	72
	327 ^{av}	C-Me	NH-3-pentyl	2,5-Me ₂ -4-MeO-Ph	45-47
	328 ^{aw}	C-Me	NEt ₂	2,5-Me ₂ -4-MeO-Ph	oil
	329 ^{ax}	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MePh	80-81
	330 ^{ay}	C-Me	NCH(Et)CH ₂ OMe	2-Cl-4-MePh	77-79
25	331 ^{az}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MePh	oil
	332 ^{ba}	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Cl-4-MePh	139-140
	333 ^{bb}	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,5-Me ₂ -4-MeOPh	120-122
	334 ^{bg}	C-Me	NEt ₂	2-Me-4-MeOPh	oil
	335 ^{bh}	C-Me	OEt	2-Me-4-MeOPh	oil
30	336 ^{bi}	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-MeOPh	oil
	337 ^{bj}	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2-Me-4-MeOPh	129
	338 ^{bk}	C-Me	NHCH(CH ₂ CH ₂ OEt) ₂	2-Me-4-MeOPh	amorph.
	339	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph	109-110
	340	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2,4-Cl ₂ -Ph	93-94
35	341	C-Me	NH-3-pentyl	2-Me-4-BrPh	118-119
	342	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-BrPh	oil

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	343	C-Me	NHCH(CH ₂ -iPr)CH ₂ OMe	2,4-Me ₂ -Ph	oil
	344	C-Me	NHCH(Pr)CH ₂ OMe	2,4-Me ₂ -Ph	94-95
	345	C-Me	NHCH(Et)CH ₂ OEt	2,4-Me ₂ -Ph	76-77
	346	C-Me	NHCH(CH ₂ OMe)CH ₂ CH ₂ OMe	2-Me-4-Me ₂ NPh	oil
5	347	C-Me	NEt ₂	2-Me-4-ClPh	oil
	348	C-Me	NH-3-pentyl	2-Me-4-ClPh	122-124
	349	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-ClPh	oil
	350	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4-ClPh	122-123
	351	C-Me	NEt ₂	2-Me-4-ClPh	oil
10	352	C-Me	NEt ₂	2-Cl-4-MePh	oil
	353	C-Me	NH-3-pentyl	2-Cl-4-MePh	120-121
	354	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh	
	355 ^{bl}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh	oil
	356 ^{bm}	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh	108-110
15	357 ^{bn}	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh	127-129
	358 ^{bo}	C-Me	NEt ₂	2-Cl-4-MeOPh	oil
	359 ^{bp}	C-Me	NH-3-pentyl	2-Cl-4-MeOPh	77-79
	360	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh	
	361	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh	
20	362	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh	
	363	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh	
	364	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	365	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	366	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph	
25	367	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph	
	368	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph	
	369	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,5-(MeO) ₂ Ph	
	370	C-Me	NEt ₂	2-Cl-4,5-(MeO) ₂ Ph	
	371	C-Me	NH-3-pentyl	2-Cl-4,5-(MeO) ₂ Ph	
30	372	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph	
	373	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph	
	374 ^{bq}	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph	137-138
	375	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph	
	376 ^{br}	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph	147-148
35	377	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,5-(MeO) ₂ Ph	
	378 ^{bs}	C-Me	NEt ₂	2-Br-4,5-(MeO) ₂ Ph	52-58

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	379	C-Me	NH-3-pentyl	2-Br-4,5-(MeO) ₂ Ph
	380	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	381	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	382	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
5	383	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
	384	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
	385	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,6-(MeO) ₂ Ph
	386	C-Me	NEt ₂	2-Cl-4,6-(MeO) ₂ Ph
	387	C-Me	NH-3-pentyl	2-Cl-4,6-(MeO) ₂ Ph
10	388	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
	389	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,6-(MeO) ₂ Ph
	390	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	391	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	392	C-Me	NHCH(Et)CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
15	393	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Me-4,6-(MeO) ₂ Ph
	395	C-Me	NEt ₂	2-Me-4,6-(MeO) ₂ Ph
	396	C-Me	NH-3-pentyl	2-Me-4,6-(MeO) ₂ Ph
	397	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
	398	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
20	399	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,6-(MeO) ₂ Ph
	400	C-Me	NEt ₂	2-Br-4,6-(MeO) ₂ Ph
	401	C-Me	NH-3-pentyl	2-Br-4,6-(MeO) ₂ Ph
	402	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4,6-(MeO) ₂ Ph
	403	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4,6-(MeO) ₂ Ph
25	404	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	405	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	406	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	407	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	408	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
30	409	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	410	C-Me	NEt ₂	2-MeO-4-MePh
	411	C-Me	NH-3-pentyl	2-MeO-4-MePh
	412	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	413	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
35	414	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	415	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh

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	416	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh	
	417	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh	
	418	C-Me	NEt ₂	2-MeO-4-MePh	
	419	C-Me	NH-3-pentyl	2-MeO-4-MePh	
5	420	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh	
	421	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh	
	423 ^{bt}	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-ClPh	oil
	424	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh	
	425	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-ClPh	
10	426	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-ClPh	
	427	C-Me	NEt ₂	2-MeO-4-ClPh	
	428	C-Me	NH-3-pentyl	2-MeO-4-ClPh	
	429	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-ClPh	
	430	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-ClPh	

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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.
- 20 b) CI-HRMS: Calcd: 406.1565, Found: 405.1573 (M + H); Analysis Calcd: C: 59.11; H: 6.20; N: 17.23; Cl: 17.45; Found: C: 59.93; H: 6.34; N: 16.50; Cl: 16.95; NMR (CDCl₃, 300 MHz): 0.95 (t, J = 8, 4H), 1.30-1.40 (m, 4H), 1.50-1.75 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.30-4.45 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H)
- 25 c) CI-HRMS: Calcd: 392.1409, Found: 392.1388 (M + H); NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 3H), 1.35 (t, J = 8, 3H), 1.41 (q, J = 8, 2H), 1.65-1.85 (m, 2H), 2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.20 (m, 4H), 7.30 (s, 2H), 7.50 (s, 1H).
- 30 d) CI-HRMS: Calcd: 404.1409, Found: 404.1408 (M + H); NMR(CDCl₃, 300 MHz): 0.35-0.45 (m, 2H), 0.52-0.62 (m, 2H), 0.98 (t, J = 8, 3H), 1.70-1.90 (m, 2H),
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- 2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.02 (m, 2H),
4.02-4.20 (m, 2H), 7.30 (s, 2H), 7.50 (s, 1H).
- 5 e) CI-HRMS: Calcd: 424.1307, Found: 424.1307 (M + H);
NMR (CDCl₃, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H),
3.40 (s, 6H), 3.75 (t, J = 8, 4H), 4.20-4.45 (m,
4H), 7.30 (s, 2H), 7.50 (s, 1H).
- 10 f) CI-HRMS: Calcd: 406.1565, Found: 406.1578 (M + H);
NMR (CDCl₃, 300 MHz): 0.90 (t, J = 8, 3H), 1.00 (t,
J = 8, 3H), 1.28-1.45 (m, 4H), 1.50-1.80 (m, 4H),
2.35 (s, 3H), 2.50 (s, 3H), 4.20-4.35 (m, 1H),
6.10-6.23 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 15 g) CI-HRMS: Calcd: 394.1201, Found: 394.1209 (M + H);
NMR (CDCl₃, 300 MHz): 1.02 (t, J = 8, 3H), 1.65-
1.90 (m, 2H), 2.35 (s, 3H), 2.48 (s, 3H), 3.40 (s,
3H), 3.50-3.60 (m, 2H), 4.35-4.45 (brs, 1H), 6.50-
6.60 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 20 h) CI-HRMS: Calcd: 364.1096, Found: 364.1093 (M + H);
Analysis: Calcd: C: 56.05; H: 5.27; N: 19.23; Cl:
19.46; Found: C: 55.96; H: 5.24; N: 18.93; Cl:
19.25;
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.30 (s,
3H), 2.40 (s, 3H), 3.95-4.15 (m, 4H), 7.30 (s, 2H),
7.50 (d, J = 1, 1H).
- 25 i) CI-HRMS: Calcd: 438.1464, Found: 438.1454 (M + H);
NMR (CDCl₃, 300 MHz): 1.22 (t, J = 8, 6H), 2.35 (s,
3H), 2.47 (s, 3H), 3.39 (q, J = 8, 4H), 3.65 (dd, J
= 8, 1, 2H), 3.73 (dd, J = 8, 1, 2H), 4.55-4.65 (m,
1H), 6.75 (d, J = 8, 1H), 7.30 (d, J = 1, 2H), 7.50
(s, 1H).
- 30 j) CI-HRMS: Calcd: 378.1252, Found: 378.1249 (M + H);
Analysis: Calcd: C: 57.15; H: 5.61; N: 18.51; Cl:
18.74; Found: C: 57.56; H: 5.65; N: 18.35; Cl:
18.45;
NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-
35 1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.35 (s, 3H), 2.50

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- (s, 3H), 4.15-4.25 (m, 1H), 6.18 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 5 k) CI-HRMS: Calcd: 398.0939, Found: 398.0922 (M + H); Analysis: Calcd: C: 60.31; H: 4.30; N: 17.58; Cl: 17.80; Found: C: 60.29; H: 4.59; N: 17.09; Cl: 17.57; NMR (CDCl₃, 300 MHz): 2.05 (s, 3H), 2.50 (s, 3H), 3.78 (s, 3H), 7.20-7.45 (m, 7H), 7.50 (d, J = 1, 1H).
- 10 l) CI-HRMS: Calcd: 392.1409, Found: 392.1391 (M + H); NMR (CDCl₃, 300 MHz): 0.98 (t, J = 8, 6H), 1.70-1.85 (m, 4H), 2.30 (s, 3H), 2.40 (s, 3H), 3.80-4.10 (m, 4H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).
- 15 m) CI-HRMS: Calcd: 392.1409, Found: 392.1415 (M + H); Analysis: Calcd: C: 58.17; H: 5.92; N: 17.85; Cl: 18.07; Found: C: 58.41; H: 5.85; N: 18.10; Cl: 17.75; NMR (CDCl₃, 300 MHz): 0.90-1.05 (m, 6H), 1.35-1.55 (m, 2H), 1.55-1.85 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.20-4.35 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).
- 20 n) CI-HRMS: Calcd: 337.0623, Found: 337.0689 (M + H); Analysis: Calcd: C: 53.43; H: 4.18; N: 16.62; Cl: 21.03, Found: C: 53.56; H: 4.33; N: 16.56; Cl: 20.75; NMR (CDCl₃, 300 MHz): 1.60 (t, J = 8, 3H), 2.40 (s, 3H), 2.55 (s, 3H), 4.80 (q, J = 8, 2H), 7.30 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.55 (d, J = 1, 1H).
- 25 o) CI-HRMS: Calcd: 383.2321, Found: 383.2309 (M + H); NMR (CDCl₃, 300 MHz): 2.00 (s, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 3.45 (s, 6H), 3.61 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.94 (s, 2H).
- 30 p) CI-HRMS: Calcd: 370.2243, Found: 370.2246 (M + H);
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- Analysis: Calcd: C: 65.02; H: 7.38; N: 18.96;
Found: C: 65.22; H: 7.39; N: 18.71;
NMR (CDCl₃, 300 MHz): 2.18 (s, 3H), 2.30 (s, 3H),
2.45 (s, 3H), 3.45 (s, 6H), 3.60 (dd, J = 8, 8,
5 2H), 3.69 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H),
6.70 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.07 (d,
J = 8, 1H), 7.10 (s, 1H).
- q) CI-HRMS: Calcd: 384.2400, Found: 384.2393 (M + H);
NMR (CDCl₃, 300 MHz): 2.16 (s, 3H), 2.25 (s, 3H),
10 2.35 (s, 3H), 2.39 (s, 3H), 3.40 (s, 6H), 3.77 (t,
J = 8, 4H), 4.20-4.45 (m, 4H), 7.02 (d, J = 8, 1H)
7.05 (s, 1H), 7.10 (d, J = 7, 1H).
- r) CI-HRMS: Calcd: 354.2294, Found: 354.2271 (M + H);
Analysis: Calcd: C: 67.96; H: 7.71; N: 19.81;
15 Found: C: 67.56; H: 7.37; N: 19.60;
NMR (CDCl₃, 300 MHz): 1.03 (t, J = 8, 3H), 1.65-
1.88 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.35 (s,
3H), 2.45 (s, 3H), 3.40 (s, 3H), 3.50-3.62 (m, 2H),
20 4.30-4.45 (m, 1H), 6.51 (d, J = 8, 1H), 7.04 (d, J
= 8, 1H), 7.10 (d, J = 8, 1H), 7.12 (s, 1H).
- s) CI-HRMS: Calcd: 338.2345, Found: 338.2332 (M + H);
Analysis: Calcd: C: 71.18; H: 8.06; N: 20.75;
Found: C: 71.43; H: 7.80; N: 20.70;
NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-
25 1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.19 (s, 3H), 2.30
(s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 4.15-4.26 (m,
1H), 6.17 (d, J = 8, 1H), 7.06 (d, J = 8, 1H), 7.10
(d, J = 1, 1H), 7.13 (s, 1H).
- t) CI-HRMS: Calcd: 324.2188, Found: 324.2188 (M + H);
NMR (CDCl₃, 300 MHz): 1.25 (t, J = 8, 6H), 2.16 (s,
30 3H), 2.28 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H),
3.95-4.20 (m, 4H), 7.05 (dd, J = 8, 1, 1H), 7.07
(s, 1H), 7.10 (d, J = 1, 1H)
- u) CI-HRMS: Calcd: 346.1780, Found: 346.1785 (M + H);
35 Analysis: Calcd: C: 66.07; H: 5.54; N: 28.39;
Found: C: 66.07; H: 5.60; N: 27.81;

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- NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.32 (s, 3H)
2.17 (s, 3H), 2.52 (s, 3H), 5.25-5.35 (m, 4H), 7.08
(s, 2H), 7.15 (s, 1H).
- 5 v) CI-HRMS: Calcd: 340.2137, Found: 340.2137 (M + H);
Analysis: Calcd: C: 67.23; H: 7.42; N: 20.63;
Found: C: 67.11; H: 7.39; N: 20.26;
NMR (CDCl₃, 300 MHz): 1.40 (d, J = 8, 3H), 2.16 (s,
3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.47 (s, 3H), 3.42
(s, 3H), 3.50-3.60 (m, 2H), 4.50-4.15 (m, 1H), 6.56
10 (d, J = 8, 1H), 7.00-7.15 (m, 3H).
- w) CI-HRMS: Calcd: 355.2134, Found: 355.2134 (M + H);
NMR (CDCl₃, 300 MHz): 1.05 (t, J = 8, 3H), 1.85-
2.00 (m, 2H), 2.17 (s, 3H), 2.36 (s, 6H), 2.50 (s,
3H), 3.41 (s, 3H), 3.45 (dd, J = 8, 3, 1H), 3.82
15 (dd, J = 8, 1, 1H), 5.70-5.80 (m, 1H), 7.00-7.20
(m, 3H).
- x) CI-HRMS: Calcd: 364.2501, Found: 364.2501 (M + H);
NMR (CDCl₃, 300 MHz): 0.35-0.43 (m, 2H), 0.50-0.60
(m, 2H), 0.98 (t, J = 8, 3H), 1.20-1.30 (m, 1H),
20 1.72-1.90 (m, 2H), 2.18 (s, 3H) 2.28 (s, 3H), 2.35
(s, 3H), 2.40 (s, 3H), 3.88-4.03 (m, 2H), 4.03-4.20
(m, 2H), 7.00-7.15 (m, 3H).
- y) CI-HRMS: Calcd: 353.2454, Found: 353.2454 (M + H);
Analysis: Calcd: C: 68.15; H: 8.02; N: 23.84;
25 Found: C: 67.43; H: 7.81; N: 23.45;
NMR (CDCl₃, 300 MHz): 1.38 (d, J = 8, 3H), 2.18 (s,
3H), 2.30-2.40 (m, 12H), 2.47 93, 3H), 2.60-2.75
(m, 2H), 4.30-4.50 (m, 1H), 6.60-6.70 (m, 1H),
7.00-7.15 (m, 3H).
- 30 z) CI-HRMS: Calcd: 361.2140, Found: 361.2128 (M + H);
NMR (CDCl₃, 300 MHz): 0.75-0.83 (m, 2H), 1.00-1.10
(m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H),
2.47 (s, 3H), 2.85 (t, J = 8, 2H), 3.30-3.40 (m,
1H), 4.40-4.55 (m, 2H), 7.00-7.18 (m, 3H).
- 35 aa) CI-HRMS: Calcd: 363.2297, Found: 363.2311 (M + H);

