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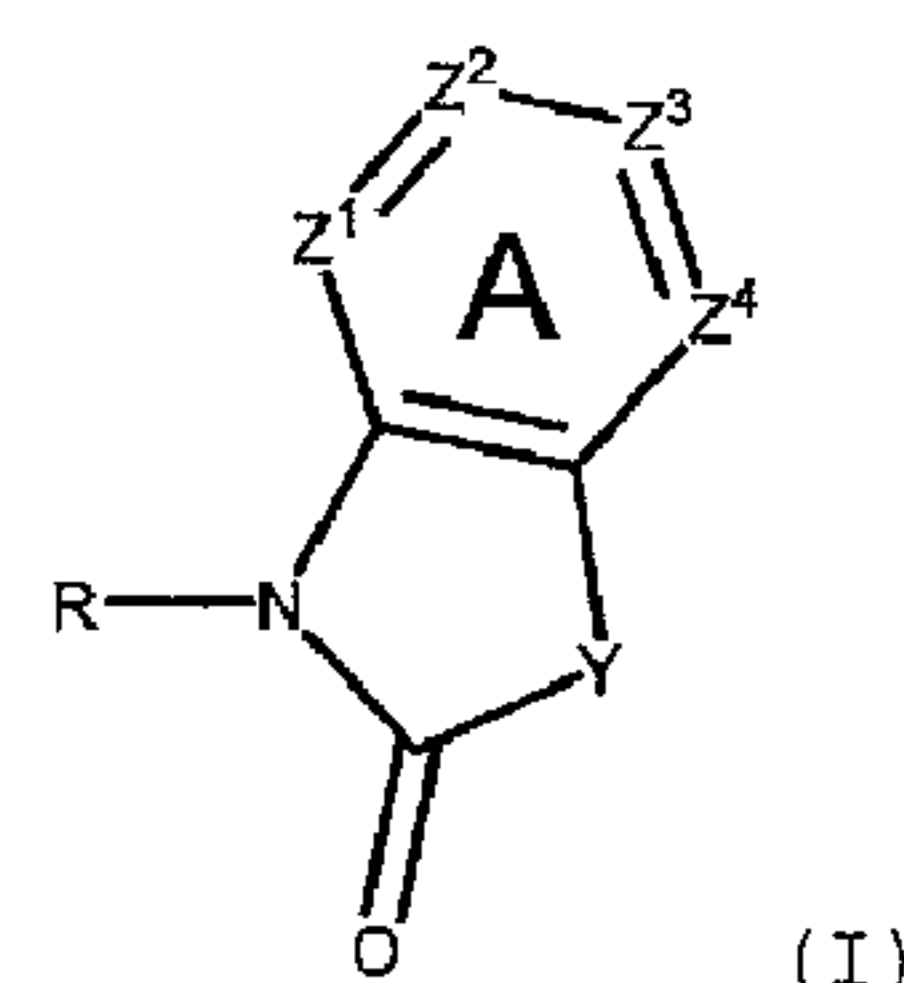
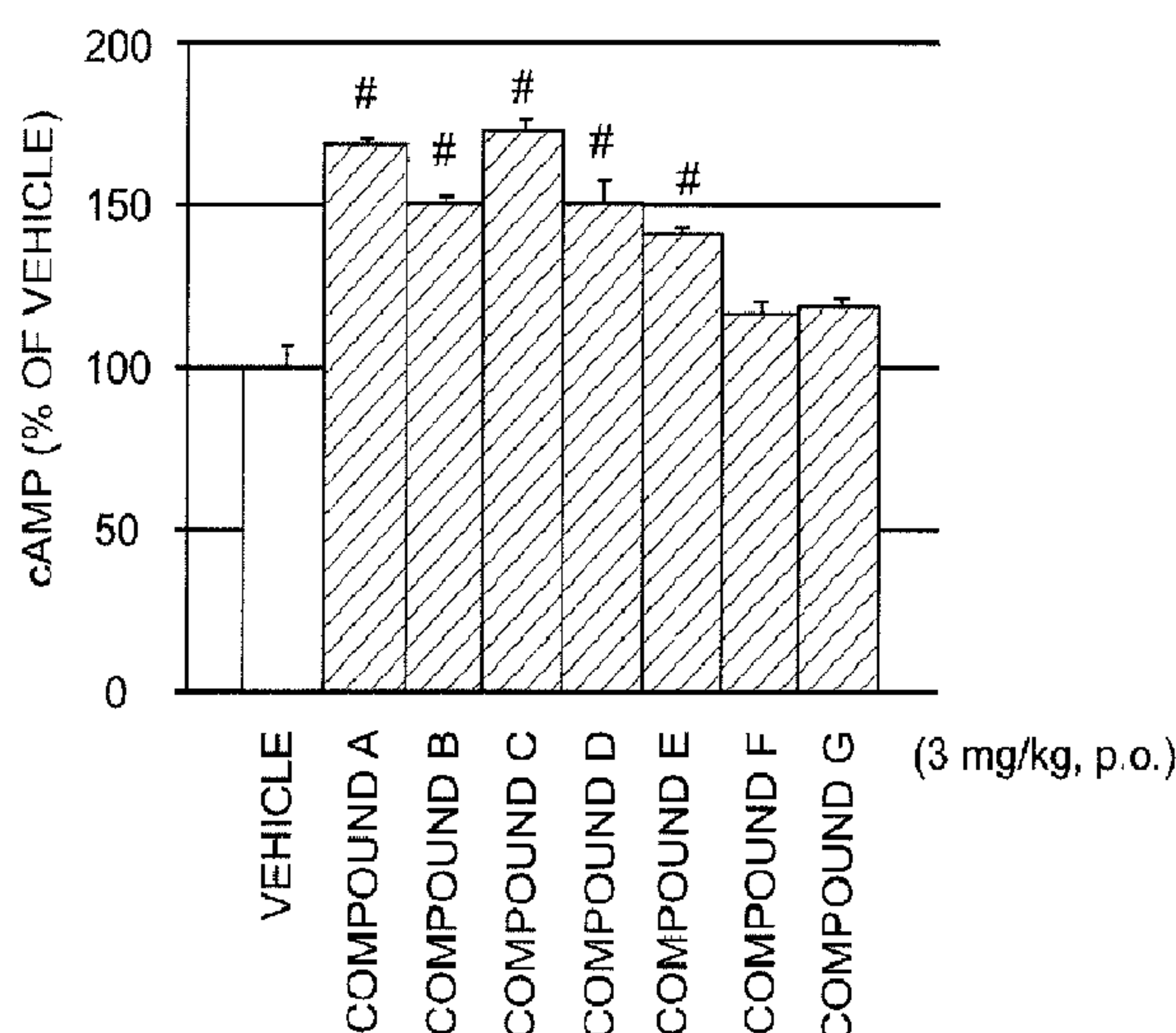
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(54) Titre : COMPOSES HETEROCYCLIQUES CONDENSES COMME INHIBITEURS DE PHOSPHODIESTERASES (PDES)

(54) Title: FUSED HETEROCYCLIC COMPOUNDS AS PHOSPHODIESTERASES (PDES) INHIBITORS



(57) Abrégé/Abstract:

The present invention provides a compound which has the effect of PDE inhibition, and which is useful as an agent for preventing or treating schizophrenia or so on represented by the formula (I) :

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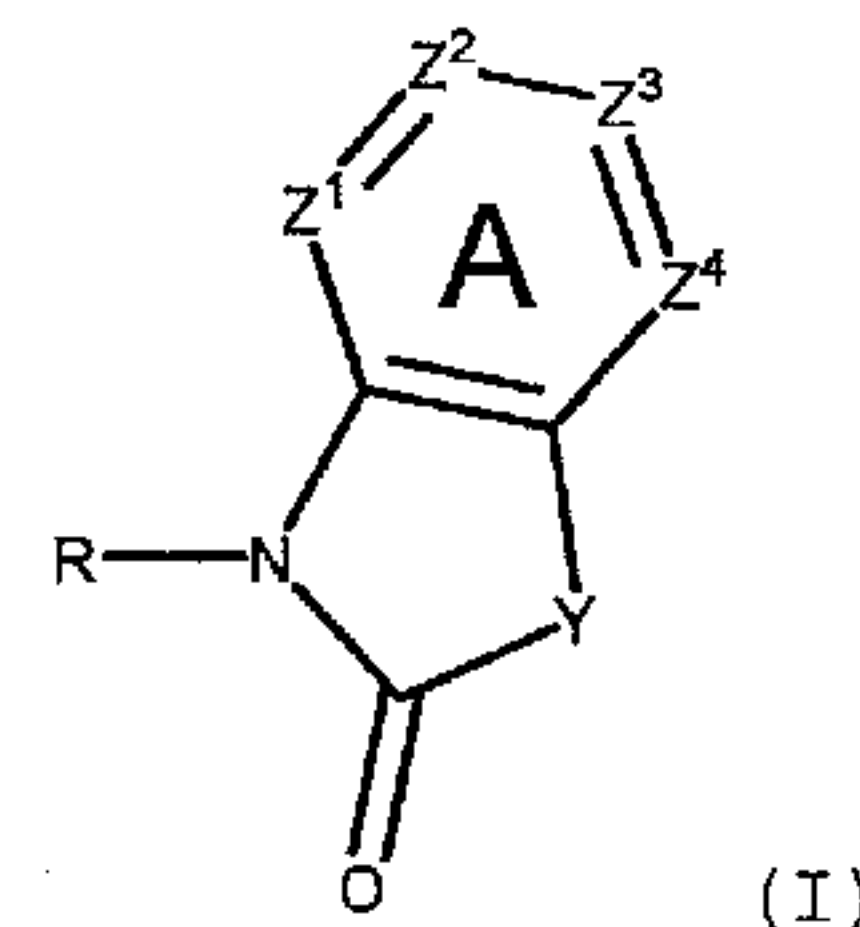
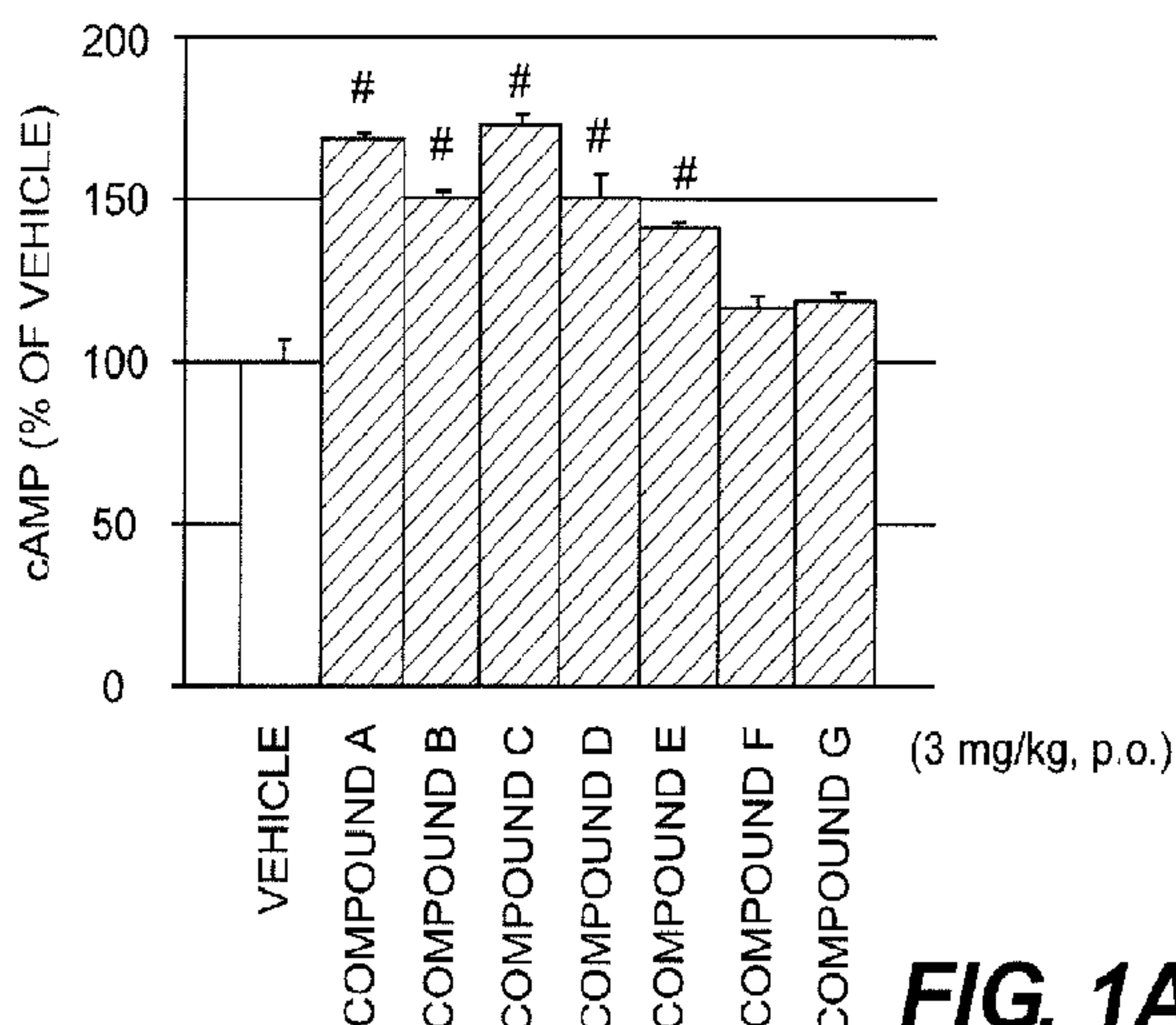
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[Continued on next page]