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- 5 NMR (CDCl₃, 300 MHz): 1.01 (t, 3H, J=8), 1.75-1.90 (m, 2H), 2.15 (s, 3H), 2.19 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.98 (t, 2H, J = 8), 3.97-4.15 (m, 2H), 4.15-4.30 (m, 2H), 7.03 (d, 1H, 1H), 7.08 (d, 1H, J = 8), 7.10 (s, 1H).
- 10 ab) CI-HRMS: Calcd: 363.2297, Found: 363.2295 (M + H); NMR (CDCl₃, 300 MHz): 1.01 (t, 3H, J = 8), 1.35-1.55 (m, 2H), 1.75-1.90 (m, 2H), 2.15 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 2.46 (s, 3H), 4.10-4.30 (m, 2H), 4.95-5.10 (br s, 2H), 7.05 (d, 1H, J = 8), 7.10 (d, 1H, J = 8), 7.15 (s, 1H).
- 15 ac) CI-HRMS: Calcd: 368.2450, Found: 368.2436; Analysis: Calcd: C, 68.62, H, 7.95, N, 19.06; Found: C, 68.73, H, 7.97, N, 19.09; NMR (CDCl₃, 300 MHz): 1.05 (t, J = 8, 3H), 1.70-1.90 (m, 2H), 2.01 (d, J = 3, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46, 2.465 (s, s, 3H), 3.42, 3.48 (s, s, 3H), 3.53-3.63 (m, 2H), 4.35-4.45 (m, 1H), 6.73 (d, J = 8, 1H), 6.97 (s, 2H).
- 20 (ad) CI- HRMS: Calcd: 352.2501, Found: 352.2500 (M + H): Analysis: Calcd: C: 71.76; H: 8.33; N: 19.92, Found: C: 71.55; H: 8.15; N: 19.28; NMR (CDCl₃, 300 MHz): 1.01 (t, J = 8, 6H), 1.58 -1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.02 (s, 6H), 2.19 (s, 3H), 2.45 (s, 3H), 4.12-4.28 (m, 1H), 6.18 (d, J = 8, 1H), 6.95 (s, 2H).
- 25 (ae) CI- HRMS: Calcd: 398.2556, Found: 398.2551 (M + H); Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62, Found: C: 66.74; H: 7.79; N: 17.70; NMR (CDCl₃, 300 MHz): 2.00 (s, 6H), 2.12 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.40 (s, 6H), 3.78 (t, J = 8, 4H), 4.25-4.40 (m, 4H), 6.93 (s, 2H).
- 30 (af) CI-HRMS: Calcd: 450.1141, Found: 450.1133 (M + H); Analysis: Calcd: C: 50.67; H: 5.37; N: 15.55; Br: 17.74; Found: C: 52.36; H: 5.84; N: 14.90; Br: 17.44;
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- 5 NMR (CDCl₃, 300 MHz): 2.32 (s, 3H), 2.57 (s, 3H), 3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.69 (q, J = 8, 2H), 3.82 (s, 3H), 4.60-4.70 (m, 1H), 6.73 (d, J = 8, 1H), 6.93 (dd, J = 8, 1, 1H), 7.22 (d, J = 8, 1H).
- ag) CI-HRMS: Calcd: 434.1192, Found: 434.1169 (M + H); Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br: 18.40; Found: C: 52.57; H: 5.60; N: 15.98; Br: 18.22;
- 10 NMR (CDCl₃, 300 MHz): 1.00-1.07 (m, 3H), 1.65-1.85 (m, 2H), 2.35 (s, 3H), 2.46, 2.47 (s, s, 3H), 3.40, 3.45 (s, s, 3H), 3.83 (s, 3H), 4.35-4.45 (m, 1H), 6.55 (d, J = 8, 1H), 6.92 (dd, J = 8, 1, 1H), 7.20-7.30 (m, 2H).
- 15 ah) CI-HRMS: Calcd: 337.2266, Found: 337.2251 (M + H); Analysis: Calcd: C: 70.18; H: 8.06; N: 20.75; Found: C: 70.69; H: 7.66; N: 20.34; NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.01 (s, 6H), 2.15 (s, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 4.07 (q, J = 8, 4H), 6.93 (s, 2H).
- 20 ai) CI-HRMS: Calcd: 412.2713, Found: 412.2687 (M + H); Analysis: Calcd: C: 67.13; H: 8.08; N: 17.02; Found : C: 67.22; H: 7.85; N: 17.13; NMR (CDCl₃, 300 MHz): 1.24 (t, J = 8, 6H), 2.00 (s, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 3.60 (q, J = 8, 4H), 3.66 (dd, J = 8, 3, 2H), 3.75 (dd, J = 8, 3, 2H), 4.55-4.65 (m, 1H), 6.75 (d, J = 8, 1H), 6.95 (s, 2H).
- 25 aj) CI-HRMS: Calcd: 398.2556, Found: 398.2545 (M + H); Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62; Found: C: 66.87; H: 7.62; N: 17.75; NMR (CDCl₃, 300 MHz): 1.95-2.10 (m, 8H), 2.20 (s, 3H), 2.32 (s, 3H), 2.44 (s, 3H), 3.38 (s, 3H), 3.42 (s, 3H), 3.50-3.70 (m, 4H), 4.58-4.70 (m, 1H), 6.87 (d, J = 8, 1H), 6.95 (s, 2H).
- 30 ak) CI-HRMS: Calcd: 338.1981, Found: 338.1971 (M + H);
- 35

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- Analysis: Calcd: C: 67.63; H: 6.87; N: 20.06;
Found: C: 67.67; H: 6.82; N: 20.31;
NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.29 (s, 3H),
2.35 (s, 3H), 2.43 (s, 3H), 3.90 (t, J = 8, 4H),
4.35-4.45 (m, 4H), 7.00-7.15 (m, 3H).
- 5
- al) CI-HRMS: Calcd: 464.1297, Found: 464.1297 (M + H);
NMR (CDCl₃, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H),
3.40 (s, 6H), 3.75 (t, J = 8, 4H), 3.83 (s, 3H),
4.20-4.50 (m, 4H), 6.93 (dd, J = 8, 1, 1H), 7.20
10 (s, 1H), 7.24 (d, J = 1, 1H).
- am) CI-HRMS: Calcd: 418.1242, Found: 418.1223 (M + H);
NMR (CDCl₃, 300 MHz): 1.00 (t, d, J = 8, 1, 6H),
1.55-1.75 (m, 4H), 2.34 (s, 3H), 2.49 (s, 3H), 2.84
(s, 3H), 4.15-4.27 (m, 1H), 6.19 (d, J = 8, 1H),
15 6.93 (dd, J = 8, 1, 1H), 7.21-7.30 (m, 2H).
- an) CI-HRMS: Calcd: 404.1086, Found: 404.1079 (M + H);
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.28 (s,
3H), 2.40 (s, 3H), 3.83 (s, 3H), 3.90-4.08 (m, 2H),
4.08-4.20 (m, 2H), 6.92 (dd, J = 8, 1, 1H), 7.20-
20 7.25 (m, 2H).
- ao) CI-HRMS: Calcd: 308.1875, Found: 308.1872 (M + H);
NMR (CDCl₃, 300 MHz): 0.75-0.80 (m, 2H), 0.93-1.00
(m, 2H), 2.16 (s, 3H), 2.28 (s, 3H), 2.35 (s, 3H),
2.53 (s, 3H), 3.00-3.10 (m, 1H), 6.50-6.55 (m, 1H),
25 7.00-7.15 (m, 3H).
- ap) CI-HRMS: Calcd: 397.1988, Found: 397.1984 (M + H);
NMR (CDCl₃, 300 MHz): 2.43 (s, 3H), 2.50 (s, 3H),
3.43 (s, 3H), 3.61 (dd, J = 8, 8, 2H), 3.69 (dd, J =
8, 8, 2H), 3.88 (s, 3H), 4.58-4.70 (m, 1H), 6.75
30 (d, J = 8, 1H), 7.20 (dd, J = 8, 1, 1H), 7.25 (d, J
= 1, 1H), 7.40 (s, 1H).
- aq) CI-HRMS: Calcd: 375.2297, Found: 375.2286 (M + H);
Analysis: Calcd: C: 70.56; H: 7.01; N: 22.44;
Found: C: 70.49; H: 6.99; N: 22.45;
35 NMR (CDCl₃, 300 MHz): 0.79-0.85 (m, 2H), 1.00-1.05
(m, 1H), 2.00 (s, 6H), 2.19 (s, 3H), 2.32 (s, 3H),

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2.44 (s, 3H), 2.84 (t, J = 8, 2H), 3.30-3.40 (m, 1H), 4.50 (t, J = 8, 2H), 6.95 (s, 2H).

- ar) CI-HRMS: Calcd: 434.1192, Found: 434.1189 (M + H);
Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br: 18.40; Found: C: 52.75; H: 5.59; N: 16.09; Br: 18.67;
NMR (CDCl₃, 300 MHz): 2.19 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.43 (s, 6H), 3.60 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8, 8, 2H), 4.58-4.70 (m, 1H), 6.71 (d, J = 8, 1H), 7.08 (d, J = 8, 1H), 7.37 (dd, J = 8, 1, 1H), 7.45 (d, J = 1, 1H).
- as) CI-HRMS: Calcd: 448.1348, Found: 448.1332 (M + H);
Analysis: Calcd: C: 53.58; H: 5.85; N: 16.62; Br: 17.82; Found: C: 53.68; H: 5.74; N: 15.52; Br: 13.03;
NMR (CDCl₃, 300 MHz): 1.95-2.10 (m, 2H), 2.20 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.67 (m, 4H), 4.55-4.70 (m, 1H), 6.89 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.47 (d, J = 1, 1H).
- at) CI-HRMS: Calcd: 400.2349, Found: 400.2348 (M + H);
Analysis: Calcd: C: C: 63.14; H: 7.32; N: 17.53; Found: C: 63.40; H: 7.08; N: 17.14;
NMR (CDCl₃, 300 MHz): 2.16 (s, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46 (s, 3H), 3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.70 (q, J = 8, 2H), 3.85 (s, 3H), 4.59-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.76 (s, 1H), 6.96 (s, 1H).
- au) CI-HRMS: Calcd: 414.2505, Found: 414.2493 (M + H);
NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.19 (s, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 3.84 (s, 3H), 4.20-4.45 (m, 4H), 6.77 (s, 1H), 6.93 (s, 1H).
- av) CI-HRMS: Calcd: 368.2450, Found: 368.2447 (M + H);
NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-1.85 (m, 4H), 2.19 (s, 3H), 2.20 (s, 3H), 2.30 (s,

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3H), 2.47 (s, 3H), 3.88 (s, 3H), 4.10-4.30 (m, 1H), 6.15 (d, J = 8, 1H), 6.78 (s, 1H), 6.98 (s, 1H).

- aw) CI-HRMS: Calcd: 353.2216, Found: 353.2197 (M + H);
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.17 (s, 3H), 2.19 (s, 3H), 2.28 (s, 3H), 2.40 (s, 3H), 3.85 (s, 3H), 3.90-4.20 (m, 4H), 6.78 (s, 1H), 6.95 (s, 1H).
- 5
- ax) CI-HRMS: Calcd: 390.1697, Found: 390.1688 (M + H);
Analysis: Calcd: C: 58.53; H: 6.20; N: 17.96; Cl: 9.09; Found: C: 58.95; H: 6.28; N: 17.73; Cl: 9.15;
NMR (CDCl₃, 300 MHz): 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (s, 3H), 3.42 (s, 6H), 3.60 (dd, J = 8, 8, 2H), 3.68 (dd, J = 8, 8, 2H), 4.59-4.72 (m, 1H), 6.72 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.23 (d, J = 8, 1H), 7.32 (s, 1H).
- 10
- 15
- ay) CI-HRMS: Calcd: 374.1748, Found: 374.1735 (M + H);
Analysis: Calcd: C: 61.04; H: 6.47; N: 18.73; Cl: 9.48; Found: C: 61.47; H: 6.54; N: 18.23; Cl: 9.61;
NMR (CDCl₃, 300 MHz): 1.01 (t, J = 8, 3H), 1.62-1.88 (m, 4H), 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (d, J = 1, 3H), 3.40, 3.45 (s, s, 3H), 3.50-3.64 (m, 2H), 4.38-4.47 (m, 1H), 6.53 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.12 (s, 1H).
- 20
- az) CI-HRMS: Calcd: 404.1853, Found: 404.1839 (M + H);
NMR (CDCl₃, 300 MHz): 2.29 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.11 (d, J = 8, 1H), 7.22 (d, J = 8, 1H), 7.31 (s, 1H).
- 25
- ba) CI-HRMS: Calcd: 404.1853, Found: 404.1859 (M + H);
Analysis: C: 59.47; H: 6.50; N: 17.34; Cl: 8.79; Found: C: 59.73; H: 6.46; N: 17.10; Cl: 8.73;
NMR (CDCl₃, 300 MHz): 1.95-2.08 (m, 2H), 2.35 (s, 3H), 2.38 (s, 3H), 2.46 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.65 (m, 4H), 4.56-4.70 (m, 1H), 6.85 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.45 (d, J = 8, 1H), 7.32 (s, 1H).
- 30
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- bb) CI-HRMS: Calcd: 391.2246, Found: 391.2258 (M + H);
Analysis: C: 67.67; H: 6.71; N: 21.52; Found: C:
67.93; H: 6.70; N: 21.48;
NMR (CDCl₃, 300 MHz): 0.76-0.84 (m, 2H), 0.84-0.91
5 (m, 2H), 1.00-1.08 (m, 2H), 2.15 (s, 3H), 2.20 (s,
3H), 2.29 (s, 3H), 2.45 (s, 3H), 2.85 (t, J = 8,
2H), 3.28-3.30 (m, 1H), 3.85 (s, 3H), 6.78 (s, 1H),
6.95 (s, 1H).
- bc) CI-HRMS: Calcd: 386.2192, Found: 386.2181 (M + H);
10 Analysis: C: 62.32; H: 7.06; N: 18.17; Found: C:
62.48; H: 6.83; N: 18.15;
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.7 (br.d, 1H,
J = 8), 4.7-4.6 (m, 1H), 3.85 (s, 3H), 3.70-3.55
15 (m, 4H), 3.45 (s, 6H), 2.5 (s, 3H), 2.3 (s, 3H),
2.15 (s, 3H).
- bd) CI-HRMS: Calcd: 400.2349, Found: 400.2336 (M + H);
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 7), 6.85 (d,
1H, J = 1), 6.75 (dd, 1H, J = 7,1), 4.45-4.25
20 (br.s, 4H), 3.75 (t, 4H, J = 7), 3.4 (s, 6H), 2.4
(s, 3H), 2.25 (s, 3H), 2.15 (s, 3H).
- be) CI-HRMS: Calcd: 370.2243, Found: 370.2247 (M + H);
Analysis: C: 65.02; H: 7.38; N: 18.96; Found: C:
65.28; H: 7.27; N: 18.71;
25 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.5 (br. d, 1H,
J = 1), 4.5-4.3 (m, 1H), 3.85 (s, 3H), 3.65-3.5 (m,
2H), 3.4 (s, 2H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s,
3H), 1.9-1.7 (m, 2H), 1.05 (t, 3H, J = 7).
- 30 bf) CI-HRMS: Calcd: 379.2246, Found: 379.2248 (M + H);
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 4.3-4.0 (m, 4H),
3.85 (s, 3H), 3.0 (t, 2H, J = 7), 2.45 (s, 3H), 2.3
(s, 3H), 2.2 (s, 3H), 1.9-1.8 (m, 2H), 1.0 (t, 3H,
35 J = 7).
- bg) CI-HRMS: Calcd: 340.2137, Found: 340.2122 (M + H);

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- NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8, 1), 4.2-4.0 (br.m, 4H), 3.85 (s, 3H), 2.4 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.35 (t, 6H, J = 7).
- 5 bh) CI-HRMS: Calcd: 313.1665, Found: 313.6664 (M + H).
 bi) CI-HRMS: Calcd: 400.2349, Found: 400.2346 (M + H);
 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 7), 6.9-6.75 (m, 3H), 4.7-4.55 (m, 1H), 3.8 (s, 3H), 3.7-3.5 (m, 4H), 3.45 (s, 3H), 3.35 (s, 3H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 2.1-1.95 (m, 2H).
- 10 bj) CI-HRMS: Calcd: 377.2090, Found: 377.2092 (M + H);
 Analysis: C: 67.00; H: 6.44; N: 22.32; Found: C: 67.35; H: 6.44; N: 22.23;
 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8, 1), 4.55-4.4 (m, 2H), 3.85 (s, 3H), 3.4-3.3 (m, 1H), 2.85 (t, 2H, J = 7), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.1-1.0 (m, 2H), 0.85-0.75 (m, 2H).
- 15 bk) CI-HRMS: Calcd: 413.2427, Found: 413.2416 (M + H);
 20 NMR (CDCl₃, 300Hz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8, 1), 4.6 (m, 1H), 3.85 (s, 3H), 3.75-3.6 (m, 4H), 3.6 (q, 4H, J = 7), 2.5 (s, 3H), 2.3 s, 3H), 2.2 (s, 3H), 1.25 (t, 6H, J = 7).
- 25 bl) CI-HRMS: Calcd: 420.1802, Found: 420.1825 (M + H);
 bm) CI-HRMS: Calcd: 390.1697, Found: 390.1707 (M + H);
 bn) CI-HRMS: Calcd: 397.1465, Found: 397.1462 (M + H);
 bo) CI-HRMS: Calcd: 360.1513, Found: 360.1514 (M + H);
 bp) CI-HRMS: Calcd: 374.1748, Found: 374.1737 (M + H);
- 30 bq) CI-HRMS: Calcd: 479.1155, Found: 479.1154 (M + H);
 br) CI-HRMS: Calcd: 463.1219, Found: 463.1211 (M + H);
 Analysis Calcd: C: 51.96, H: 5.23, N, 15.15, Br: 17.28; Found: C: 52.29, H: 5.62, N: 14.79, Br: 17.47
- 35 bs) CI-HRMS: Calcd: 433.1113, Found: 433.1114 (M, ⁷⁹Br);
 bt) NH₃-CI MS: Calcd: 406, Found: 406 (M + H)+;

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NMR (CDCl₃, 300 MHz) : δ 7.28 (d, J=10Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.7 (d, J=9, 1H), 4.63 (m, 1H), 3.79 (s, 3H), 3.6 (m, 4H), 3.42 (s, 6H), 2.47 (s, 3H), 2.32 (s, 3H).

5

EXAMPLE 431

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)

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 taken up in toluene (10 mL) and trimethyl orthoacetate (0.36 g, 3 mmol) was added to the suspension. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and stirred for 16 hours. After being cooled to ambient temperature, the reaction mixture was concentrated in vacuo to give an oily solid. Column chromatography (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).

35

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,
5 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
10 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
15 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).

20

EXAMPLE 433

7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine
(Formula 1 where A is CH, R1 is Me, R3 is Cl,
25 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
30 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-
35 a]pyrimidine (900 mg, 84% yield) as a yellow oil: NMR

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(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).

5

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)

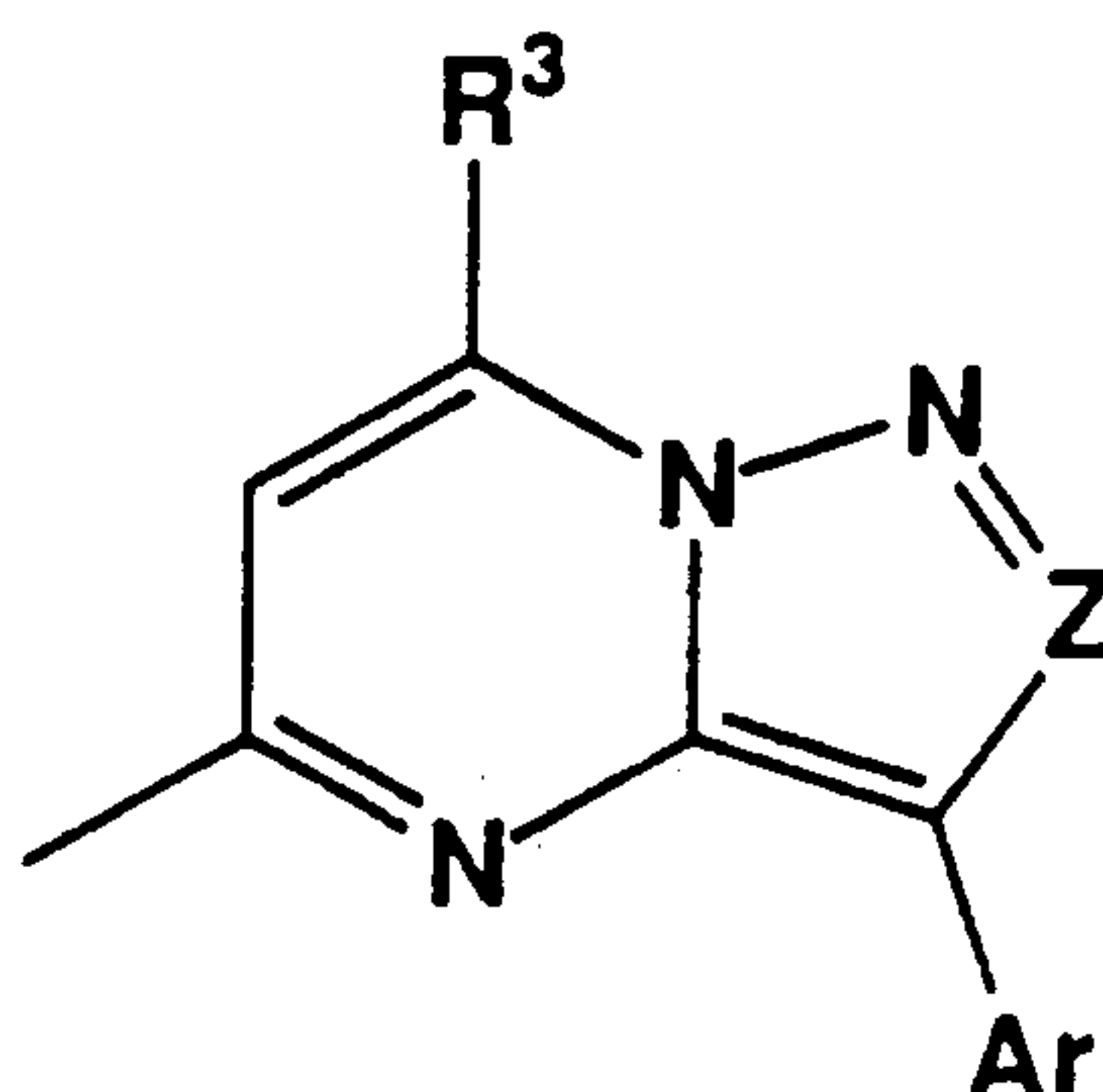
A solution of 3-pentylamine (394mg, 6.5 mmol) and 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (200 mg, 0.65 mmol) in dimethylsulfoxide (DMSO, 10 mL) was stirred at 150°C for 2 hours; then it was cooled to ambient temperature. The reaction mixture was then poured onto water (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 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.

30

The examples delineated in TABLE 2 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, EtOAc is ethyl acetate.

35

TABLE 2



5	Ex.	Z	R ₃	Ar	mp (°C)
	435 ^b	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	71-73
	436 ^c	C-Me	N(Bu)Et	2,4-Cl ₂ -Ph	86-87
	437 ^d	C-Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	110-111
	438 ^e	C-Me	N(Pr)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph	83-85
10	439 ^f	C-Me	NH-3-pentyl	2,4-Cl ₂ -Ph	175-176
	440 ^g	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	107
	441 ^h	C-Me	NHCH(Et) ₂	2,4-Me ₂ -Ph	oil
	442 ⁱ	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	103-105
	443 ^j	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	87-89
15	444 ^k	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	133(dec)
	445 ^l	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl,4-MePh	77-78
	446 ^m	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl,4-MePh	131-133
	447 ⁿ	C-Me	NHCH(Et) ₂	2-Cl,4-MePh	139-141
	448 ^o	C-Me	NEt ₂	2,4-Me ₂ -Ph	92-94
20	449 ^p	C-Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	143-144
	450 ^q	C-Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	115-117
	451 ^r	C-Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	oil
	452 ^s	C-Me	NHCH(Et) ₂	2-Me,4-MeOPh	104-106
	453 ^t	C-Me	NHCH(CH ₂ OMe) ₂	2-Me,4-MeOPh	115-116
25	454 ^u	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me,4-MeOPh	oil
	455 ^v	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)-(CH ₂ OMe)	2-Me,4-MeOPh	oil
	456 ^w	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)-(CH ₂ OMe)	2,4-Me ₂ -Ph	oil

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	457 ^x	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me, 4-ClPh	oil
	458 ^y	C-Me	NHEt	2, 4-Me ₂ -Ph	oil
	459 ^z	C-Me	NHCH(Et) ₂	2-Me, 4-ClPh	94-96
	460 ^{aa}	C-Me	NHCH(CH ₂ OMe) ₂	2-Me, 4-ClPh	113-114
5	461 ^{ab}	C-Me	N(Ac)Et	2, 4-Me ₂ -Ph	oil
	462 ^{ac}	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe) - (CH ₂ OMe)	2-Me, 4-ClPh	oil
	463 ^{ad}	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Me, 4-MeOPh	118-119
	464 ^{ae}	C-Me	NEt ₂	2-Me, 4-MeOPh	97-99
10	465 ^{af}	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe) - (CH ₂ OMe)	2-Cl, 4-MePh	101-103
	466 ^{ag}	C-Me	NEt ₂	2-Cl, 4-MePh	129-130
	467 ^{ah}	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Me, 4-MeOPh	177-178
	468 ^{ai}	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl, 4-MePh	162-163
15	469 ^{aj}	C-Me	NHCH(Et)CH ₂ OMe	2-Me, 4-MeOPh	oil
	470 ^{ak}	C-Me	NHCH(Et)CH ₂ OMe	2-Cl, 4-MePh	111-113
	471	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh	
	472	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh	
	473	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh	
20	474	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh	
	475	C-Me	NEt ₂	2-Cl-4-MeOPh	
	476	C-Me	NH-3-pentyl	2-Cl-4-MeOPh	
	477	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh	
	478	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh	
25	479	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh	
	480	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh	
	481	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	482	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	483	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4, 5-(MeO) ₂ Ph	
30	484	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4, 5-(MeO) ₂ Ph	
	485	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4, 5-(MeO) ₂ Ph	
	486	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4, 5-(MeO) ₂ Ph	
	487	C-Me	NEt ₂	2-Cl-4, 5-(MeO) ₂ Ph	99-101
	488	C-Me	NH-3-pentyl	2-Cl-4, 5-(MeO) ₂ Ph	169-170
35	489	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4, 5-(MeO) ₂ Ph	

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	490	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Cl-4, 5- (MeO) ₂ Ph	
	491	C-Me	NHCH (CH ₂ OMe) ₂	2-Br-4, 5- (MeO) ₂ Ph	90-93
	492	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4, 5- (MeO) ₂ Ph	110
	493	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Br-4, 5- (MeO) ₂ Ph	
5	494	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Br-4, 5- (MeO) ₂ Ph	
	495	C-Me	NEt ₂	2-Br-4, 5- (MeO) ₂ Ph	
	496	C-Me	NH-3-pentyl	2-Br-4, 5- (MeO) ₂ Ph	
	497	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Br-4, 5- (MeO) ₂ Ph	
	498	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Br-4, 5- (MeO) ₂ Ph	
10	499	C-Me	NHCH (CH ₂ OMe) ₂	2-Cl-4, 6- (MeO) ₂ Ph	
	500	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4, 6- (MeO) ₂ Ph	
	501	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Cl-4, 6- (MeO) ₂ Ph	
	502	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Cl-4, 6- (MeO) ₂ Ph	
	503	C-Me	NEt ₂	2-Cl-4, 6- (MeO) ₂ Ph	
15	504	C-Me	NH-3-pentyl	2-Cl-4, 6- (MeO) ₂ Ph	
	505	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Cl-4, 6- (MeO) ₂ Ph	
	506	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Cl-4, 6- (MeO) ₂ Ph	
	507	C-Me	NHCH (CH ₂ OMe) ₂	2-Me-4, 6- (MeO) ₂ Ph	
	508	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Me-4, 6- (MeO) ₂ Ph	
20	509	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4, 6- (MeO) ₂ Ph	
	510	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Me-4, 6- (MeO) ₂ Ph	
	511	C-Me	NEt ₂	2-Me-4, 6- (MeO) ₂ Ph	
	512	C-Me	NH-3-pentyl	2-Me-4, 6- (MeO) ₂ Ph	
	513	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4, 6- (MeO) ₂ Ph	
25	514	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Me-4, 6- (MeO) ₂ Ph	
	515	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Br-4, 6- (MeO) ₂ Ph	
	516	C-Me	NEt ₂	2-Br-4, 6- (MeO) ₂ Ph	
	517	C-Me	NH-3-pentyl	2-Br-4, 6- (MeO) ₂ Ph	
	518	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Br-4, 6- (MeO) ₂ Ph	
30	519	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Br-4, 6- (MeO) ₂ Ph	
	520	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	521	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	522	C-Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh	
	523	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh	
35	524	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-MeO-4-MePh	
	525	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh	

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	526	C-Me	NEt ₂	2-MeO-4-MePh
	527	C-Me	NH-3-pentyl	2-MeO-4-MePh
	528	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	529	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
5	530	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	531	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	532	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
	533	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	534	C-Me	NEt ₂	2-MeO-4-MePh
10	535	C-Me	NH-3-pentyl	2-MeO-4-MePh
	536	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	537	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	538	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-ClPh
	539	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
15	540	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-ClPh
	541	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-ClPh
	542	C-Me	NEt ₂	2-MeO-4-ClPh
	543	C-Me	NH-3-pentyl	2-MeO-4-ClPh
	544	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-ClPh
20	545	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-ClPh

NOTES FOR TABLE 2:

- b) CI-HRMS: Calcd: 423.1355; Found: 423.1337 (M + H).
- 25 c) Analysis: Calcd: C, 61.38, H, 6.18, N, 14.32;
Found: C, 61.54, H, 6.12, N, 14.37.
- d) Analysis: Calcd: C: 58.02, H, 5.65, N, 14.24;
Found: C, 58.11, H, 5.52, N, 14.26.
- e) Analysis: Calcd: C, 59.71, H, 5.26, N, 14.85;
30 Found: C, 59.94, H, 5.09, N, 17.23.
- f) Analysis: Calcd: C, 60.48, H, 5.89, N, 14.85,
Found: C, 60.62, H, 5.88, N, 14.82.
- h) CI-HRMS: Calcd: 337.2388; Found: 337.2392 (M + H).
- i) Analysis: Calcd: C, 68.45, H, 7.669, N, 15.21,
35 Found: C, 68.35, H, 7.49 N, 14.91.

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- j) Analysis: Calcd: C, 69.08, H, 7.915, N, 14.65,
Found: C, 68.85, H, 7.83, N, 14.54.
- k) Analysis: Calcd: C, 73.51, H, 7.01, N, 19.48,
Found: C, 71.57, H, 7.15, N, 19.12.
- 5 l) CI-HRMS: Calcd: 403.1899; Found: 403.1901 (M + H).
m) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl,
9.13; Found: C, 61.90, H, 6.66, N, 13.62, Cl, 9.25.
n) Analysis: Calcd: 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.
- 10 o) Analysis: Calcd: C, 74.50, H, 8.14, N, 17.38,
Found: C, 74.43, H, 7.59, N, 17.16.
p) Analysis: Calcd: C, 73.10, H, 7.54, N, 19.37,
Found: C, 73.18, H, 7.59, N, 18.81.
q) Analysis: Calcd: C, 73.57, H, 7.78, N, 18.65,
15 Found: C, 73.55, H, 7.79, N, 18.64.
r) CI-HRMS: Calcd: 353.2333; Found: 353.2341 (M + H).
s) Analysis: Calcd: C, 71.56, H, 8.02, N, 15.90,
Found: C, 71.45, H, 7.99, N, 15.88.
t) Analysis: Calcd: C, 65.60, H, 7.34, N, 14.57,
20 Found: C, 65.42, H, 7.24, N, 14.37.
u) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).
v) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).
w) CI-HRMS: Calcd: 383.2450; Found: 383.2447 (M + H).
x) CI-HRMS: Calcd: 403.1887; Found: 403.1901 (M + H).
25 y) CI-HRMS: Calcd: 295.1919; Found: 295.1923 (M + H).
z) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70,
Found: C, 67.12, H, 6.86, N, 15.53.
aa) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl,
9.13; Found: C, 62.06, H, 6.37, N, 14.25, Cl, 9.12.
- 30 ab) CI-HRMS: Calcd: 337.2017; Found: 337.2028 (M + H).
ac) CI-HRMS: Calcd: 403.1893; Found: 403.1901 (M + H).
ad) Analysis: Calcd: C, 70.00, H, 7.22, N, 18.55,
Found: C, 70.05, H, 7.22, N, 18.36.
ae) Analysis: Calcd: C, 70.98, H, 7.74, N, 16.55,
35 Found: C, 71.15, H, 7.46, N, 16.56.