(54) Title: FUSED HETEROCYCLIC COMPOUNDS AS PHOSPHODIESTERASES (PDES) INHIBITORS

**FIG. 1A**

(57) **Abstract:** The present invention provides a compound which has the effect of PDE inhibition, and which is useful as an agent for preventing or treating schizophrenia or so on represented by the formula (I) :

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DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD,
SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
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COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

DESCRIPTION**Title of Invention**

FUSED HETEROCYCLIC COMPOUNDS AS PHOSPHODIESTERASES (PDES) INHIBITORS

Technical Field

5 [0001]

The present invention relates to fused heterocyclic compounds.

Background of the Invention

[0002]

10 Phosphodiesterases (PDEs) are a superfamily of enzymes encoded by 21 genes and subdivided into 11 distinct families according to structural and functional properties. These enzymes metabolically inactivate the ubiquitous intracellular second messengers, cyclic adenosine monophosphate (cAMP) and
15 cyclic guanosine monophosphate (cGMP); PDEs selectively catalyze the hydrolysis of the 3'-ester bond, forming the inactive 5'-monophosphate. On the basis of substrate specificity, the PDE families can be further classified into three groups: i) the cAMP-PDEs (PDE4, PDE7, PDE8), ii) the
20 cGMP-PDEs (PDE5, PDE6 and PDE9), and iii) the dual-substrate PDEs (PDE1, PDE2, PDE3, PDE10 and PDE11).

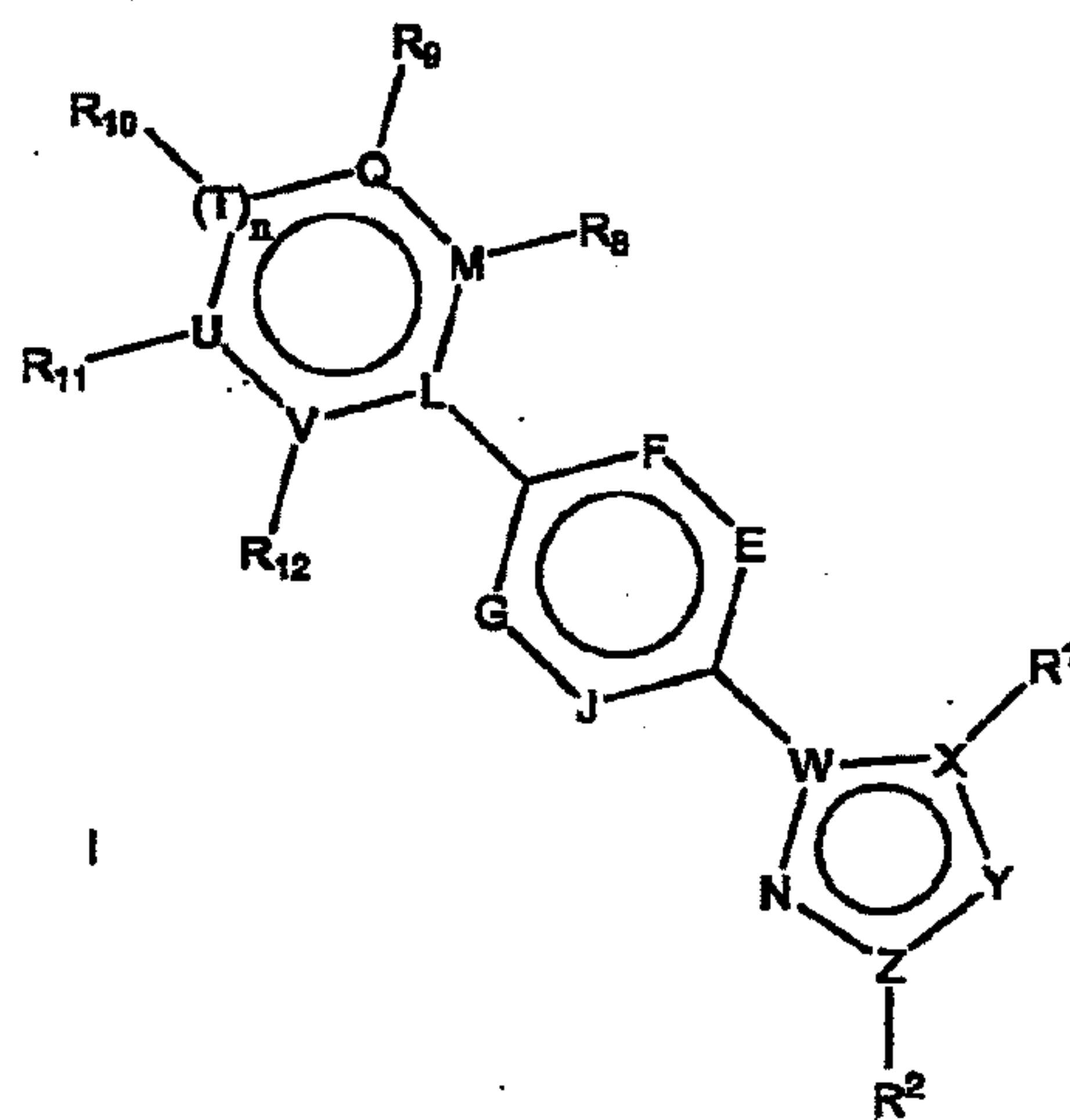
The cAMP and cGMP are involved in the regulation of virtually every physiological process such as pro-inflammatory mediator production and action, ion channel function, muscle
25 relaxation, learning and memory formation, differentiation, apoptosis, lipogenesis, glycogenolysis and gluconeogenesis. Especially, in neurons, these second messengers have important role in the regulation of synaptic transmission as well as in neuronal differentiation and survival (Nat. Rev. Drug Discov.
30 2006, vol. 5: 660-670). Regulation of these processes by cAMP and cGMP are accompanied by activation of protein kinase A (PKA) and protein kinase G (PKG), which in turn phosphorylate a variety of substrates, including transcription factors, ion channels and receptors that regulate a variety of
35 physiological processes. Intracellular cAMP and cGMP

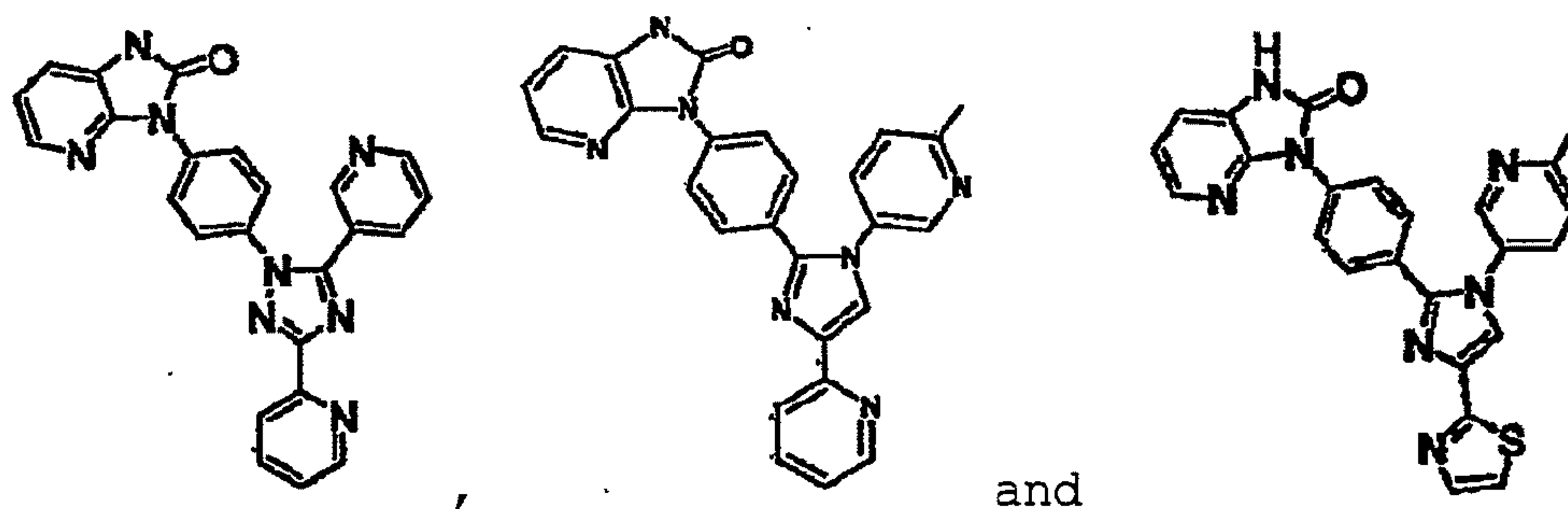
concentrations seem to be temporally, spatially, and functionally compartmentalized by regulation of adenylyl and guanylyl cyclases in response to extracellular signaling and their degradation by PDEs (Circ. Res. 2007, vol. 100(7): 950-
5 966). PDEs provide the only means of degrading the cyclic nucleotides cAMP and cGMP in cells, thus PDEs play an essential role in cyclic nucleotide signaling. Thereby, PDEs could be promising targets for various therapeutic drugs.