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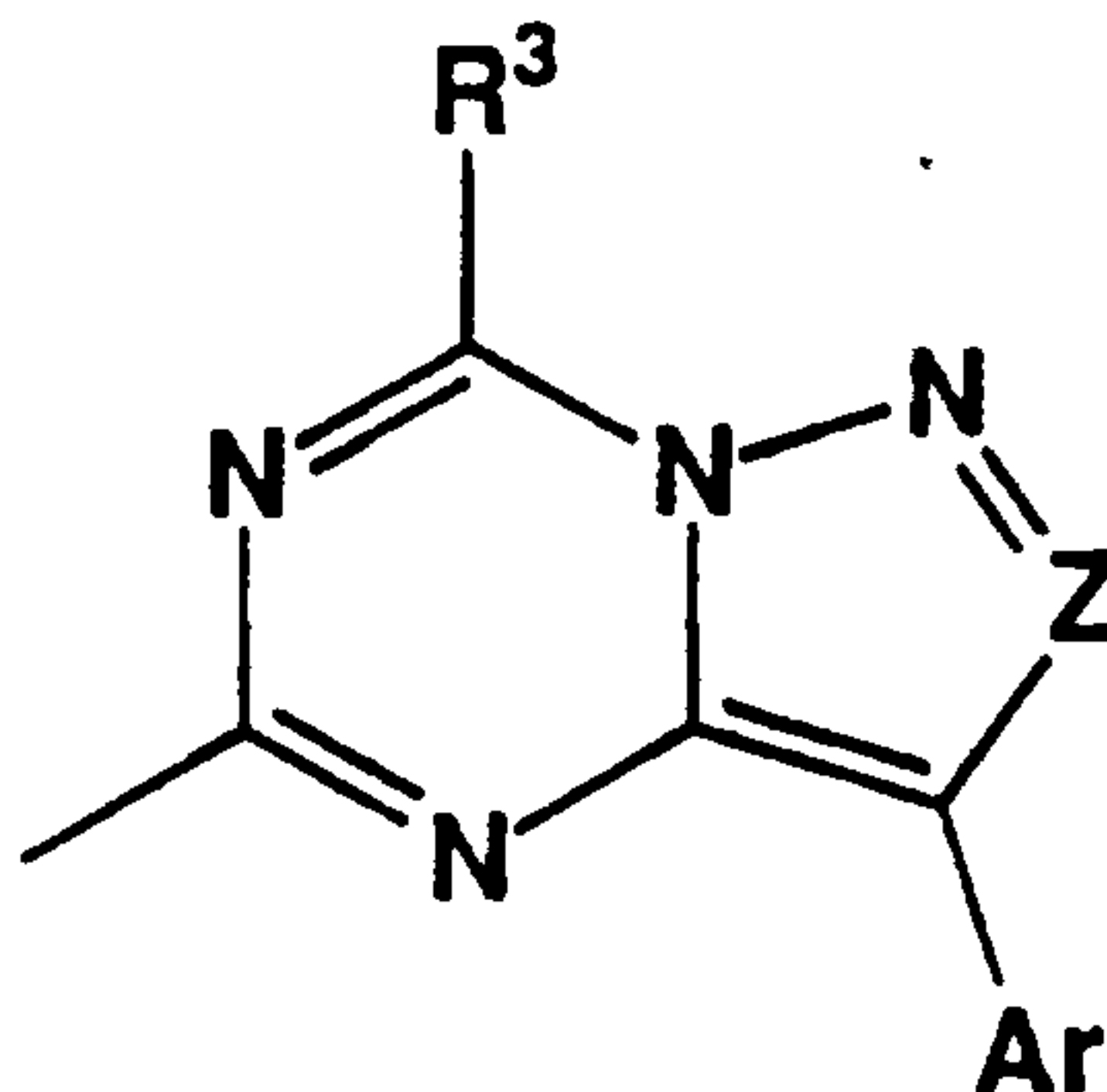
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- ag) Analysis: Calcd: C, 66.59, H, 6.76, N, 16.34,
Found: C, 66.69, H, 6.82, N, 16.20.
- ah) Analysis: Calcd: C, 70.38, H, 6.71, N, 18.65,
Found: C, 70.35, H, 6.82, N, 18.83.
- 5 ai) Analysis: Calcd: C, 66.39, H, 5.85, N, 18.44, Cl,
9.33;
Found: C, 66.29, H, 5.51, N, 18.36, Cl, 9.31.
- aj) CI-HRMS: Calcd: 369.2278; Found: 369.2291 (M + H).
- ak) Analysis: Calcd: C, 64.42, H, 6.77, N, 15.02,
10 Found: C, 64.59, H, 6.51, N, 14.81.

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

TABLE 3

20



Ex.	Z	R ₃	Ar	mp (°C)
546 ^a	C-Me	NHCH(Et) ₂	2-Me-4-Me ₂ N-Ph	164-166
25 547 ^b	C-Me	S-NHCH(CH ₂ CH ₂ OMe) -CH ₂ OMe	2,4-Me ₂ -Ph	oil
548 ^c	C-Me	S-NHCH(CH ₂ CH ₂ OMe) -CH ₂ OMe	2-Me-4-Cl-Ph	oil
549 ^d	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Me-4-Cl-Ph	115-116

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	550 ^e	C-Me	NHCH(Et)CH ₂ CN	2-Me-4-Cl-Ph	131-132
	551 ^f	C-Me	N(Et) ₂	2,3-Me ₂ -4-OMe-Ph	oil
	552 ^g	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ OH	2,4-Cl ₂ -Ph	oil
	553 ^h	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,3-Me ₂ -4-OMe-Ph	oil
5	554 ⁱ	C-Me	NHCH(Et) ₂	2,3-Me ₂ -4-OMePh	123-124
	555 ^j	C-Me	N(CH ₂ -c-Pr)Pr	2-Me-4-Cl-Ph	oil
	556 ^k	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2,3-Me ₂ -4-OMePh	158-160
	557	C-Me	N(c-Pr)Et	2-Cl-4-OMePh	
	558	C-Me	N(c-Pr)Me	2-Cl-4-OMePh	
10	559	C-Me	N(c-Pr)Pr	2-Cl-4-OMePh	
	560	C-Me	N(c-Pr)Bu	2-Cl-4-OMePh	
	561 ^l	C-Me	N(Et) ₂	2-Cl-4-CN-Ph	115-117
	562	C-Me	N(c-Pr) ₂	2-Cl-4-OMe	127-129
	563 ^m	C-Me	NHCH(CH ₂ OH) ₂	2,4-Cl ₂ -Ph	128-129
15	564	C-Me	N(c-Pr)Et	2-Br-4,5-(MeO) ₂ Ph	
	565	C-Me	N(c-Pr)Me	2-Br-4,5-(MeO) ₂ Ph	
	566	C-Me	NH-c-Pr	2-Me-4-MeOPh	126-128
	567	C-Me	NHCH(Et)CH ₂ OH	2-Me-4-MeOPh	60-62
	568	C-Me	NMe ₂	2-Br-4,5-(MeO) ₂ Ph	
20	569	C-Me	NHCH(Et) ₂	2-Me-4-MeOPh	103-105
	570	C-Me	N(c-Pr)Et	2-Me-4-MeOPh	173-174
	571	C-Me	NH-2-pentyl	2,4-Cl ₂ -Ph	118-120
	572	C-Me	NHCH(Et)CH ₂ CN	2,4-Cl ₂ -Ph	141-142
	573	C-Me	NHCH(Pr)CH ₂ OMe	2,4-Cl ₂ -Ph	87-88
25	574	C-Me	NHCH(CH ₂ -iPr)CH ₂ OMe	2,4-Cl ₂ -Ph	amorphous
	575	C-Me	NH-2-butyl	2,4-Me ₂ -Ph	oil
	576	C-Me	NH-2-pentyl	2,4-Me ₂ -Ph	oil
	577	C-Me	NH-2-hexyl	2,4-Me ₂ -Ph	oil
	578	C-Me	NHCH(i-Pr)Me	2,4-Me ₂ -Ph	oil
30	579	C-Me	NHCH(Me)CH ₂ -iPr	2,4-Me ₂ -Ph	oil
	580	C-Me	NHCH(Me)-c-C ₆ H ₁₁	2,4-Me ₂ -Ph	oil
	581	C-Me	NH-2-indanyl	2,4-Me ₂ -Ph	oil
	582	C-Me	NH-1-indanyl	2,4-Me ₂ -Ph	oil
	583	C-Me	NHCH(Me)Ph	2,4-Me ₂ -Ph	oil
35	584	C-Me	NHCH(Me)CH ₂ -(4-ClPh)	2,4-Me ₂ -Ph	oil

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	585	C-Me	NHCH (Me) CH ₂ COCH ₃	2,4-Me ₂ -Ph	oil
	586	C-Me	NHCH (Ph) CH ₂ Ph	2,4-Me ₂ -Ph	oil
	587	C-Me	NHCH (Me) (CH ₂) ₃ NEt ₂	2,4-Me ₂ -Ph	oil
	588	C-Me	NH- (2-Ph-c-C ₃ H ₄)	2,4-Me ₂ -Ph	oil
5	589	C-Me	NHCH (Et) CH ₂ CN	2,4-Me ₂ -Ph	119-120
	590	C-Me	NH-3-hexyl	2,4-Me ₂ -Ph	oil
	591 ⁿ	C-Me	NEt ₂	2-MeO-4-ClPh	oil
	592 ^o	C-Me	NHCH (Et) ₂	2-MeO-4-ClPh	oil
	593 ^p	C-Me	NHCH (Et) CH ₂ OMe	2-MeO-4-ClPh	oil
10	594	C-Me	NMe ₂	2-MeO-4-ClPh	oil
	595 ^q	C-Me	NHCH (Et) ₂	2-OMe-4-MePh	oil
	596 ^r	C-Me	NEt ₂	2-OMe-4-MePh	oil
	597 ^s	C-c-Pr	NHCH (CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	oil
	598	C-Me	N (c-Pr) Et	2,4-Me ₂ -Ph	
15	599	C-Me	N (c-Pr) Et	2,4-Cl ₂ -Ph	
	600	C-Me	N (c-Pr) Et	2,4,6-Me ₃ -Ph	
	601	C-Me	N (c-Pr) Et	2-Me-4-Cl-Ph	
	602	C-Me	N (c-Pr) Et	2-Cl-4-Me-Ph	
	603	C-Me	NHCH (c-Pr) ₂	2,4-Cl ₂ -Ph	
20	604	C-Me	NHCH (c-Pr) ₂	2,4-Me ₂ -Ph	
	605	C-Me	NHCH (c-Pr) ₂	2-Me-4-Cl-Ph	
	606	C-Me	NHCH (c-Pr) ₂	2-Cl-4-Me-Ph	
	607	C-Me	NHCH (c-Pr) ₂	2-Me-4-OMe-Ph	
	608	C-Me	NHCH (c-Pr) ₂	2-Cl-4-OMe-Ph	
25	609	C-Me	NHCH (CH ₂ OMe) ₂	2-Cl-5-F-OMePh	
	610	C-Me	NEt ₂	2-Cl-5-F-OMePh	
	611	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Cl-5-F-OMePh	
	612	C-Me	NHCH (Et) ₂	2-Cl-5-F-OMePh	
	613	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-5-F-OMePh	
30	614	C-Me	NEt ₂	2,6-Me ₂ -pyrid-3-yl	
	615	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2,6-Me ₂ -pyrid-3-yl	
	616	C-Me	NHCH (Et) ₂	2,6-Me ₂ -pyrid-3-yl	
	617	C-Me	N (CH ₂ CH ₂ OMe) ₂	2,6-Me ₂ -pyrid-3-yl	
	618	C-OH	NHCH (CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
35	619	C-OH	NEt ₂	2,4-Me ₂ -Ph	
	620	C-OH	N (c-Pr) CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	

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	621	C-OH	NHCH(Et) ₂	2,4-Me ₂ -Ph
	623	C-OH	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	624	C-NEt ₂	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	625	C-NEt ₂	NEt ₂	2,4-Me ₂ -Ph
5	626	C-NEt ₂	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	627	C-NEt ₂	NHCH(Et) ₂	2,4-Me ₂ -Ph
	628	C-NEt ₂	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	629	C-Me	NHCH(Et) ₂	2-Me-4-CN-Ph
	630	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-CN-Ph

10

Notes for Table 3:

- a) CI-HRMS: Calcd:367.2610, Found: 367.2607 (M + H);
- b) CI-HRMS: Calcd:384.2400, Found: 384.2393 (M + H);
- 15 c) CI-HRMS: Calcd:404.1853, Found: 404.1844 (M + H);
- d) CI-HRMS: Calcd:381.1594, Found: 381.1596 (M + H);
- Analysis: Calcd: C: 63.07, H, 5.57, N, 22.07, Cl, 9.32;
- Found: C: 63.40, H, 5.55, N, 21.96, Cl: 9.15
- 20 e) CI-HRMS: Calcd:369.1594, Found: 369.1576 (M + H);
- f) CI-HRMS: Calcd:354.2216, Found: 354.2211 (M + H);
- g) CI-HRMS: Calcd:410.1072, Found: 410.1075 (M + H);
- h) CI-HRMS: Calcd:414.2427, Found: 414.2427 (M + H);
- i) CI-HRMS: Calcd:368.2372, Found: 368.2372 (M + H);
- 25 j) CI-HRMS: Calcd:384.1955, Found: 384.1947 (M + H);
- k) CI-HRMS: Calcd:391.2168, Found: 391.2160 (M + H);
- l) CI-HRMS: Calcd:335.1984, Found: 335.1961 (M + H);
- m) CI-HRMS: Calcd:382.0759, Found: 382.0765 (M + H);
- n) NH₃-CI MS: Calcd: 360, Found: 360 (M + H)+
- 30 o) NH₃-CI MS: Calcd: 374, Found: 374 (M + H)+;
- NMR (CDCl₃, 300 MHz) : δ 7.29 (d, J=8.4Hz, 1H), 7.04 (dd, J=1.8,8Hz, 1H), 6.96 (d, J=1.8Hz, 1H), 6.15 (d, J=10, 1H), 4.19 (m, 1H), 3.81 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.65 (m, 4H), 0.99 (t, J=7.32Hz, 6H)
- 35 p) NH₃-CI MS: Calcd: 390, Found: 390 (M + H)+;

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NMR (CDCl₃, 300 MHz) : δ 7.28 (d, J=8Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.52 (d, J=9Hz, 1H), 4.36 (m, 1H), 3.8 (s, 3H), 3.55 (m, 2H), 3.39 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.76 (m, 2H), 1.01 (t, J=7.32Hz, 3H).

5

- q) CI-HRMS: Calcd: 354.2294, Found: 354.2279 (M + H)⁺
 r) CI-HRMS: Calcd: 340.2137, Found: 340.2138 (M + H)⁺
 s) CI-HRMS: Calcd: 436.1307, Found: 436.1296 (M + H)⁺

10

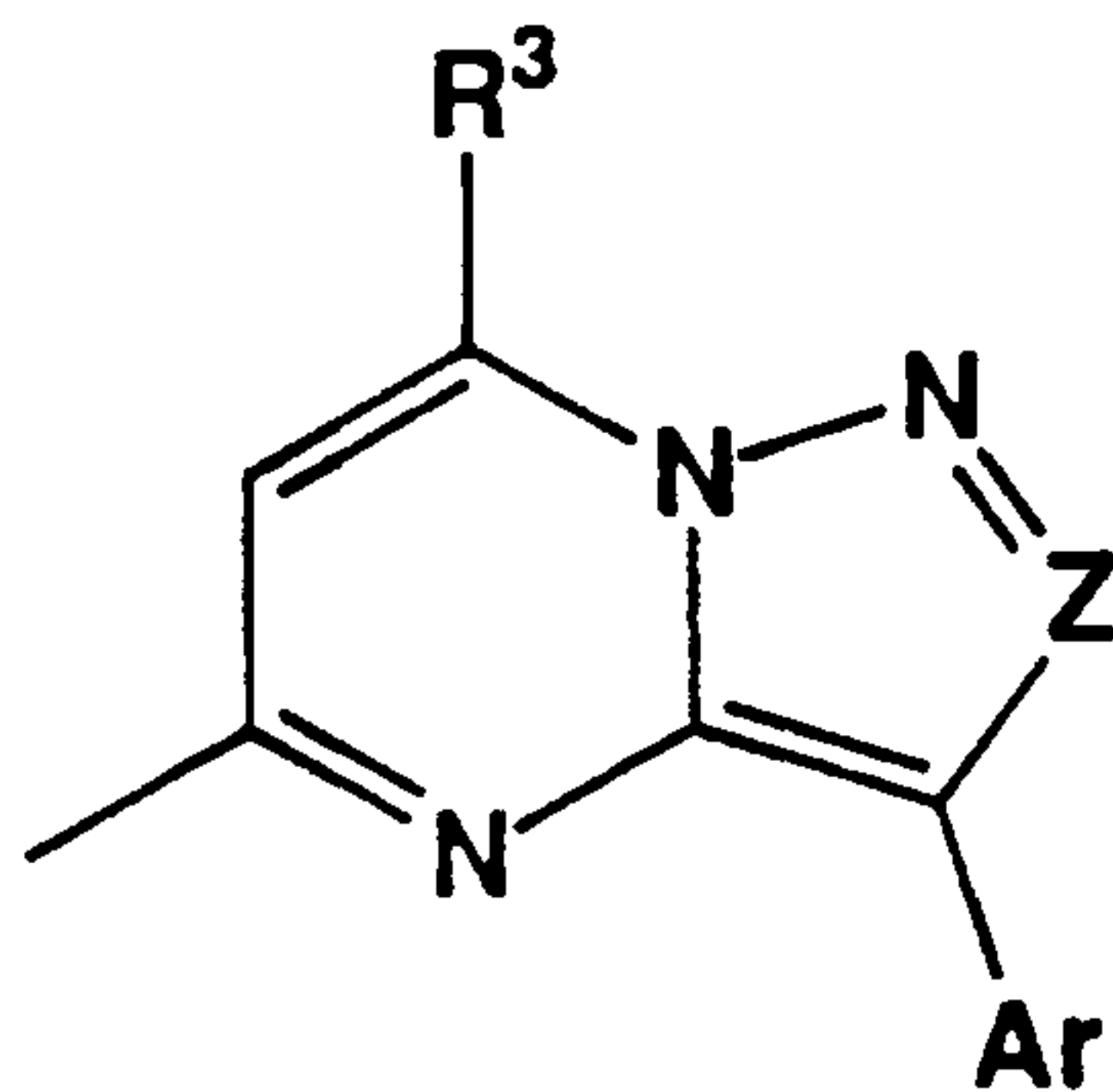
The examples delineated in TABLE 4 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434.

Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is

15 Example, EtOAc is ethyl acetate.

TABLE 4

20



25	Ex.	Z	R ³	Ar	mp (°C)
	631	C-Me	NHCH(Et) ₂	2-Br-4,5-(MeO) ₂ Ph	160-161
	632	C-Me	NHCH(Et) ₂	2-Br-4-MeOPh	110-111
	633	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-MeOPh	74-76
	634	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-MeOPh	128-130

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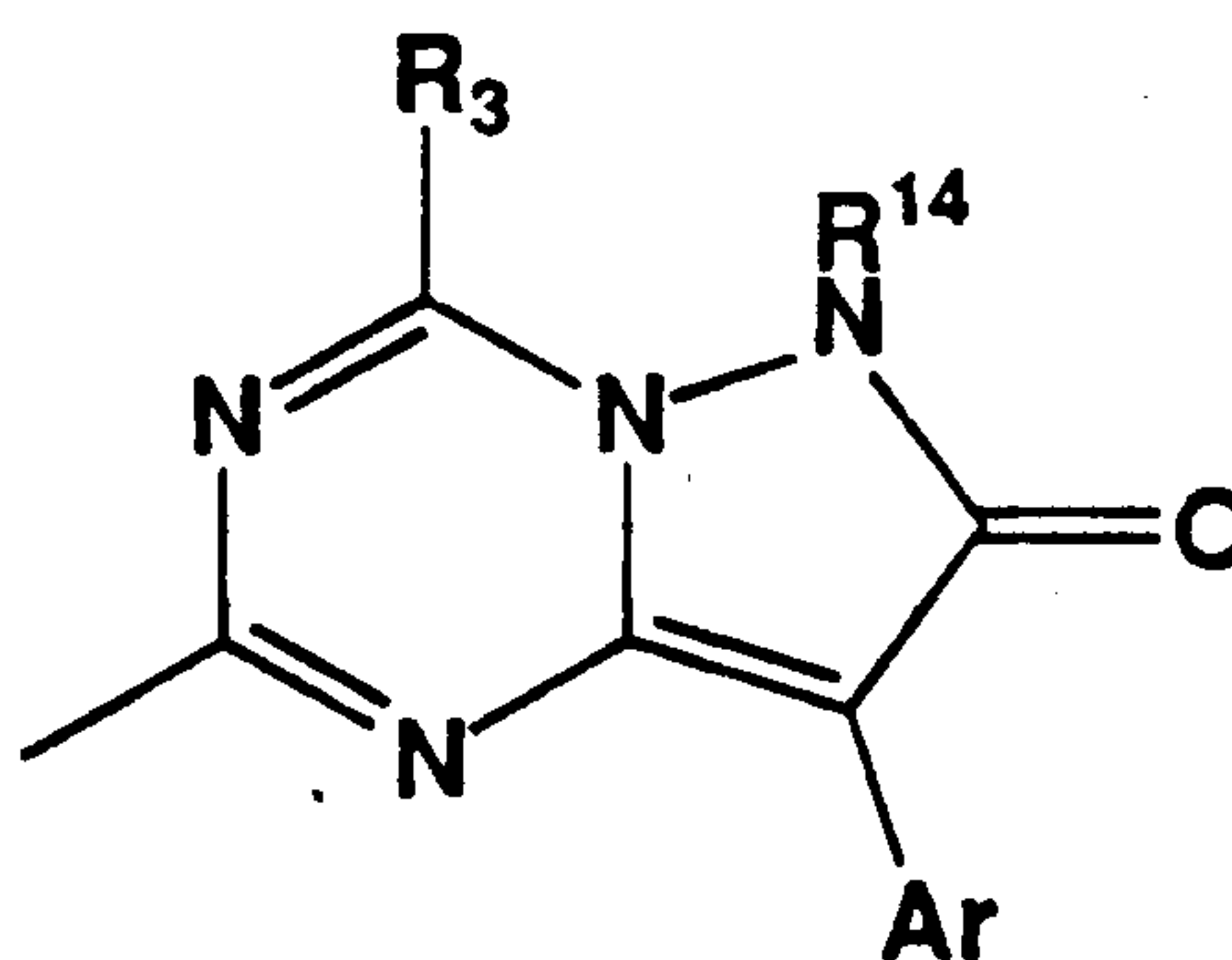
	635	C-Me	N(Et) ₂	2-Me-4-ClPh	113-114
	636	C-Me	N(c-Pr)Et	2,4-Cl ₂ Ph	
	637	C-Me	N(c-Pr)Et	2,4-Me ₂ Ph	
	638	C-Me	N(c-Pr)Et	2,4,6-Me ₃ Ph	
5	639	C-Me	N(c-Pr)Et	2-Me-4-MeOPh	
	640	C-Me	N(c-Pr)Et	2-Cl-4-MeOPh	
	641	C-Me	N(c-Pr)Et	2-Cl-4-MePh	
	642	C-Me	N(c-Pr)Et	2-Me-4-ClPh	
	643	C-Me	NHCH(c-Pr) ₂	2,4-Cl ₂ -Ph	
10	644	C-Me	NHCH(c-Pr) ₂	2,4-Me ₂ -Ph	
	645	C-Me	NHCH(c-Pr) ₂	2-Me-4-Cl-Ph	
	646	C-Me	NHCH(c-Pr) ₂	2-Cl-4-Me-Ph	
	647	C-Me	NHCH(c-Pr) ₂	2-Me-4-OMe-Ph	
	648	C-Me	NHCH(c-Pr) ₂	2-Cl-4-OMe-Ph	
15	649	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-5-F-OMePh	
	650	C-Me	NEt ₂	2-Cl-5-F-OMePh	
	651	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-5-F-OMePh	
	652	C-Me	NHCH(Et) ₂	2-Cl-5-F-OMePh	
	653	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-5-F-OMePh	
20	654	C-Me	NEt ₂	2,6-Me ₂ -pyrid-3-yl	
	655	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2,6-Me ₂ -pyrid-3-yl	
	656	C-Me	NHCH(Et) ₂	2,6-Me ₂ -pyrid-3-yl	
	657	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,6-Me ₂ -pyrid-3-yl	
	658	C-OH	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
25	659	C-OH	NEt ₂	2,4-Me ₂ -Ph	
	660	C-OH	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
	661	C-OH	NHCH(Et) ₂	2,4-Me ₂ -Ph	
	662	C-OH	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
	663	C-NEt ₂	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
30	664	C-NEt ₂	NEt ₂	2,4-Me ₂ -Ph	
	665	C-NEt ₂	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
	666	C-NEt ₂	NHCH(Et) ₂	2,4-Me ₂ -Ph	
	667	C-NEt ₂	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
	668	C-Me	NHCH(Et) ₂	2-Me-4-CN-Ph	
35	669	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-CN-Ph	

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The examples in Tables 5 or 6 may be prepared by the methods illustrated in Examples 1A, 1B, 2, 3, 6, 431, 432, 433, 434 or by appropriate combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

Table 5



Ex.	R ₁₄	R ₃	Ar
670	Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
671	Me	NHCHPr ₂	2,4-Cl ₂ -Ph
672	Me	NEtBu	2,4-Cl ₂ -Ph
20 673	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Cl ₂ -Ph
674	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
675	Me	NH-3-heptyl	2,4-Cl ₂ -Ph
676	Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
677	Me	NEt ₂	2,4-Cl ₂ -Ph
25 678	Me	NHCH(CH ₂ OEt) ₂	2,4-Cl ₂ -Ph
679	Me	NH-3-pentyl	2,4-Cl ₂ -Ph
680	Me	NMePh	2,4-Cl ₂ -Ph
681	Me	NPr ₂	2,4-Cl ₂ -Ph
682	Me	NH-3-hexyl	2,4-Cl ₂ -Ph
30 683	Me	morpholino	2,4-Cl ₂ -Ph

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	684	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Cl ₂ -Ph
	685	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Cl ₂ -Ph
	686	Me	NH-4-tetrahydropyranyl	2,4-Cl ₂ -Ph
	687	Me	NH-cyclopentyl	2,4-Cl ₂ -Ph
5	688	Me	OEt	2,4-Cl ₂ -Ph
	689	Me	OCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
	690	Me	OCH ₂ Ph	2,4-Cl ₂ -Ph
	691	Me	O-3-pentyl	2,4-Cl ₂ -Ph
	692	Me	SEt	2,4-Cl ₂ -Ph
10	693	Me	S(O)Et	2,4-Cl ₂ -Ph
	694	Me	SO ₂ Et	2,4-Cl ₂ -Ph
	695	Me	Ph	2,4-Cl ₂ -Ph
	696	Me	2-CF ₃ -Ph	2,4-Cl ₂ -Ph
	697	Me	2-Ph-Ph	2,4-Cl ₂ -Ph
15	698	Me	3-pentyl	2,4-Cl ₂ -Ph
	699	Me	cyclobutyl	2,4-Cl ₂ -Ph
	700	Me	3-pyridyl	2,4-Cl ₂ -Ph
	701	Me	CH(Et)CH ₂ CONMe ₂	2,4-Cl ₂ -Ph
	702	Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Cl ₂ -Ph
20	703	Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
	704	Me	NHCHPr ₂	2,4,6-Me ₃ -Ph
	705	Me	NEtBu	2,4,6-Me ₃ -Ph
	706	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4,6-Me ₃ -Ph
	707	Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
25	708	Me	NH-3-heptyl	2,4,6-Me ₃ -Ph
	709	Me	NHCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	710	Me	NEt ₂	2,4,6-Me ₃ -Ph
	711	Me	NHCH(CH ₂ OEt) ₂	2,4,6-Me ₃ -Ph
	712	Me	NH-3-pentyl	2,4,6-Me ₃ -Ph
30	713	Me	NMePh	2,4,6-Me ₃ -Ph
	714	Me	NPr ₂	2,4,6-Me ₃ -Ph
	715	Me	NH-3-hexyl	2,4,6-Me ₃ -Ph
	716	Me	morpholino	2,4,6-Me ₃ -Ph
	717	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4,6-Me ₃ -Ph
35	718	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4,6-Me ₃ -Ph
	719	Me	NH-4-tetrahydropyranyl	2,4,6-Me ₃ -Ph

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	720	Me	NH-cyclopentyl	2,4,6-Me ₃ -Ph
	721	Me	OEt	2,4,6-Me ₃ -Ph
	722	Me	OCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	723	Me	OCH ₂ Ph	2,4,6-Me ₃ -Ph
5	724	Me	O-3-pentyl	2,4,6-Me ₃ -Ph
	725	Me	SEt	2,4,6-Me ₃ -Ph
	726	Me	S(O)Et	2,4,6-Me ₃ -Ph
	727	Me	SO ₂ Et	2,4,6-Me ₃ -Ph
	728	Me	CH(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
10	729	Me	C(Et)(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
	730	Me	CH(Et)CH ₂ OH	2,4,6-Me ₃ -Ph
	731	Me	CH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	732	Me	CONMe ₂	2,4,6-Me ₃ -Ph
	733	Me	COCH ₃	2,4,6-Me ₃ -Ph
15	734	Me	CH(OH)CH ₃	2,4,6-Me ₃ -Ph
	735	Me	C(OH)Ph-3-pyridyl	2,4,6-Me ₃ -Ph
	736	Me	Ph	2,4,6-Me ₃ -Ph
	737	Me	2-Ph ⁺ Ph	2,4,6-Me ₃ -Ph
	738	Me	3-pentyl	2,4,6-Me ₃ -Ph
20	739	Me	cyclobutyl	2,4,6-Me ₃ -Ph
	740	Me	3-pyridyl	2,4,6-Me ₃ -Ph
	741	Me	CH(Et)CH ₂ CONMe ₂	2,4,6-Me ₃ -Ph
	742	Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4,6-Me ₃ -Ph
	743	Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
25	744	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	745	Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	746	Me	NH-3-pentyl	2,4-Me ₂ -Ph
	747	Me	NEt ₂	2,4-Me ₂ -Ph
	748	Me	N(CH ₂ CN) ₂	2,4-Me ₂ -Ph
30	749	Me	NHCH(Me)CH ₂ OMe	2,4-Me ₂ -Ph
	750	Me	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	751	Me	NPr-c-C ₃ H ₅	2,4-Me ₂ -Ph
	752	Me	NHCH(Me)CH ₂ NMe ₂	2,4-Me ₂ -Ph
	753	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
35	754	Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	755	Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph

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	756	Me	NHCHPr ₂	2,4-Me ₂ -Ph
	757	Me	NEtBu	2,4-Me ₂ -Ph
	758	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Me ₂ -Ph
	759	Me	NH-3-heptyl	2,4-Me ₂ -Ph
5	760	Me	NEt ₂	2,4-Me ₂ -Ph
	761	Me	NHCH(CH ₂ OEt) ₂	2,4-Me ₂ -Ph
	762	Me	NH-3-pentyl	2,4-Me ₂ -Ph
	763	Me	NMePh	2,4-Me ₂ -Ph
	764	Me	NPr ₂	2,4-Me ₂ -Ph
10	765	Me	NH-3-hexyl	2,4-Me ₂ -Ph
	766	Me	morpholino	2,4-Me ₂ -Ph
	767	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Me ₂ -Ph
	768	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Me ₂ -Ph
	769	Me	NH-4-tetrahydropyranyl	2,4-Me ₂ -Ph
15	770	Me	NH-cyclopentyl	2,4-Me ₂ -Ph
	771	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-MeO-Ph
	772	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-MeO-Ph
	773	Me	NHCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph
	774	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-MeO-Ph
20	775	Me	OCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph
	776	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-MeO-Ph
	777	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-MeO-Ph
	778	Me	NHCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph
	779	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-MeO-Ph
25	780	Me	OCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph
	781	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph
	782	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph
	783	Me	NHCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph
	784	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-NMe ₂ -Ph
30	785	Me	OCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph
	786	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph
	787	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph
	788	Me	NHCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph
	789	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-NMe ₂ -Ph
35	790	Me	OCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph
	791	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph

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	792	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph
	793	Me	NHCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph
	794	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-i-Pr-Ph
	795	Me	OCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph
5	796	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-Me-Ph
	797	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-Me-Ph
	798	Me	NHCH(Et)CH ₂ OMe	2-Br-4-Me-Ph
	799	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-Me-Ph
	800	Me	OCH(Et)CH ₂ OMe	2-Br-4-Me-Ph
10	801	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-Br-Ph
	802	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-Br-Ph
	803	Me	NHCH(Et)CH ₂ OMe	2-Me-4-Br-Ph
	804	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-Br-Ph
	805	Me	OCH(Et)CH ₂ OMe	2-Me-4-Br-Ph
15	806	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph
	807	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph
	808	Me	NHCH(CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph
	809	Me	N(CH ₂ CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph
	810	Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
20	811	Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	812	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph
	813	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph
	814	Me	NHCH(CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph
	815	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph
25	816	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph
	817	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph
	818	Me	NHCH(CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	819	Me	N(CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	820	Me	NHCH(CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph
30	821	Me	N(CH ₂ CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph
	822	Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl
	823	Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl
	824	Me	NHCH(CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph
	825	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph
35	826	Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	827	Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph

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	828	Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	829	Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	830	Me	NHCH(CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	831	Me	N(CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
5	832	Me	NHCH(CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	833	Me	N(CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	834	Me	NHCH(CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	835	Me	N(CH ₂ CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	836	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-N(Me) ₂ -6-MeO-Ph
10	837	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-N(Me) ₂ -6-MeO-Ph
	838	Me	NEt ₂	2-Br-4-MeO-Ph
	839	Me	NH-3-pentyl	2-Br-4-MeO-Ph
	840	Me	NHCH(CH ₂ OMe) ₂	2-CN-4-Me-Ph
	841	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4,6-Me ₃ -Ph
15	842	Me	NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-Br-Ph
	843	Me	NHCH(CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph
	844	Me	N(CH ₂ CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph
	845	Me	NH-3-pentyl	2,5-Me ₂ -4-MeO-Ph
	846	Me	NEt ₂	2,5-Me ₂ -4-MeO-Ph
20	847	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MePh
	848	Me	NCH(Et)CH ₂ OMe	2-Cl-4-MePh
	849	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MePh
	850	Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Cl-4-MePh
	851	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,5-Me ₂ -4-MeOPh
25	852	Me	NEt ₂	2-Me-4-MeOPh
	853	Me	OEt	2-Me-4-MeOPh
	854	Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-MeOPh
	855	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2-Me-4-MeOPh
	856	Me	NHCH(CH ₂ CH ₂ OEt) ₂	2-Me-4-MeOPh
30	857	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph
	858	Me	NEt ₂	2-Me-4-ClPh
	859	Me	NH-3-pentyl	2-Me-4-ClPh
	860	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-ClPh
	861	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-ClPh
35	862	Me	NEt ₂	2-Me-4-ClPh
	863	Me	NEt ₂	2-Cl-4-MePh

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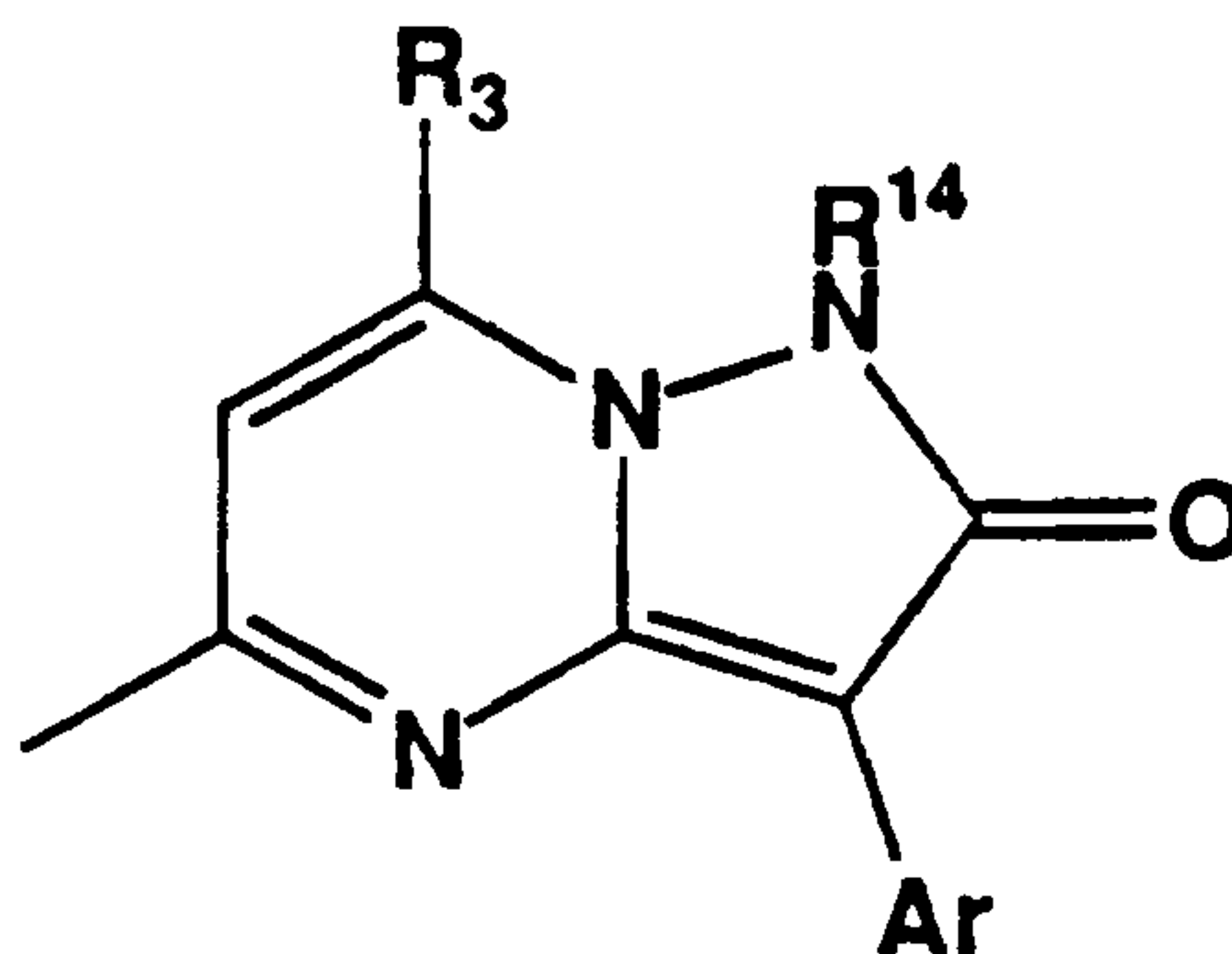
	864	Me	NH-3-pentyl	2-Cl-4-MePh
	865	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh
	866	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh
	867	Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh
5	868	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh
	869	Me	NEt ₂	2-Cl-4-MeOPh
	870	Me	NH-3-pentyl	2-Cl-4-MeOPh
	871	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	872	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
10	873	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	874	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	875	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	876	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	877	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
15	878	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
	879	Me	NHCH(Et)CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	880	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,5-(MeO) ₂ Ph
	881	Me	NEt ₂	2-Cl-4,5-(MeO) ₂ Ph
	882	Me	NH-3-pentyl	2-Cl-4,5-(MeO) ₂ Ph
20	883	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	884	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	885	Me	NHCH(CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
	886	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
	887	Me	NHCH(Et)CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
25	888	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,5-(MeO) ₂ Ph
	889	Me	NEt ₂	2-Br-4,5-(MeO) ₂ Ph
	890	Me	NH-3-pentyl	2-Br-4,5-(MeO) ₂ Ph
	891	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
	892	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
30	893	Me	NEt ₂	2-Cl-4,6-(MeO) ₂ Ph
	894	Me	NH-3-pentyl	2-Cl-4,6-(MeO) ₂ Ph
	895	Me	NHCH(CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	896	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	897	Me	NHCH(Et)CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
35	898	Me	NEt ₂	2-Me-4,6-(MeO) ₂ Ph
	899	Me	NH-3-pentyl	2-Me-4,6-(MeO) ₂ Ph

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	900	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	901	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	902	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh
	903	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
5	904	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-MePh
	905	Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh
	906	Me	NEt ₂	2-MeO-4-MePh
	907	Me	NH-3-pentyl	2-MeO-4-MePh
	908	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-MeO-4-MePh
10	909	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-MeO-4-MePh
	910	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh
	911	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	912	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-MePh
	913	Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh
15	914	Me	NEt ₂	2-MeO-4-MePh
	915	Me	NH-3-pentyl	2-MeO-4-MePh
	916	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-ClPh
	917	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
	918	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-ClPh
20	919	Me	NEt ₂	2-MeO-4-ClPh
	920	Me	NH-3-pentyl	2-MeO-4-ClPh

Table 6



5	Ex.	R ₁₄	R ₃	Ar
	921	Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
	922	Me	NHCHPr ₂	2,4-Cl ₂ -Ph
	923	Me	NEtBu	2,4-Cl ₂ -Ph
10	924	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Cl ₂ -Ph
	925	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
	926	Me	NH-3-heptyl	2,4-Cl ₂ -Ph
	927	Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
	928	Me	NEt ₂	2,4-Cl ₂ -Ph
15	929	Me	NHCH(CH ₂ OEt) ₂	2,4-Cl ₂ -Ph
	930	Me	NH-3-pentyl	2,4-Cl ₂ -Ph
	931	Me	NMePh	2,4-Cl ₂ -Ph
	932	Me	NPr ₂	2,4-Cl ₂ -Ph
	933	Me	NH-3-hexyl	2,4-Cl ₂ -Ph
20	934	Me	morpholino	2,4-Cl ₂ -Ph
	935	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Cl ₂ -Ph
	936	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Cl ₂ -Ph
	937	Me	NH-4-tetrahydropyranyl	2,4-Cl ₂ -Ph
	938	Me	NH-cyclopentyl	2,4-Cl ₂ -Ph
25	939	Me	OEt	2,4-Cl ₂ -Ph
	940	Me	OCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
	941	Me	OCH ₂ Ph	2,4-Cl ₂ -Ph
	942	Me	O-3-pentyl	2,4-Cl ₂ -Ph
	943	Me	SEt	2,4-Cl ₂ -Ph

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	944	Me	S(O)Et	2,4-Cl ₂ -Ph
	945	Me	SO ₂ Et	2,4-Cl ₂ -Ph
	946	Me	Ph	2,4-Cl ₂ -Ph
	947	Me	2-CF ₃ -Ph	2,4-Cl ₂ -Ph
5	948	Me	2-Ph-Ph	2,4-Cl ₂ -Ph
	949	Me	3-pentyl	2,4-Cl ₂ -Ph
	950	Me	cyclobutyl	2,4-Cl ₂ -Ph
	951	Me	3-pyridyl	2,4-Cl ₂ -Ph
	952	Me	CH(Et)CH ₂ CONMe ₂	2,4-Cl ₂ -Ph
10	953	Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Cl ₂ -Ph
	954	Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
	955	Me	NHCHPr ₂	2,4,6-Me ₃ -Ph
	956	Me	NEtBu	2,4,6-Me ₃ -Ph
	957	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4,6-Me ₃ -Ph
15	958	Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
	959	Me	NH-3-heptyl	2,4,6-Me ₃ -Ph
	960	Me	NHCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	961	Me	NEt ₂	2,4,6-Me ₃ -Ph
	962	Me	NHCH(CH ₂ OEt) ₂	2,4,6-Me ₃ -Ph
20	963	Me	NH-3-pentyl	2,4,6-Me ₃ -Ph
	964	Me	NMePh	2,4,6-Me ₃ -Ph
	965	Me	NPr ₂	2,4,6-Me ₃ -Ph
	966	Me	NH-3-hexyl	2,4,6-Me ₃ -Ph
	967	Me	morpholino	2,4,6-Me ₃ -Ph
25	968	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4,6-Me ₃ -Ph
	969	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4,6-Me ₃ -Ph
	970	Me	NH-4-tetrahydropyranyl	2,4,6-Me ₃ -Ph
	971	Me	NH-cyclopentyl	2,4,6-Me ₃ -Ph
	972	Me	OEt	2,4,6-Me ₃ -Ph
30	973	Me	OCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	974	Me	OCH ₂ Ph	2,4,6-Me ₃ -Ph
	975	Me	O-3-pentyl	2,4,6-Me ₃ -Ph
	976	Me	SEt	2,4,6-Me ₃ -Ph
	977	Me	S(O)Et	2,4,6-Me ₃ -Ph
35	978	Me	SO ₂ Et	2,4,6-Me ₃ -Ph
	979	Me	CH(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph

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	980	Me	C(Et)(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
	981	Me	CH(Et)CH ₂ OH	2,4,6-Me ₃ -Ph
	982	Me	CH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	983	Me	CONMe ₂	2,4,6-Me ₃ -Ph
5	984	Me	COCH ₃	2,4,6-Me ₃ -Ph
	985	Me	CH(OH)CH ₃	2,4,6-Me ₃ -Ph
	986	Me	C(OH)Ph-3-pyridyl	2,4,6-Me ₃ -Ph
	987	Me	Ph	2,4,6-Me ₃ -Ph
	988	Me	2-Ph-Ph	2,4,6-Me ₃ -Ph
10	989	Me	3-pentyl	2,4,6-Me ₃ -Ph
	990	Me	cyclobutyl	2,4,6-Me ₃ -Ph
	991	Me	3-pyridyl	2,4,6-Me ₃ -Ph
	992	Me	CH(Et)CH ₂ CONMe ₂	2,4,6-Me ₃ -Ph
	993	Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4,6-Me ₃ -Ph
15	994	Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	995	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	996	Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	997	Me	NH-3-pentyl	2,4-Me ₂ -Ph
	998	Me	NEt ₂	2,4-Me ₂ -Ph
20	999	Me	N(CH ₂ CN) ₂	2,4-Me ₂ -Ph
	1000	Me	NHCH(Me)CH ₂ OMe	2,4-Me ₂ -Ph
	1001	Me	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	1002	Me	NPr-c-C ₃ H ₅	2,4-Me ₂ -Ph
	1003	Me	NHCH(Me)CH ₂ NMe ₂	2,4-Me ₂ -Ph
25	1004	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	1005	Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	1006	Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	1007	Me	NHCHPr ₂	2,4-Me ₂ -Ph
	1008	Me	NEtBu	2,4-Me ₂ -Ph
30	1009	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Me ₂ -Ph
	1010	Me	NH-3-heptyl	2,4-Me ₂ -Ph
	1011	Me	NEt ₂	2,4-Me ₂ -Ph
	1012	Me	NHCH(CH ₂ OEt) ₂	2,4-Me ₂ -Ph
	1013	Me	NH-3-pentyl	2,4-Me ₂ -Ph
35	1014	Me	NMePh	2,4-Me ₂ -Ph
	1015	Me	NPr ₂	2,4-Me ₂ -Ph

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	1016	Me	NH-3-hexyl	2,4-Me ₂ -Ph
	1017	Me	morpholino	2,4-Me ₂ -Ph
	1018	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Me ₂ -Ph
	1019	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Me ₂ -Ph
5	1020	Me	NH-4-tetrahydropyranyl	2,4-Me ₂ -Ph
	1021	Me	NH-cyclopentyl	2,4-Me ₂ -Ph
	1022	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-MeO-Ph
	1023	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-MeO-Ph
	1024	Me	NHCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph
10	1025	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-MeO-Ph
	1026	Me	OCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph
	1027	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-MeO-Ph
	1028	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-MeO-Ph
	1029	Me	NHCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph
15	1030	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-MeO-Ph
	1031	Me	OCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph
	1032	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph
	1033	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph
	1034	Me	NHCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph
20	1035	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-NMe ₂ -Ph
	1036	Me	OCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph
	1037	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph
	1038	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph
	1039	Me	NHCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph
25	1040	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-NMe ₂ -Ph
	1041	Me	OCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph
	1042	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph
	1043	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph
	1044	Me	NHCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph
30	1045	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-i-Pr-Ph
	1046	Me	OCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph
	1047	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-Me-Ph
	1048	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-Me-Ph
	1049	Me	NHCH(Et)CH ₂ OMe	2-Br-4-Me-Ph
35	1050	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-Me-Ph
	1051	Me	OCH(Et)CH ₂ OMe	2-Br-4-Me-Ph

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	1052	Me	NHCH (CH ₂ OMe) ₂	2-Me-4-Br-Ph
	1053	Me	N (CH ₂ CH ₂ OMe) ₂	2-Me-4-Br-Ph
	1054	Me	NHCH (Et) CH ₂ OMe	2-Me-4-Br-Ph
	1055	Me	N (Pr) CH ₂ CH ₂ CN	2-Me-4-Br-Ph
5	1056	Me	OCH (Et) CH ₂ OMe	2-Me-4-Br-Ph
	1057	Me	NHCH (CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph
	1058	Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph
	1059	Me	NHCH (CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph
	1060	Me	N (CH ₂ CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph
10	1061	Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	1062	Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	1063	Me	NHCH (CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph
	1064	Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph
	1065	Me	NHCH (CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph
15	1066	Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph
	1067	Me	NHCH (CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph
	1068	Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph
	1069	Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	1070	Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
20	1071	Me	NHCH (CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph
	1072	Me	N (CH ₂ CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph
	1073	Me	NHCH (CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl
	1074	Me	N (CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl
	1075	Me	NHCH (CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph
25	1076	Me	N (CH ₂ CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph
	1077	Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	1078	Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	1079	Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	1080	Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
30	1081	Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	1082	Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	1083	Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	1084	Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	1085	Me	NHCH (CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
35	1086	Me	N (CH ₂ CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	1087	Me	NHCH (CH ₂ OMe) ₂	2-Br-4-N (Me) ₂ -6-MeO-Ph