Phosphodiesterase 10A (PDE10A) was discovered in 1999 by
10 three independent groups (Proc. Natl. Acad. Sci. USA 1999, vol. 96: 8991-8996, J. Biol. Chem. 1999, vol. 274: 18438-18445, Gene 1999, vol. 234: 109-117). Expression studies have shown that PDE10A has the most restricted distribution within the all known PDE families; the PDE10A mRNA is highly expressed
15 only in brain and testes (Eur. J. Biochem. 1999, vol. 266: 1118-1127, J. Biol. Chem. 1999, vol. 274: 18438-18445). In the brain, mRNA and protein of PDE10A are highly enriched in medium spiny neurons (MSNs) of the striatum (Eur. J. Biochem. 1999, vol. 266: 1118-1127, Brain Res. 2003, vol. 985: 113-126).
20 MSNs are classified into two groups: the MSN that express D₁ dopamine receptors responsible for a direct (striatonigral) pathway and the MSN that express D₂ dopamine receptors responsible for an indirect (striatopallidal) pathway. The function of direct pathway is to plan and execution, while
25 indirect pathway is to act as a brake on behavioral activation. As PDE10A expresses in both MSNs, PDE10A inhibitors could activate both of these pathways. The antipsychotic efficacy of current medications, D₂ or D₂/5-HT_{2A} antagonists, mainly derives from their activation of the indirect pathway in the striatum.
30 As PDE10A inhibitors are able to activate this pathway, this suggests that PDE10A inhibitors are promising as antipsychotic drugs. The excessive D₂ receptor antagonism in the brain by D₂ antagonists causes problems of extrapyramidal side effects and hyperprolactinaemia. However the expression of PDE10A is
35 limited to these striatal pathways in the brain, thus side

effects by PDE10A inhibitors were expected to be weaker compared with current D₂ antagonists. Regarding hyperprolactinaemia, PDE10A inhibitors would produce no prolactin elevation due to lack of D₂ receptor antagonism in the pituitary. Moreover, the presence of PDE10A in a direct pathway makes it likely that PDE10A inhibition will have some advantage over current D₂ antagonists; the direct pathway is thought to promote desired action, and activation of this pathway by PDE10A inhibitors may counteract extrapyramidal symptoms induced by excessive D₂ receptor antagonism. In addition, activation of this pathway could facilitate striatal-thalamic outflow, promoting the execution of procedural strategies. Furthermore, enhancement of second messenger levels without blockade of dopamine and/or other neurotransmitter receptors may also provide therapeutic advantages with fewer adverse side-effects compared with current antipsychotics (e.g., hyperprolactinaemia and weight gain). This unique distribution and function in the brain indicates that PDE10A represents an important new target for the treatment of neurological and psychiatric disorders, in particular psychotic disorders like schizophrenia.

As a phosphodiesterase (PDE) 10 inhibitor, compounds represented by the formulae:



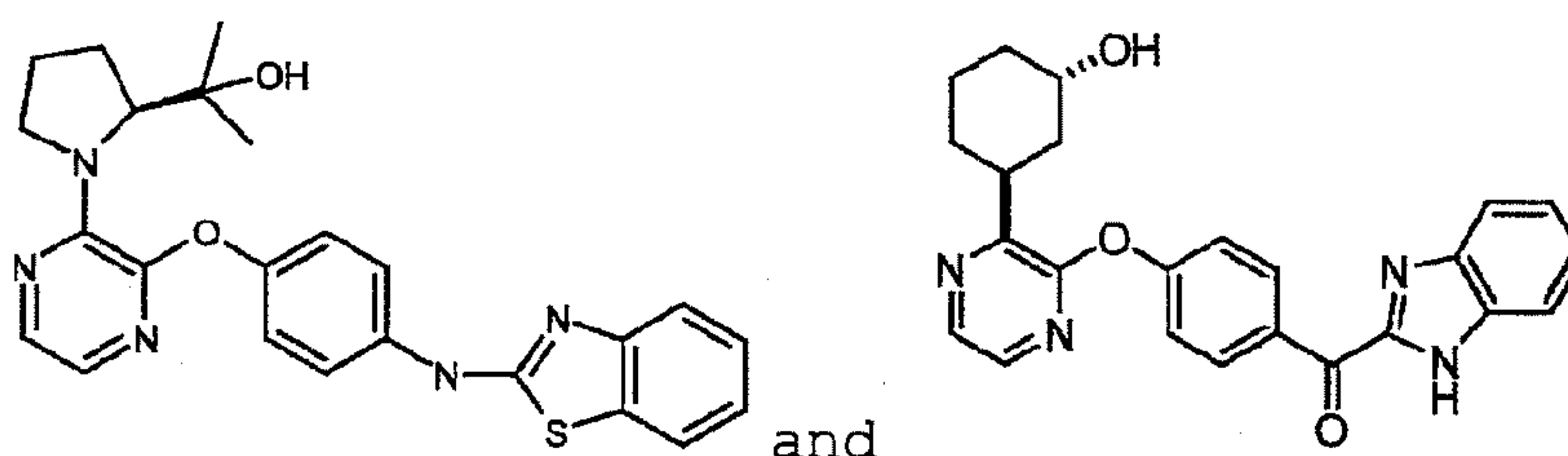
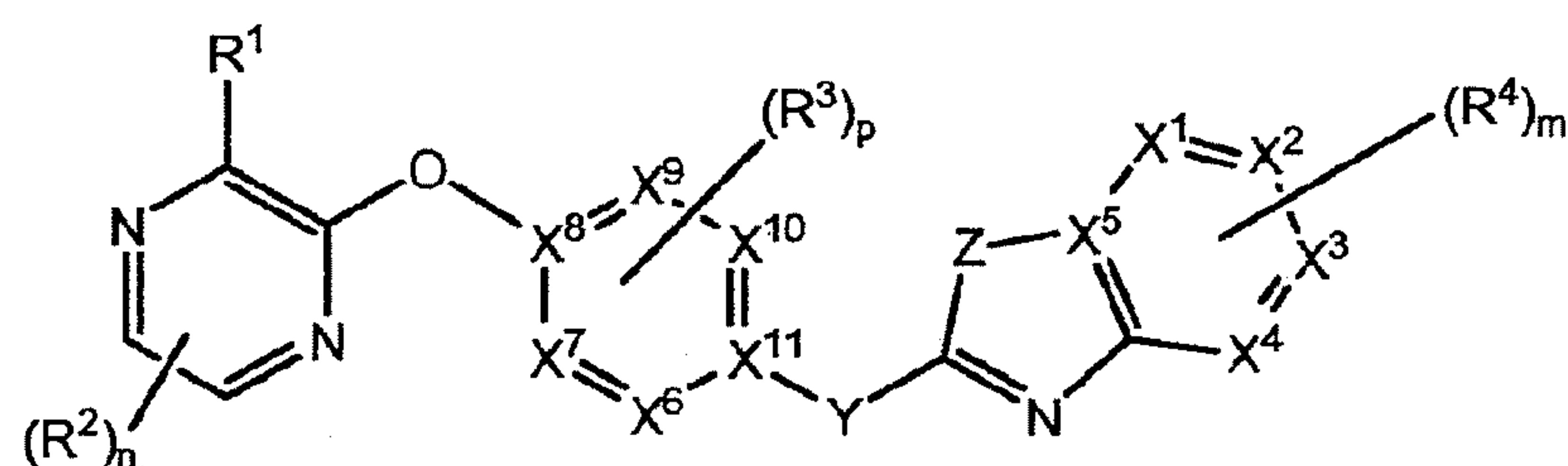


and

were disclosed in WO2008/004117 Pamphlet.

Further, as a phosphodiesterase (PDE) 10 inhibitor, compounds represented by the formulae:

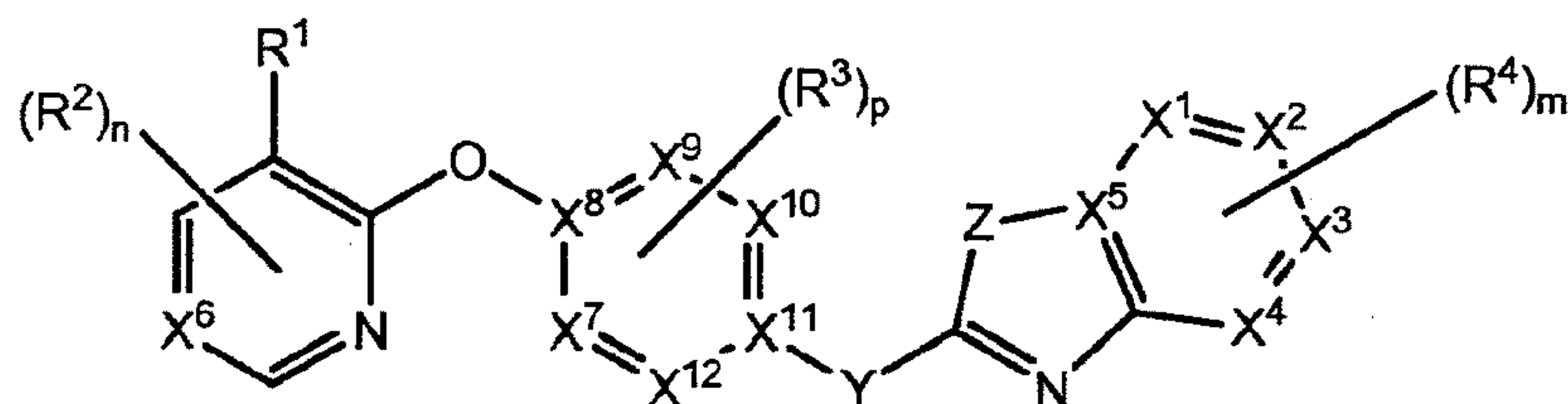
5 [0003]

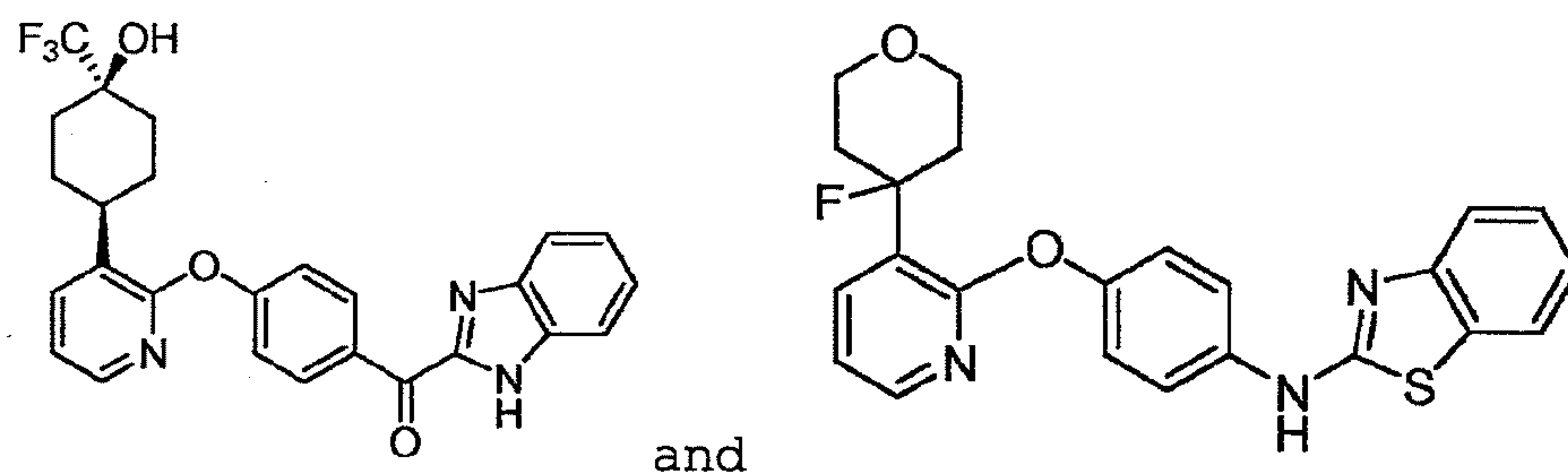


and

were disclosed in WO2010/0057121 Pamphlet.

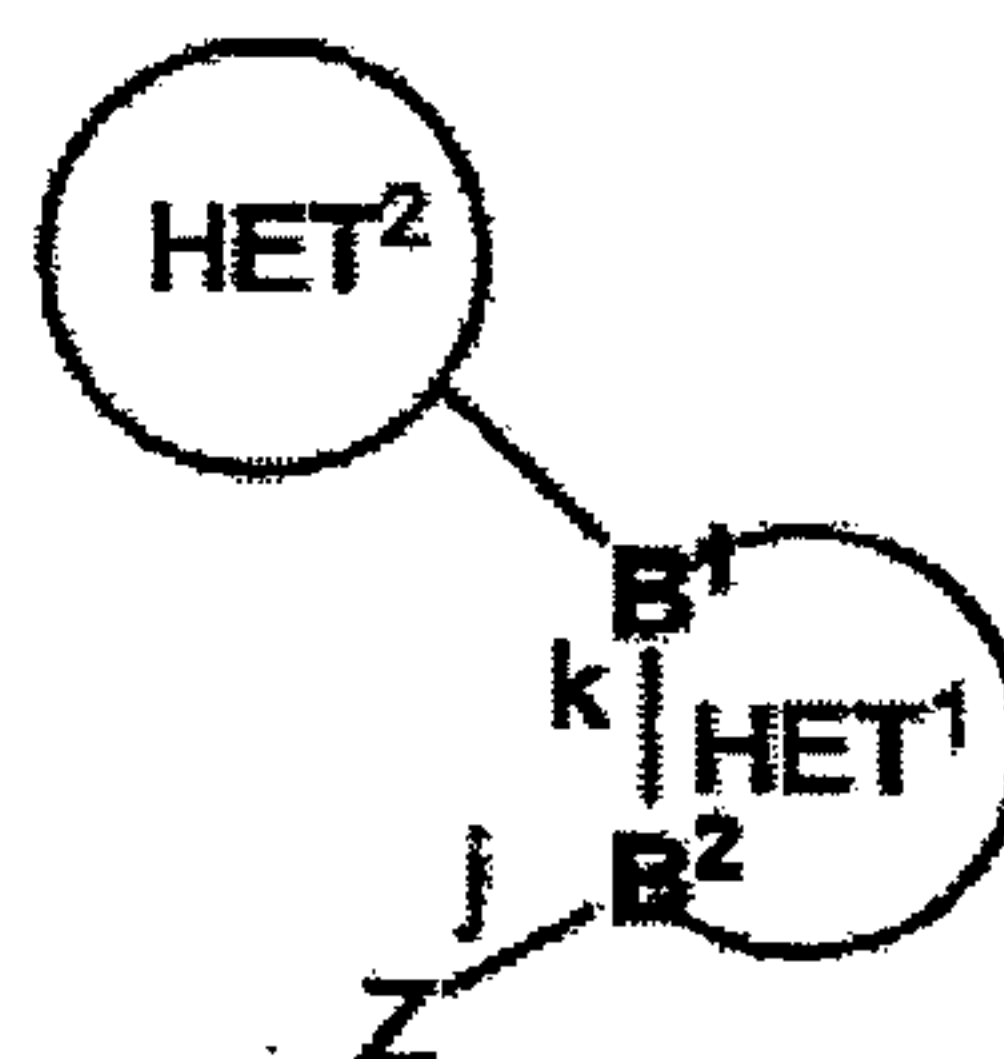
Further, as a phosphodiesterase (PDE) 10 inhibitor, compounds represented by the formulae:



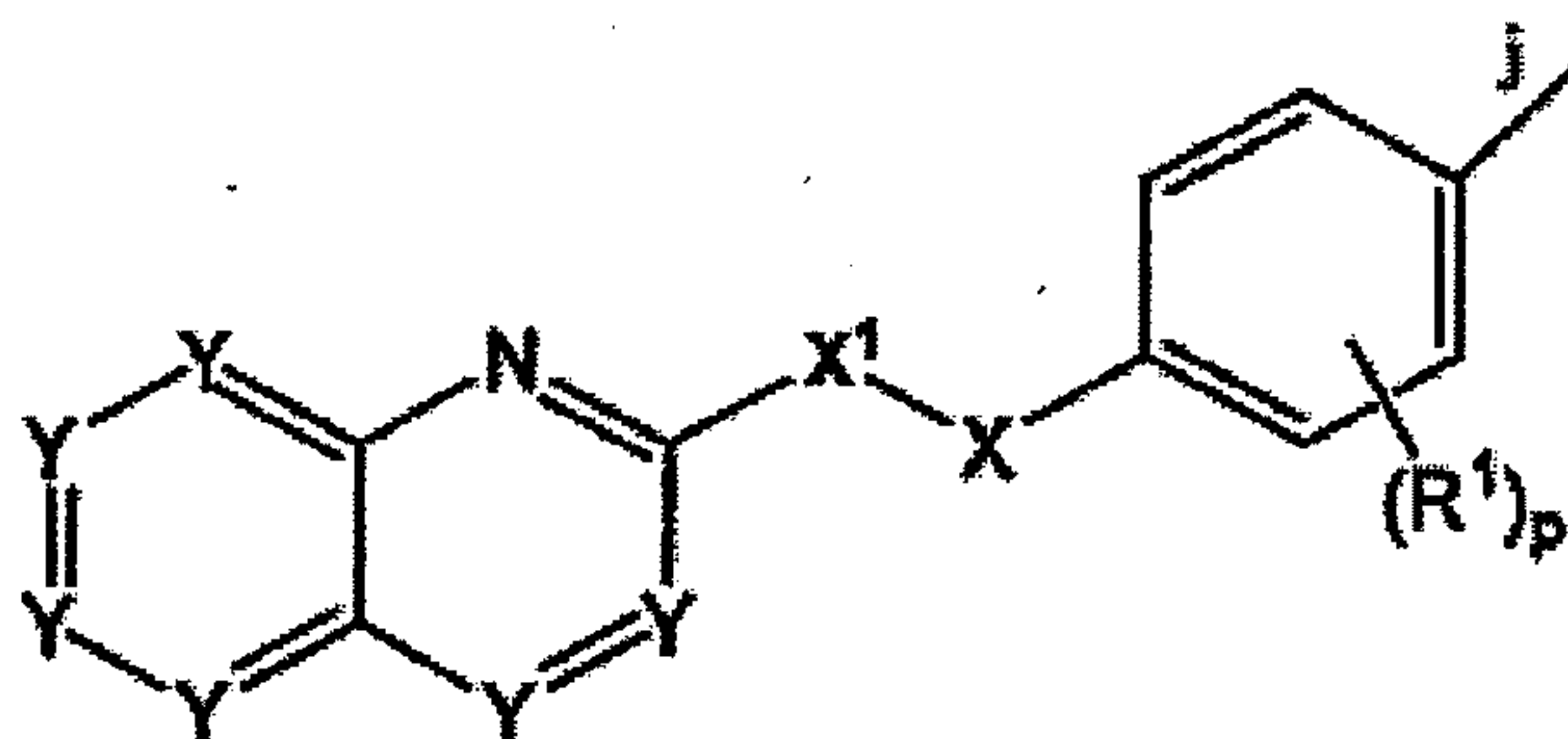


were also disclosed in W02010/57126 Pamphlet.