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	1088	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-N(Me) ₂ -6-MeO-Ph
	1089	Me	NEt ₂	2-Br-4-MeO-Ph
	1090	Me	NH-3-pentyl	2-Br-4-MeO-Ph
	1091	Me	NHCH(CH ₂ OMe) ₂	2-CN-4-Me-Ph
5	1092	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4,6-Me ₃ -Ph
	1093	Me	NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-Br-Ph
	1094	Me	NHCH(CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph
	1095	Me	N(CH ₂ CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph
	1096	Me	NH-3-pentyl	2,5-Me ₂ -4-MeO-Ph
10	1097	Me	NEt ₂	2,5-Me ₂ -4-MeO-Ph
	1098	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MePh
	1099	Me	NCH(Et)CH ₂ OMe	2-Cl-4-MePh
	1100	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MePh
	1101	Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Cl-4-MePh
15	1102	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,5-Me ₂ -4-MeOPh
	1103	Me	NEt ₂	2-Me-4-MeOPh
	1104	Me	OEt	2-Me-4-MeOPh
	1105	Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-MeOPh
	1106	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2-Me-4-MeOPh
20	1107	Me	NHCH(CH ₂ CH ₂ OEt) ₂	2-Me-4-MeOPh
	1108	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph
	1109	Me	NEt ₂	2-Me-4-ClPh
	1110	Me	NH-3-pentyl	2-Me-4-ClPh
	1111	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-ClPh
25	1112	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-ClPh
	1113	Me	NEt ₂	2-Me-4-ClPh
	1114	Me	NEt ₂	2-Cl-4-MePh
	1115	Me	NH-3-pentyl	2-Cl-4-MePh
	1116	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh
30	1117	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh
	1118	Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh
	1119	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh
	1120	Me	NEt ₂	2-Cl-4-MeOPh
	1121	Me	NH-3-pentyl	2-Cl-4-MeOPh
35	1123	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	1124	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh

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	1125	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	1126	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	1127	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	1128	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
5	1129	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
	1130	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
	1131	Me	NHCH(Et)CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	1132	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,5-(MeO) ₂ Ph
	1133	Me	NEt ₂	2-Cl-4,5-(MeO) ₂ Ph
10	1134	Me	NH-3-pentyl	2-Cl-4,5-(MeO) ₂ Ph
	1135	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	1136	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	1137	Me	NHCH(CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
	1138	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
15	1139	Me	NHCH(Et)CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	1140	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,5-(MeO) ₂ Ph
	1141	Me	NEt ₂	2-Br-4,5-(MeO) ₂ Ph
	1142	Me	NH-3-pentyl	2-Br-4,5-(MeO) ₂ Ph
	1143	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
20	1144	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
	1145	Me	NEt ₂	2-Cl-4,6-(MeO) ₂ Ph
	1146	Me	NH-3-pentyl	2-Cl-4,6-(MeO) ₂ Ph
	1147	Me	NHCH(CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	1148	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
25	1149	Me	NHCH(Et)CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
	1150	Me	NEt ₂	2-Me-4,6-(MeO) ₂ Ph
	1151	Me	NH-3-pentyl	2-Me-4,6-(MeO) ₂ Ph
	1152	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	1153	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
30	1154	Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	1155	Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	1156	Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
	1157	Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	1158	Me	NEt ₂	2-MeO-4-MePh
35	1159	Me	NH-3-pentyl	2-MeO-4-MePh
	1160	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh

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	1161	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-MeO-4-MePh
	1162	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh
	1163	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	1164	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-MePh
5	1165	Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh
	1166	Me	NEt ₂	2-MeO-4-MePh
	1167	Me	NH-3-pentyl	2-MeO-4-MePh
	1168	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-ClPh
	1169	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
10	1170	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-ClPh
	1171	Me	NEt ₂	2-MeO-4-ClPh
	1172	Me	NH-3-pentyl	2-MeO-4-ClPh

15

Utility

20

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

The following is a description of the
25 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
30 and the coding region was amplified by PCR from start to
stop codons. The resulting PCR fragment was cloned into
the EcoRV site of pGEMV, from whence the insert was
reclaimed using XhoI + XbaI and cloned into the XhoI +
XbaI sites of vector pm3ar (which contains a CMV
35 promoter, the SV40 't' splice and early poly A signals,
an Epstein-Barr viral origin of replication, and a

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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 surviving 4 weeks

5 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 form a pellet and frozen.

10 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 MgCl₂, 2 mM EGTA, 1 μ g/ml aprotinin, 1 μ g/ml leupeptin

15 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 resuspended to a protein concentration of 360 μ g/ml to

20 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 ¹²⁵I-

25 ovine-CRF (¹²⁵I-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

30 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 ¹²⁵I-o-CRF binding to

35 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
5 a K_i value of less than about 10000 nM for the inhibition of CRF.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

10 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°
15 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
20 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/ ^{32}P ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCl, 45 mM ATP and 2% sodium dodecyl sulfate. In
25 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 [^{32}P]cAMP from [^{32}P]ATP is performed by sequential elution over Dowex and alumina columns.

30

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
35 the art. Illustrative of these tests include the

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Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (1990). Compounds may be tested in any species of rodent or small mammal.

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

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

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

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mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

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

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

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

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

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for

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parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances.

- 5 Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain
- 10 preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

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

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

Capsules

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

25

Soft Gelatin Capsules

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

Tablets

- 35 A large number of tablets are prepared by conventional procedures so that the dosage unit was

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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
5 increase palatability or delayed adsorption.

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

10

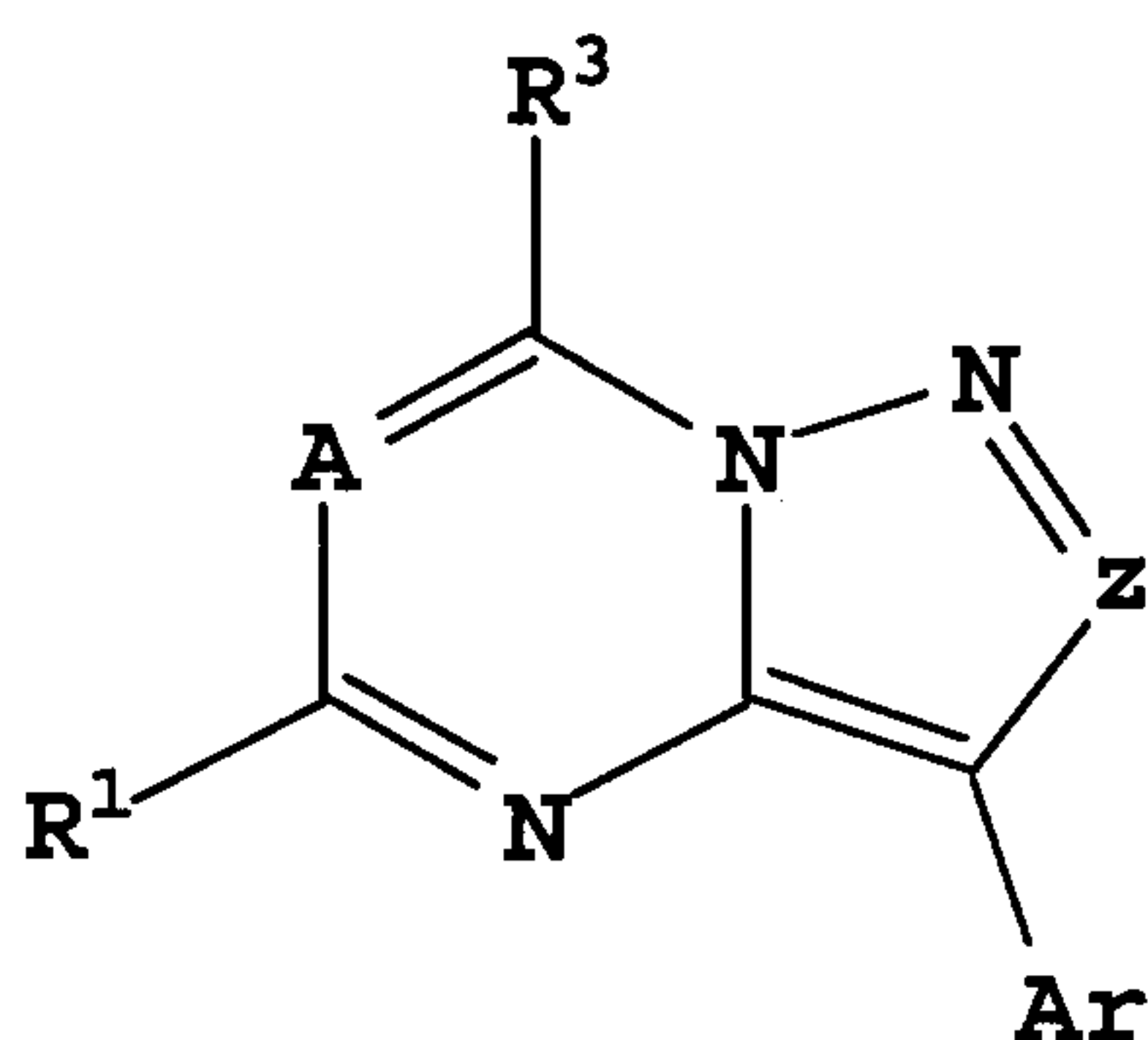
Although the present invention has been
described and exemplified in terms of certain
preferred embodiments, other embodiments will be
apparent to those skilled in the art. The invention
15 is, therefore, not limited to the particular
embodiments described and exemplified, but is capable
of modification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

20

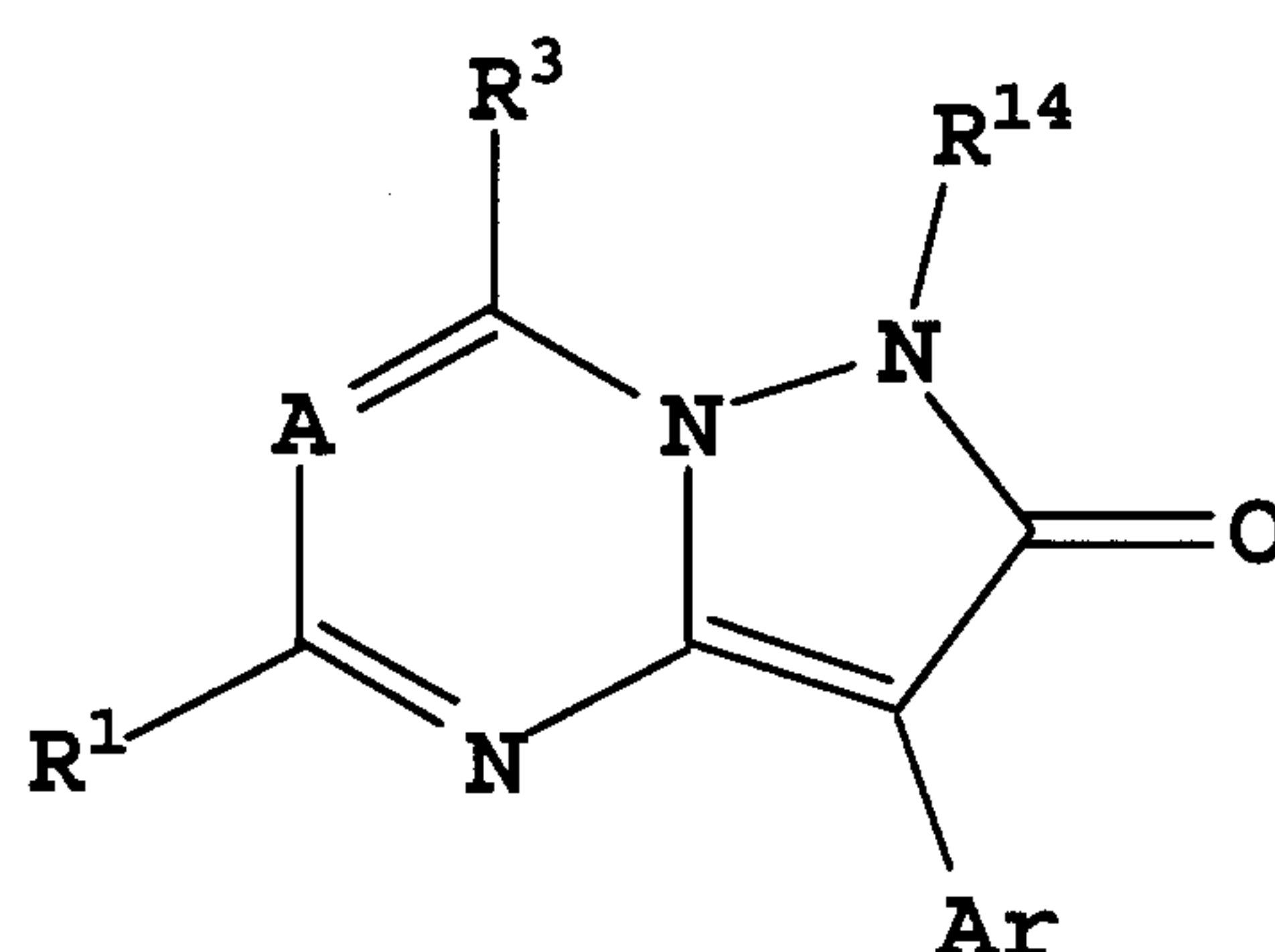
CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formulae (1) or (2):



(1)



(2)

10

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein:

15

A is CR;

Z is N or CR²;

20

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is attached to an unsaturated carbon atom;

25

R is independently selected at each occurrence from
 H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo,
 5 CN, C₁-C₄ haloalkyl;

R¹ is independently selected at each occurrence from
 H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
 10 C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
 cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
 C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or
 S(O)_nR¹²;

15 R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
 C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
 cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
 -NR⁶R⁷, NR⁹COR¹⁰, C₁-C₄ haloalkyl, -OR⁷, SH or
 -S(O)_nR¹²;

20

R³ is selected from:

-H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
 OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
 NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
 25 CONR⁶R⁷, aryl, heteroaryl and
 heterocyclyl, or
 -C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
 C₁₂ cycloalkylalkyl or C₆-C₁₀
 30 cycloalkenylalkyl, each optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence
 from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 35 S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,

NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl and heterocyclyl;

R⁴ is independently selected at each occurrence
5 from: C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-
C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, NO₂, halo, CN, C₁-
C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷, NR⁸CO₂R⁷, COR⁷,
OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷, or S(O)_nR⁷,
10 where each such C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,
C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-
C₁₂ cycloalkylalkyl are optionally substituted
with 1 to 3 substituents independently selected
at each occurrence from C₁-C₄ alkyl, NO₂, halo,
15 CN, NR⁶R⁷, NR⁸COR⁷, NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷,
CO₂R⁷, CO(NOR⁹)R⁷, or S(O)_nR⁷;

R⁶ and R⁷, R^{6a} and R^{7a} are independently selected at
each occurrence from:
20 -H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
25 or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at
each occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
30 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl),
alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
5 piperidine, pyrrolidine, piperazine, N-
methylpiperazine, morpholine or thiomorpholine, each
optionally substituted with 1-3 C₁-C₄ alkyl groups;

10 R⁸ is independently selected at each occurrence from
H or C₁-C₄ alkyl;

R⁹ and R¹⁰ are independently selected at each
occurrence from H, C₁-C₄ alkyl, or C₃-C₆
cycloalkyl;

15 R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄
haloalkyl, or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;

20 R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl,
C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-,
heteroaryl or heteroaryl(C₁-C₄ alkyl)-;

25 R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl,
C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-
C₁₂ cycloalkylalkyl, each optionally
substituted with 1 to 3 substituents
30 independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-
C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵,
CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,

and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and
C₁-C₆ alkylsulfonyl;

5 R¹⁵ and R¹⁶ are independently selected at each
occurrence from H, C₁-C₆ alkyl, C₃-C₁₀
cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that
for S(O)_nR¹⁵, R¹⁵ cannot be H;

10 aryl is phenyl or naphthyl, each optionally
substituted with 1 to 5 substituents
independently selected at
each occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano,
OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵,
15 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵,
NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heteroaryl is pyridyl, pyrimidinyl, triazinyl,
furanyl, pyranyl, quinolinyl, isoquinolinyl,
20 thienyl, imidazolyl, thiazolyl, indolyl,
pyrrolyl, oxazolyl, benzofuranyl, benzothienyl,
benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-
dihydrobenzothienyl or 2,3-dihydrobenzofuranyl,
each being optionally substituted with 1 to 5
25 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and
30 CONR¹⁶R¹⁵;

heterocyclyl is saturated or partially saturated
heteroaryl, optionally substituted with 1 to 5
substituents independently selected at each
35 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,

halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
 CONR¹⁶R¹⁵;

5

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

with the provisos that:

- 10 (1) when R is H, and Z is CR², Ar is not phenyl or
 substituted phenyl;
- (2) when Z is CR², then R² is not -NR⁶SO₂R⁷ or
 -SO₂NR⁶R⁷;
- 15 (3) when R is H, Z is CR², R¹ is OR¹¹, R² is H, R³ is
 OR⁷, and R⁷ and R¹¹ are both H, then Ar is not
 pyridyl or naphthyl;
- 20 (4) when R¹ is -(C₁-C₂ alkylene)-O-(C₁-C₂ alkyl) or
 -(C₁-C₂ alkylene)-OH, then at least one of the
 following conditions (i), (ii) and (iii) is
 true:
- (i) the compound is a compound of formula (2);
- 25 (ii) Ar is selected from optionally substituted
 naphthyl, triazinyl, furanyl, thienyl,
 benzothienyl, benzofuranyl, 2,3-
 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl,
 indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-
 30 benzopyranyl, and tetralinyl;
- (iii) R³ is selected from H, SH, S(O)_nR¹³ wherein
 n = 1, CO₂R⁷, OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂,
 NR⁸CONR⁶R⁷, NR⁸CO₂R¹³, N(OR⁷)R⁶, CONR⁶R⁷, aryl
 other than optionally substituted phenyl,
 35 heteroaryl other than (a) optionally
 substituted pyrazinyl, (b) optionally

substituted pyrimidyl or (c) optionally substituted pyridazinyl, or heterocyclyl; and

- (5) when R^3 is C_5-C_8 cycloalkenyl or C_6-C_{10} cycloalkenylalkyl, then at least one of the following conditions (i), (ii) and (iii) is true:
- (i) the compound is a compound of formula (2);
 - (ii) Ar is selected from optionally substituted naphthyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, and tetralinyl;
 - (iii) R^1 is selected from C_2-C_4 alkenyl, C_2-C_4 alkynyl, CN, C_1-C_4 haloalkyl, C_3-C_{12} hydroxyalkyl-, C_4-C_{12} alkoxyalkyl other than $-(C_1-C_2 \text{ alkylene})-O-(C_1-C_2 \text{ alkyl})$, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{16} , C_1-C_4 alkyl- NR^9R^{10} , NR^9COR^{16} , OR^{11} , SH or $S(O)_nR^{12}$.