Further as a phosphodiesterase (PDE) 10 inhibitor, a compound represented by the formula:



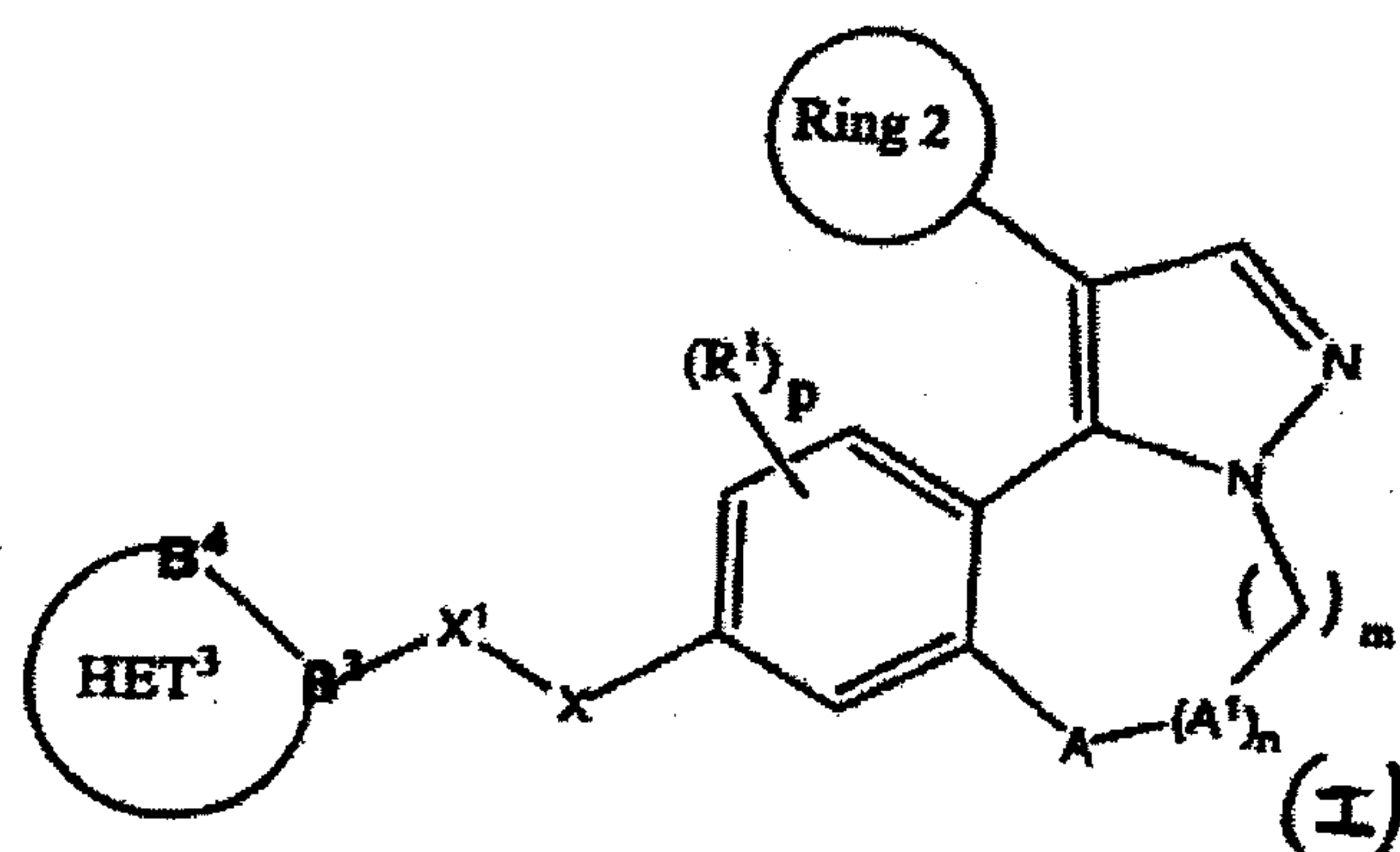
wherein Z is



5

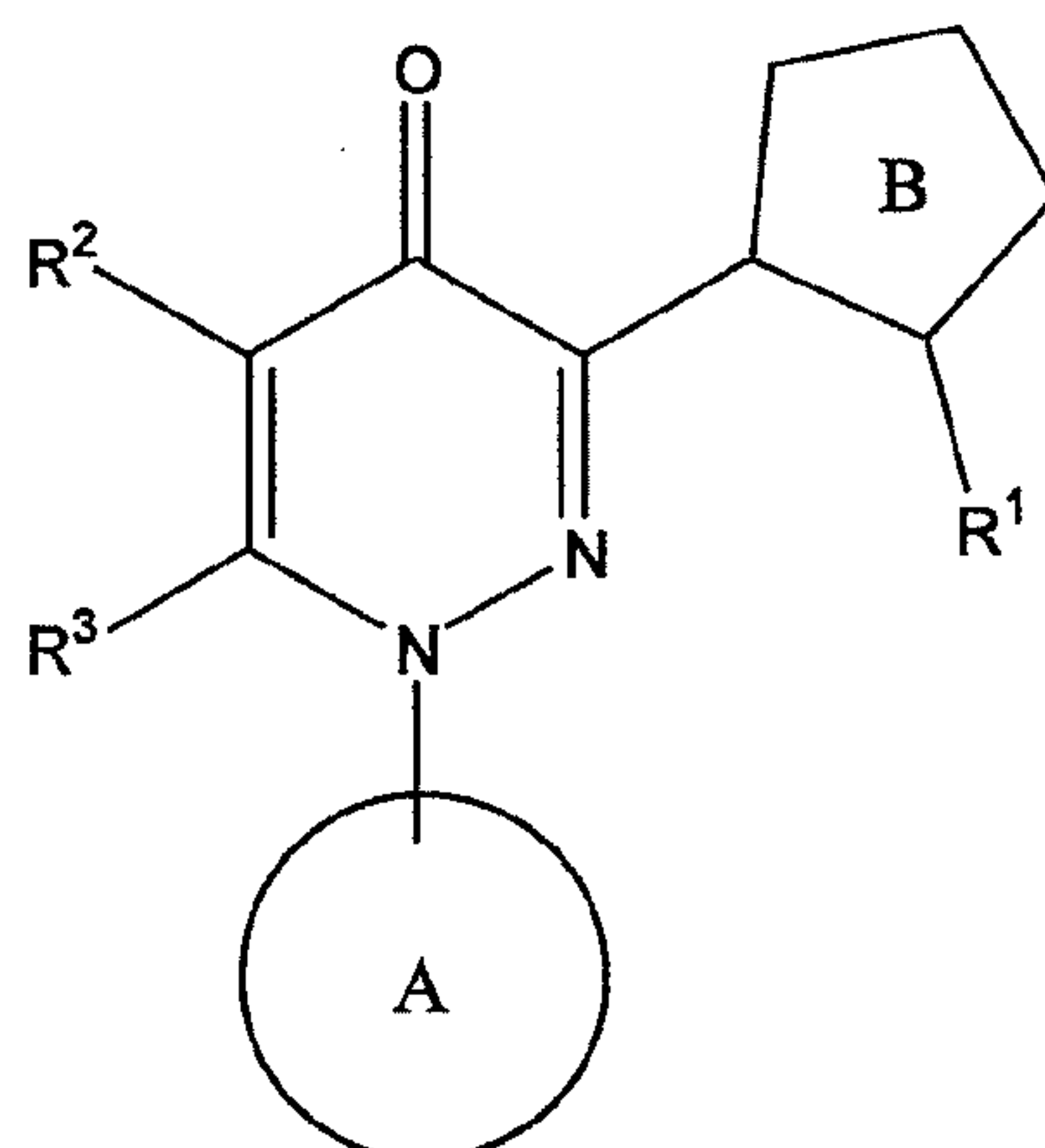
was disclosed in W02006/072828 Pamphlet.

Further, as a phosphodiesterase (PDE) 10 inhibitor, a compound represented by the general formula



was also disclosed in W02008/001182 Pamphlet.

Further, as a phosphodiesterase (PDE) 10 inhibitor, a compound represented by the general formula



was also disclosed in W02010/090737 Pamphlet.

Summary of Invention

Technical Problem

10 [0004]

However, development of new phosphodiesterase (PDE) 10A inhibitors is further requested.

Solution to Problem

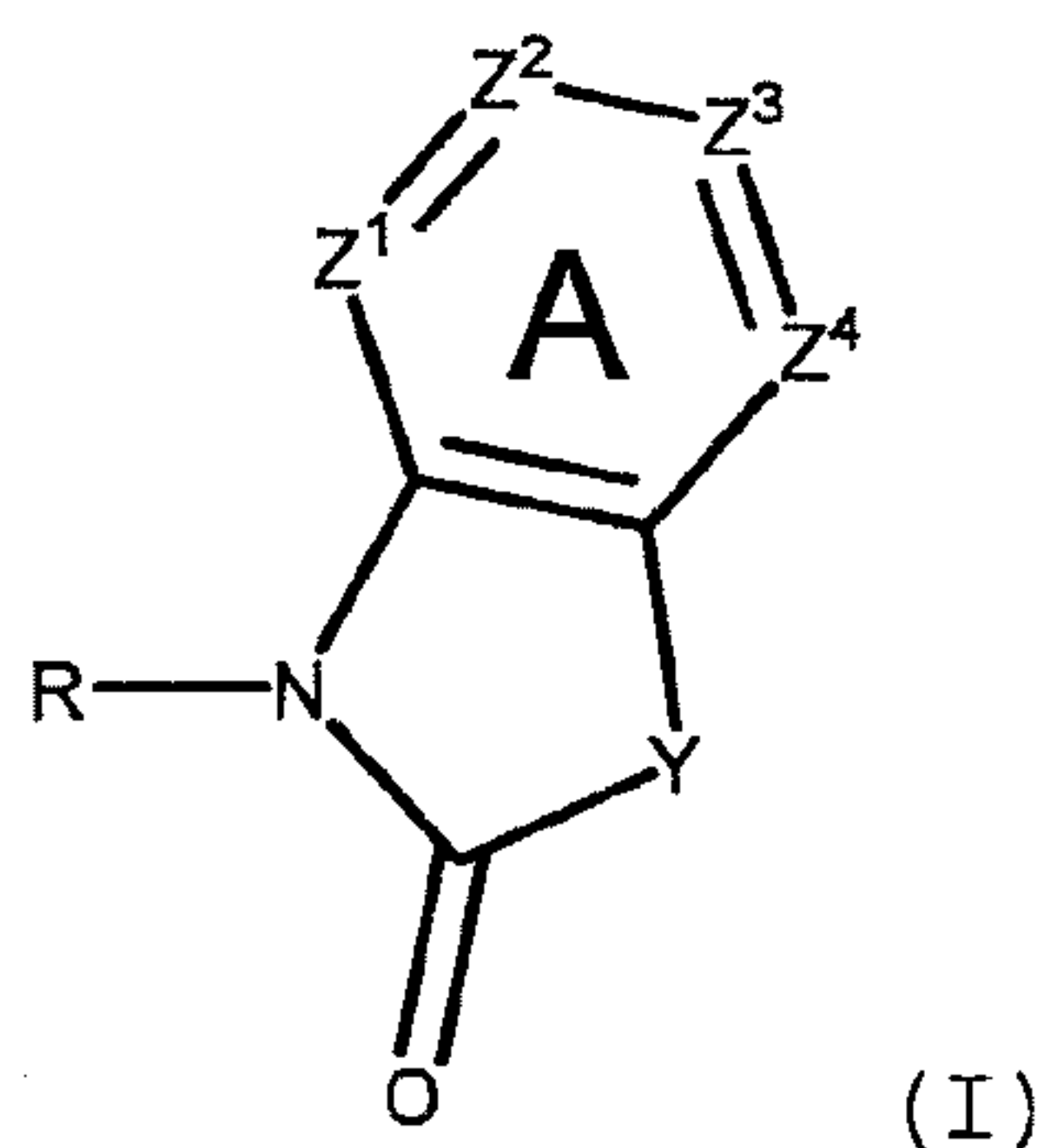
[0005]

15 The present inventors discovered that a compound expressed by the formula (I) or a salt thereof (referred to as compound (I) in this specification) has a PDE 10A inhibitory action and after extensive investigation, completed the present invention.

In this specification, the compound (I) or a prodrug thereof is also referred to the compound of the present invention.

That is, the present invention provides the following.

5 [1] A compound represented by the formula (I):



wherein

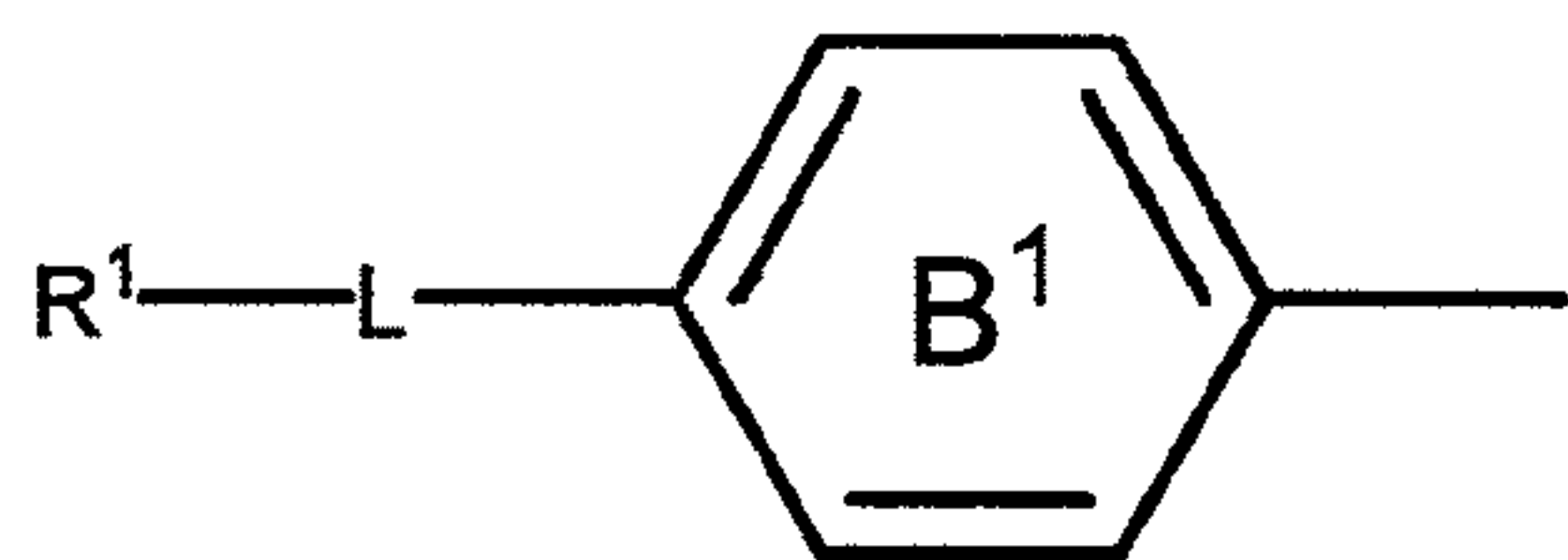
ring A represents an optionally substituted 6-membered ring, any one or two of Z^1 to Z^4 represent $-N=$, and the others

10 represent $-CH=$,

Y represents an oxygen atom, a sulfur atom, an optionally substituted methylene group or $-NR^c-$ wherein R^c represents a hydrogen atom or a substituent, and

R represents

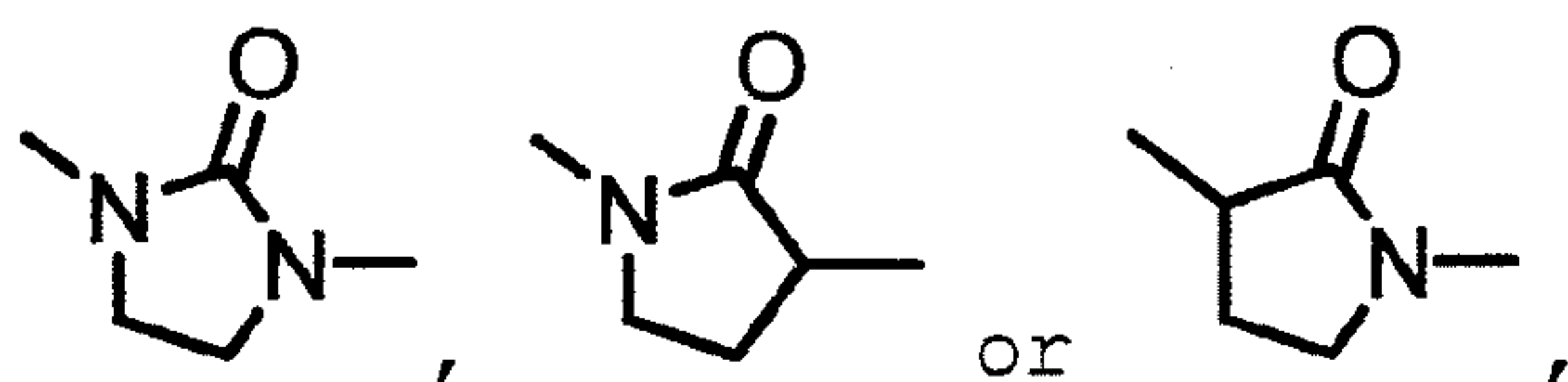
15 (1) a group represented by the formula:



wherein

R^1 is a phenyl group or a 5- to 10-membered heterocyclic group, each of which is optionally substituted,

20 L is a sulfur atom, an oxygen atom, an optionally substituted methylene group, $-CO-$, $-NR^a-$, $-CH_2O-$, $-OCH_2-$, $-NR^aCOO-$, $-OCONR^a-$, $-NR^aCONR^b-$, $-NR^aCOCH_2-$, $-CH_2CONR^a-$, $-NR^aCO-$, $-CONR^a-$,

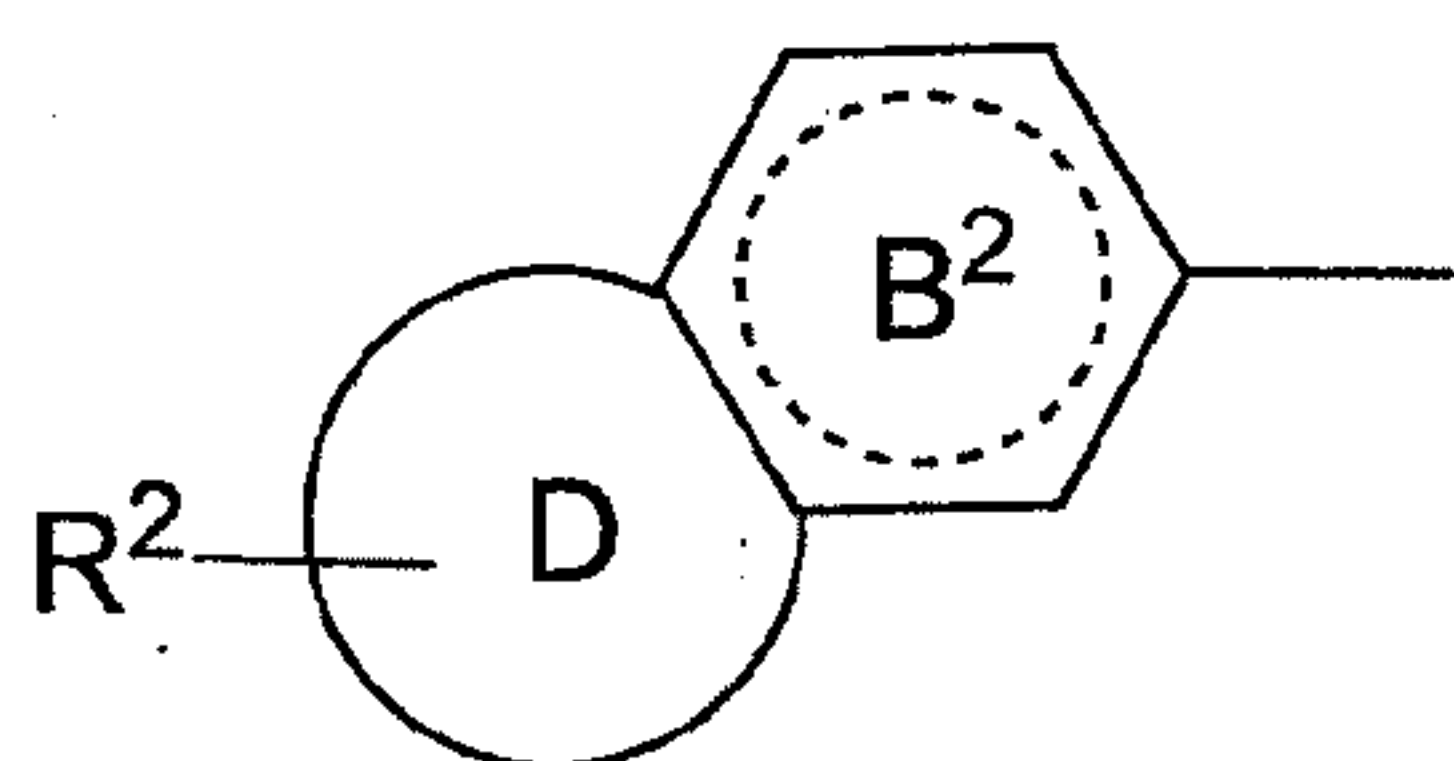


25 wherein

R^a and R^b are the same or different and each is a hydrogen atom or an optionally substituted C_{1-6} alkyl group, or