2. A compound of claim 1 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 1.

4. A compound of Formula (2) of claim 1 and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

5. A compound of claim 4 and isomers thereof,
5 stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.
10
6. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is
15 NR^{6a}R^{7a} or OR⁷.
7. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically
20 acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.
- 25 8. A compound of Formula (1) of claim 1 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR².
30
9. A compound of claim 8 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is
35 phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

10. A compound of claim 8 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
5 acceptable salt or pro-drug forms thereof wherein R^3 is
NR^{6a}R^{7a} or OR⁷.

11. A compound of claim 8 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
10 stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein Ar is
phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar
is optionally substituted with 1 to 4 R^4 substituents,
and R^3 is NR^{6a}R^{7a} or OR⁷.

15

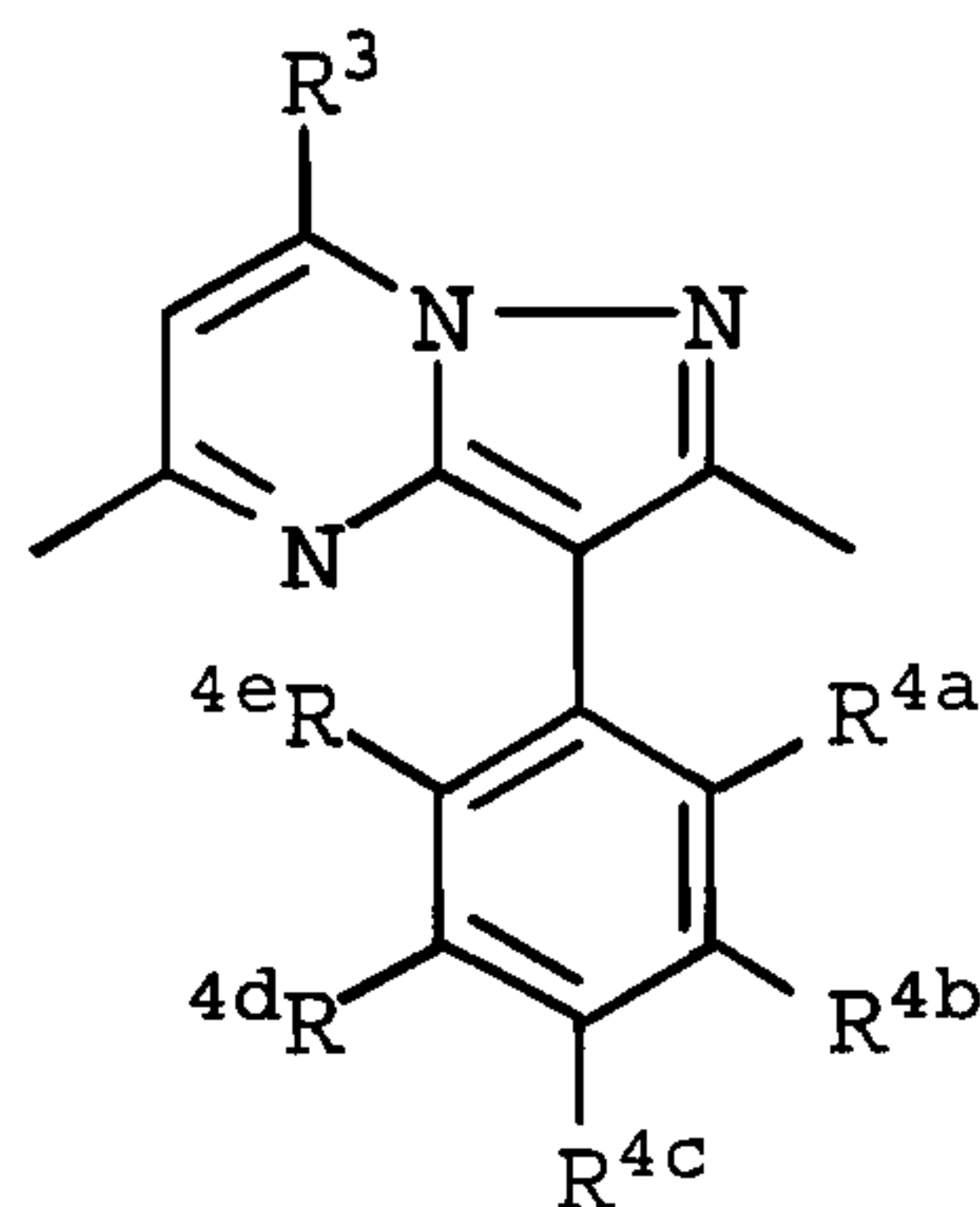
12. A compound of claim 11 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
20 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
and each such C₁-C₁₀ alkyl is optionally
substituted with 1 to 3 substituents independently
selected at each occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵,
25 SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵,
N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵,
CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

13. A compound of claim 8 and isomers thereof,
30 stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl,
and each Ar is optionally substituted with 1
35 to 4 R^4 substituents,
-R³ is NR^{6a}R^{7a} or OR⁷ and

-R¹ and R² are independently selected from H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl.

5 14. A compound of claim 13 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
 10 and each such C₁-C₁₀ alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵,
 15 N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

15. A compound of Formula (51)



20 FORMULA (51)

and isomers thereof, stereoisomeric forms thereof, or
 25 mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:

- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(n-Bu)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 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 (51) 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 H;
- 10 a compound of Formula (51) wherein R^3 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 (51) wherein R^3 is
(S)-NHCH(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 (51) wherein R^3 is
-NHCH(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 (51) wherein R^3 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 (51) wherein R^3 is -NHCH(n-Pr)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e}
is H;
- 35 a compound of Formula (51) wherein R^3 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;
- a compound of Formula (51) wherein R^3 is
(S)-NHCH(CH₂CH₂OMe)CH₂OMe, 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 (51) wherein R^3 is
 $-NHCH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c}
 is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is
 $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is
 H;
- 15 a compound of Formula (51) wherein R^3 is
 $(S) -NHCH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H,
 R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is
 $-NHCH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c}
 is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a}
 is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is
 $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is
 $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is
 Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is
 $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is
 $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is
 Me, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) 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;
- 5 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$,
 R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e}
is H;
- 10 a compound of Formula (51) wherein R^3 is
 $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is
 $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a}
is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) 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;
- 30 a compound of Formula (51) wherein R^3 is
 $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
 R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is
 $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
 R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is
 $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
 R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e}
is H;
- 5 a compound of Formula (51) wherein R^3 is
 $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
 R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e}
is H;
- 15 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e}
is H;
- 20 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e}
is H;
- 25 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e}
is H;
- 30 a compound of Formula (51) wherein R^3 is
 $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H.
- 35 16. A compound of claim 13 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof, wherein
said compound is 7-(3-pentylamino)-2,5-dimethyl-3-
(2-methyl-4-methoxyphenyl)-[1,5-a]-
40 pyrazolopyrimidine.

17. A compound of claim 13 and and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 7-(diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine.

18. A compound of claim 13 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

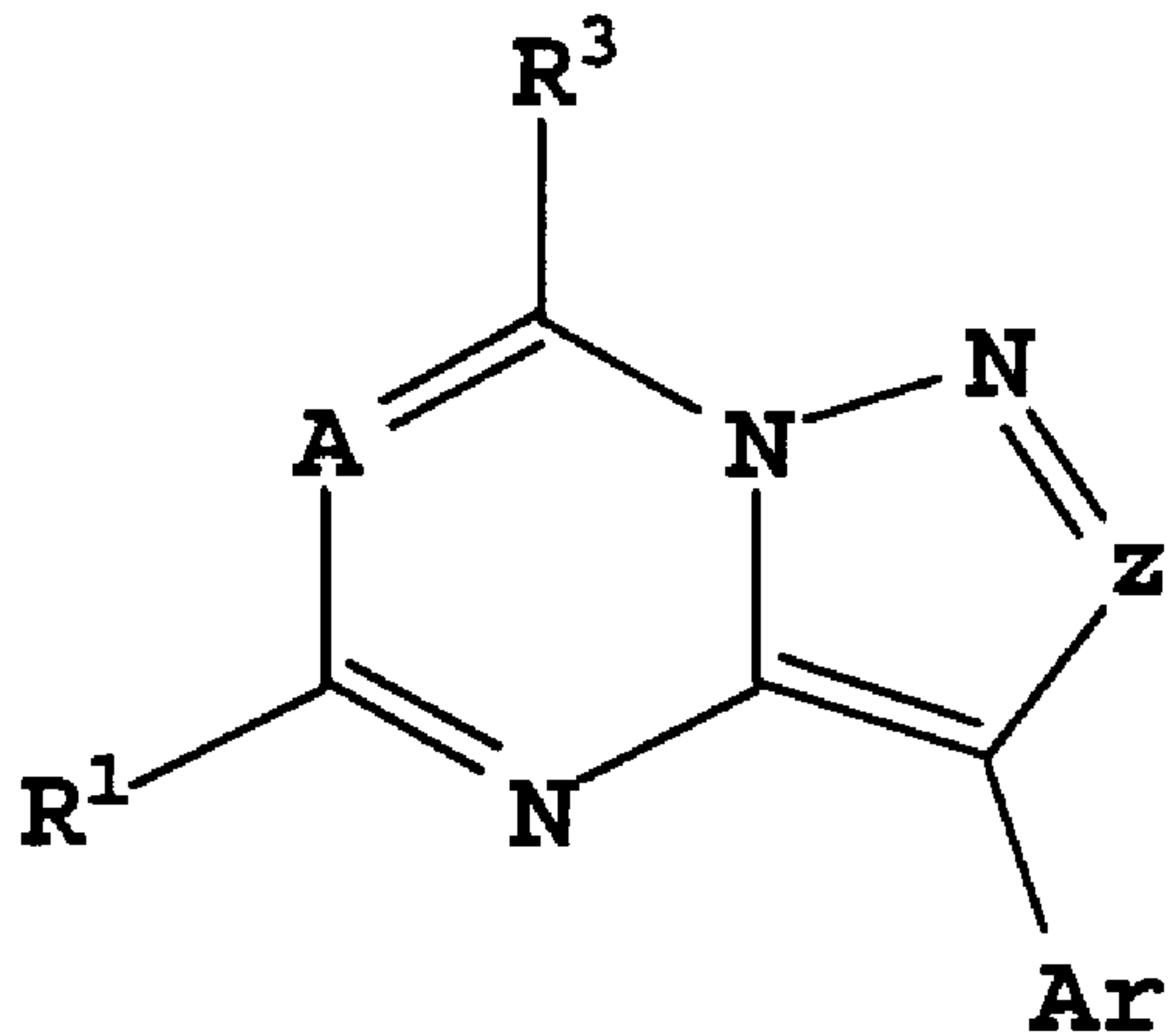
19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 15.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 16.

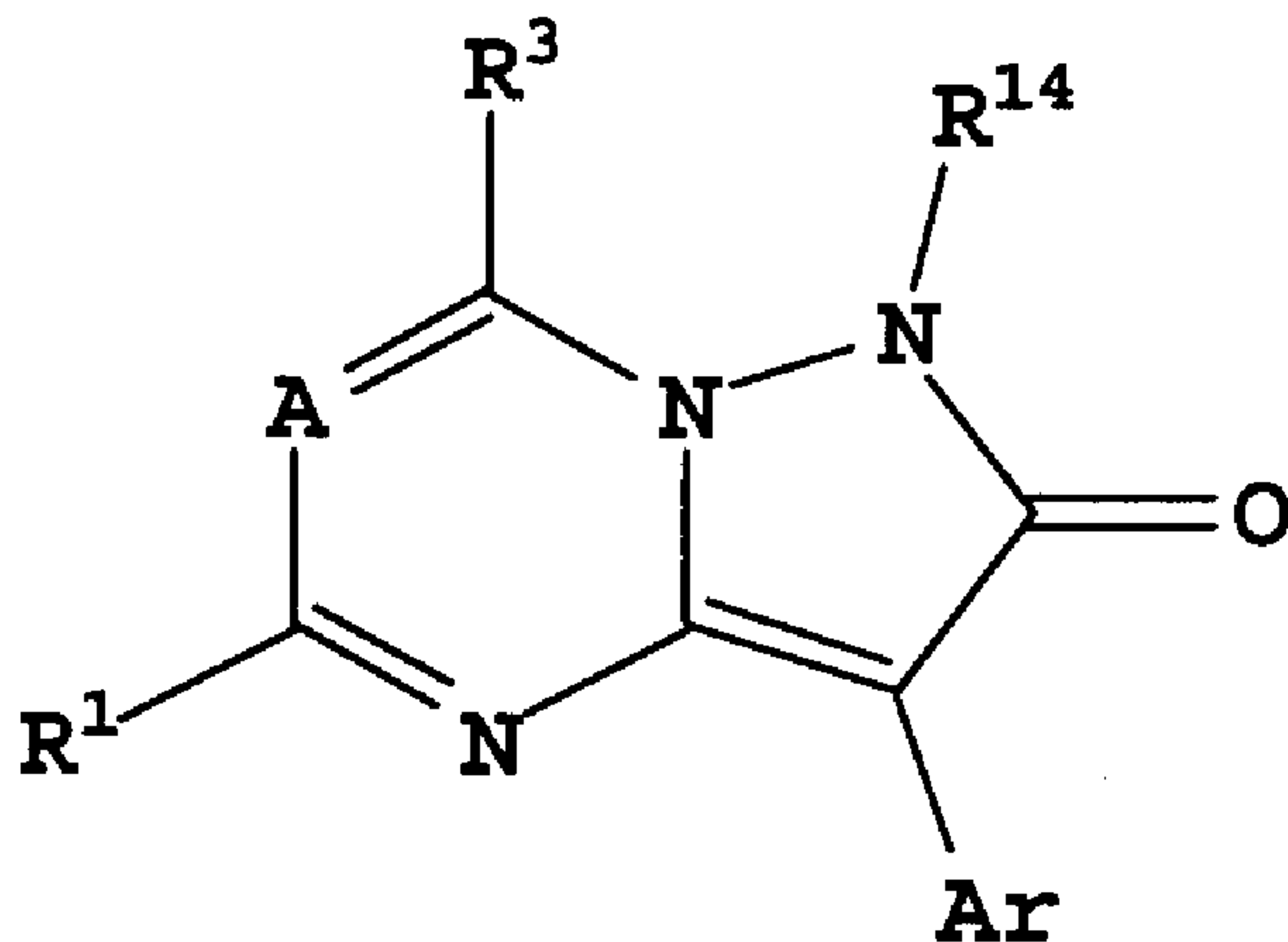
21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 17.

22. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 18.

23. Use of a compound according to any one of
claims 1 or 15-18 in the manufacture of a medicament
for treating affective disorder, anxiety,
depression, headache, irritable bowel syndrome,
5 post-traumatic stress disorder, supranuclear palsy,
immune suppression, Alzheimer's disease,
gastrointestinal diseases, anorexia nervosa or other
feeding disorder, drug addiction, drug or alcohol
withdrawal symptoms, inflammatory diseases,
10 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
15 can be effected or facilitated by antagonizing CRF,
including but not limited to disorders induced or
facilitated by CRF, in mammals.



(I)



(II)