L and R^1 in combination optionally form an optionally substituted bi- or tri-cyclic fused heterocyclic group, and
 5 ring B^1 is a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted, or

(2) a group represented by the formula:



10

wherein

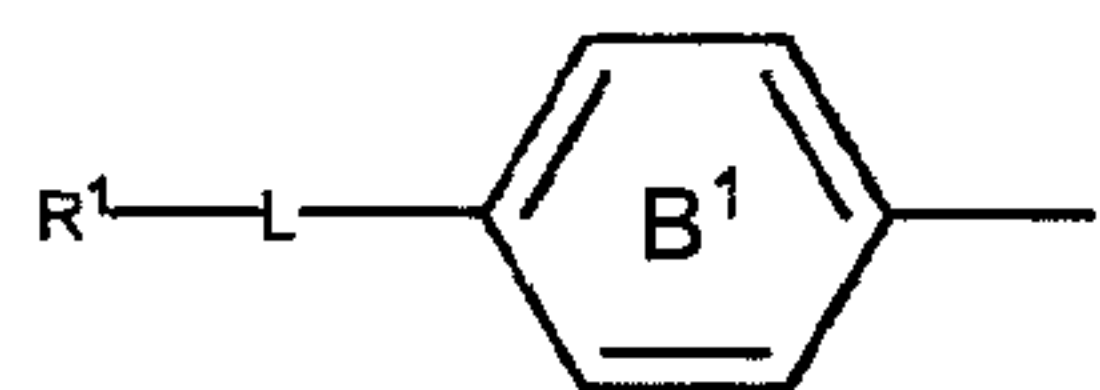
R^2 is a phenyl group or a 5- to 10-membered heterocyclic group, each of which is optionally substituted,
 ring B^2 is a benzene ring, a pyridine ring, a pyrimidine
 15 ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted, and
 ring D is an optionally further substituted 5- or 6-membered ring,

provided that

20 3,3'-benzene-1,4-diylbis(1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one),
 1-cyclohexyl-3-(4-{[4-(methanesulfonyl)piperazin-1-yl]methyl}phenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one,
 3-(4-phenoxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one,
 25 3,3'-benzene-1,4-diylbis(1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one), and
 3-[8-(4-methylpiperazin-1-yl)naphthalen-2-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
 are excluded,
 30 or a salt thereof.

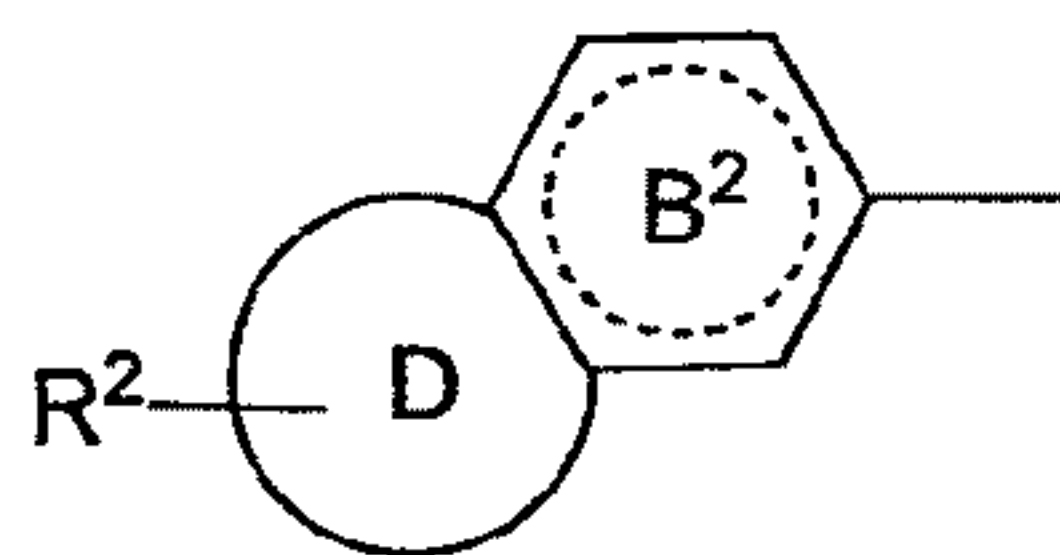
[1'] The compound of the aforementioned [1], wherein R is

(1) a group represented by the formula:



wherein each symbol is as defined in the aforementioned [1],
or

(2) a group represented by the formula:



5

wherein ring B² is a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted, and

ring D is an optionally further substituted 5- or 6-membered
10 ring,

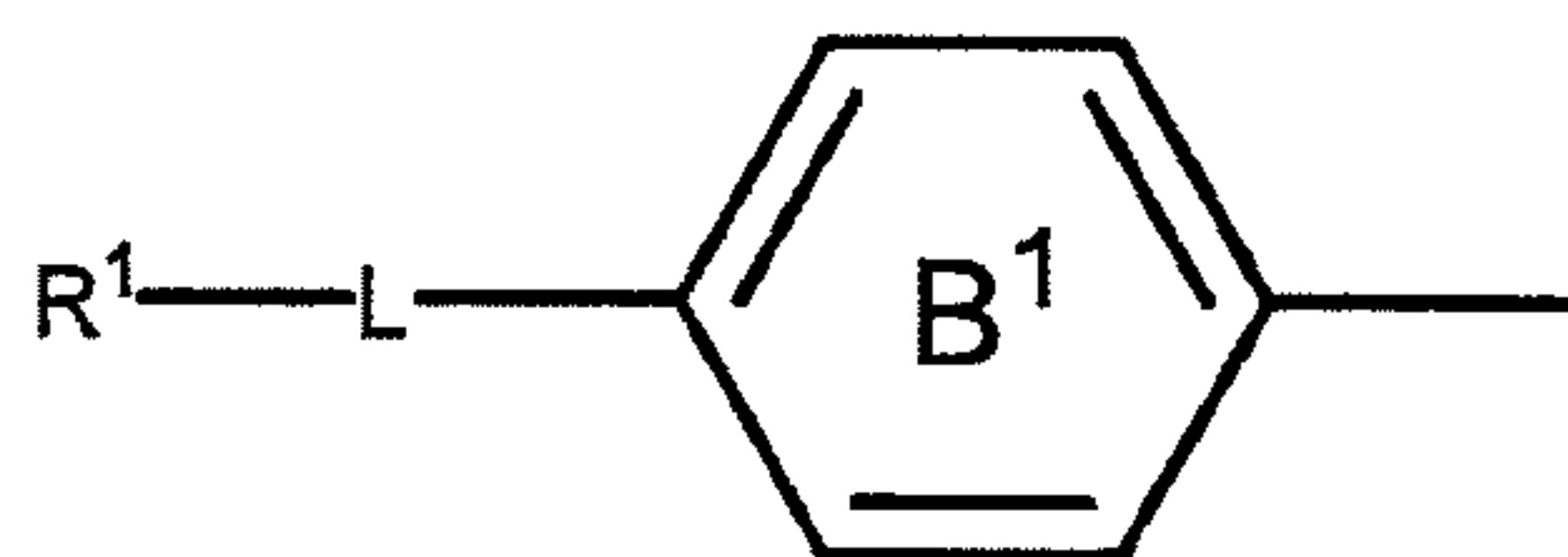
R² is as defined in the aforementioned [1],

provided that when ring B² is a benzene ring, ring D is not a benzene ring,

or a salt thereof.

15 [1''] The compound of the aforementioned [1], wherein R is

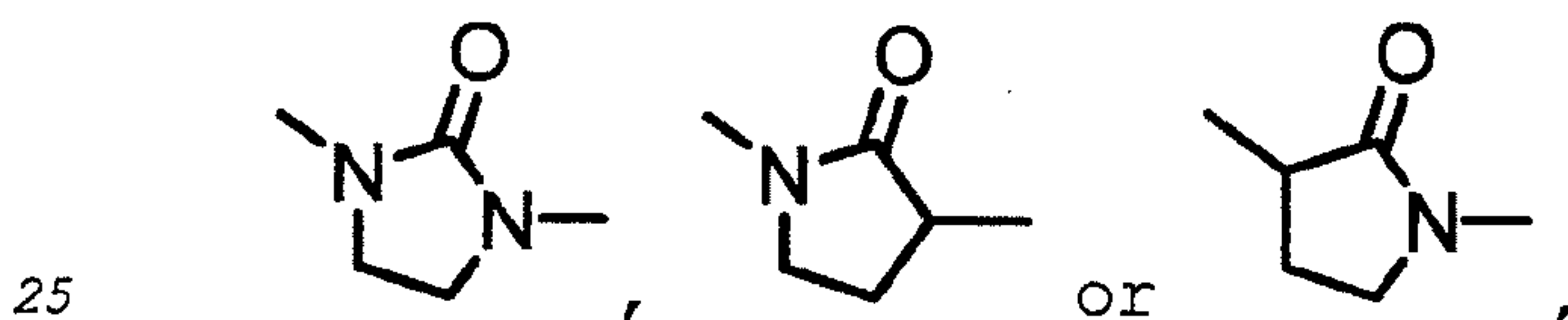
(1) a group represented by the formula:



wherein

R¹ is a phenyl group or a 5- to 10-membered heterocyclic
20 group, each of which is optionally substituted,

L is a sulfur atom, an oxygen atom, an optionally substituted methylene group, -CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-, -NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



25

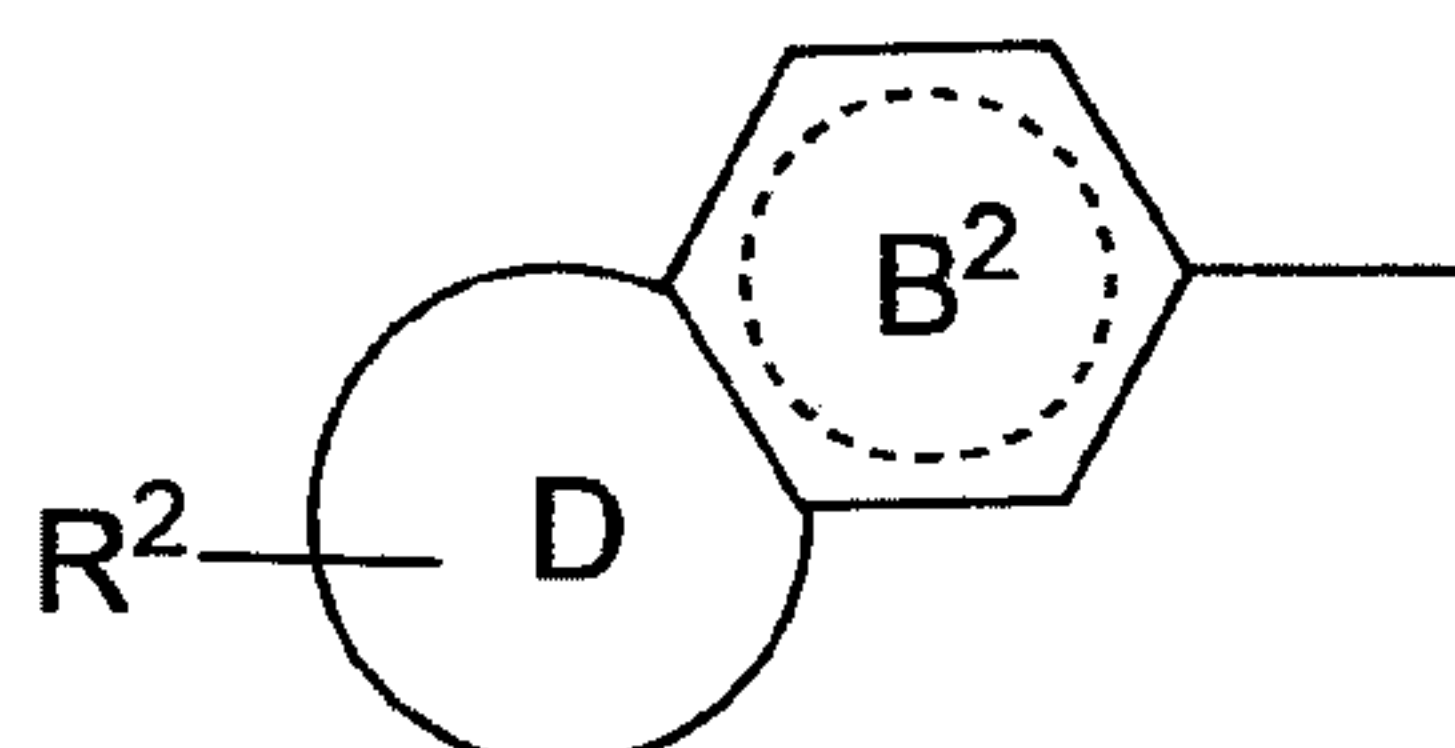
wherein

R^a and R^b are as defined in the aforementioned [1], or
L and R¹ in combination optionally form an optionally

substituted bi- or tri-cyclic fused heterocyclic group, and ring B¹ is a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted,

5 provided that when L is an oxygen atom, R¹ is not an optionally substituted phenyl, or

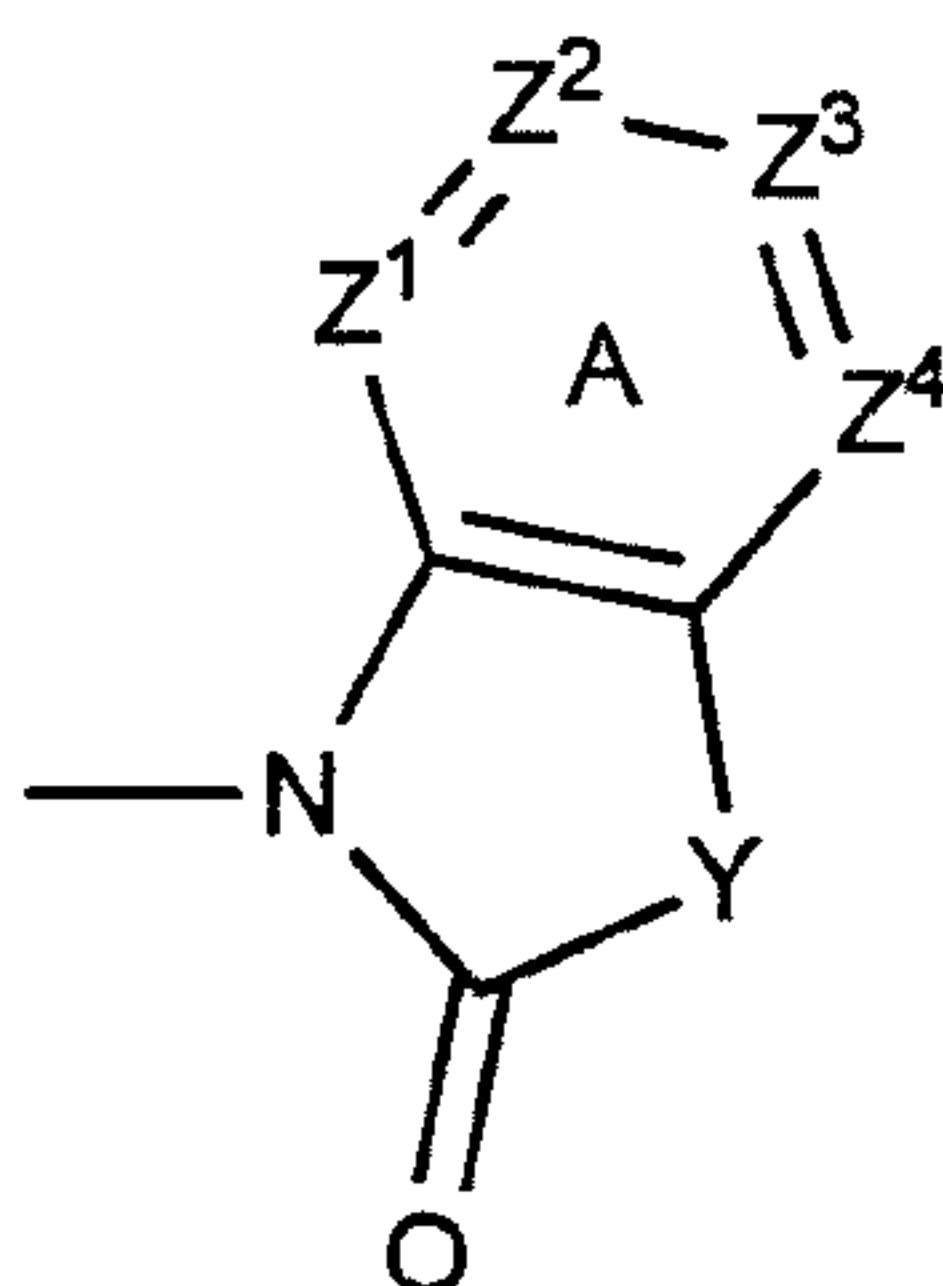
(2) a group represented by the formula:



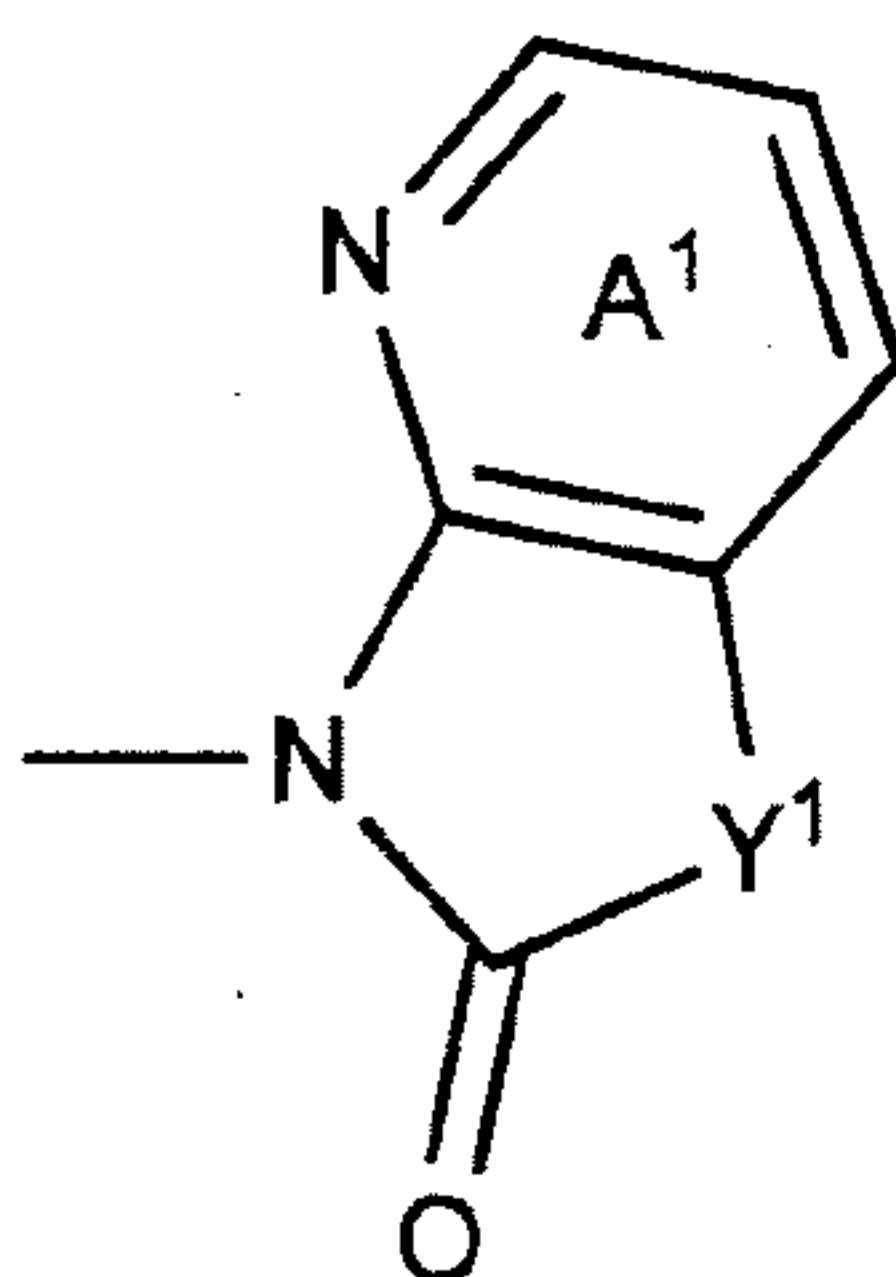
wherein each symbol is as defined in the aforementioned [1],
10 or a salt thereof.

[2] The compound of the aforementioned [1], wherein any one of Z¹ to Z⁴ is -N=, and the others are -CH=, or a salt thereof.

[3] The compound of the aforementioned [1], wherein the
15 partial structure of the formula (I):



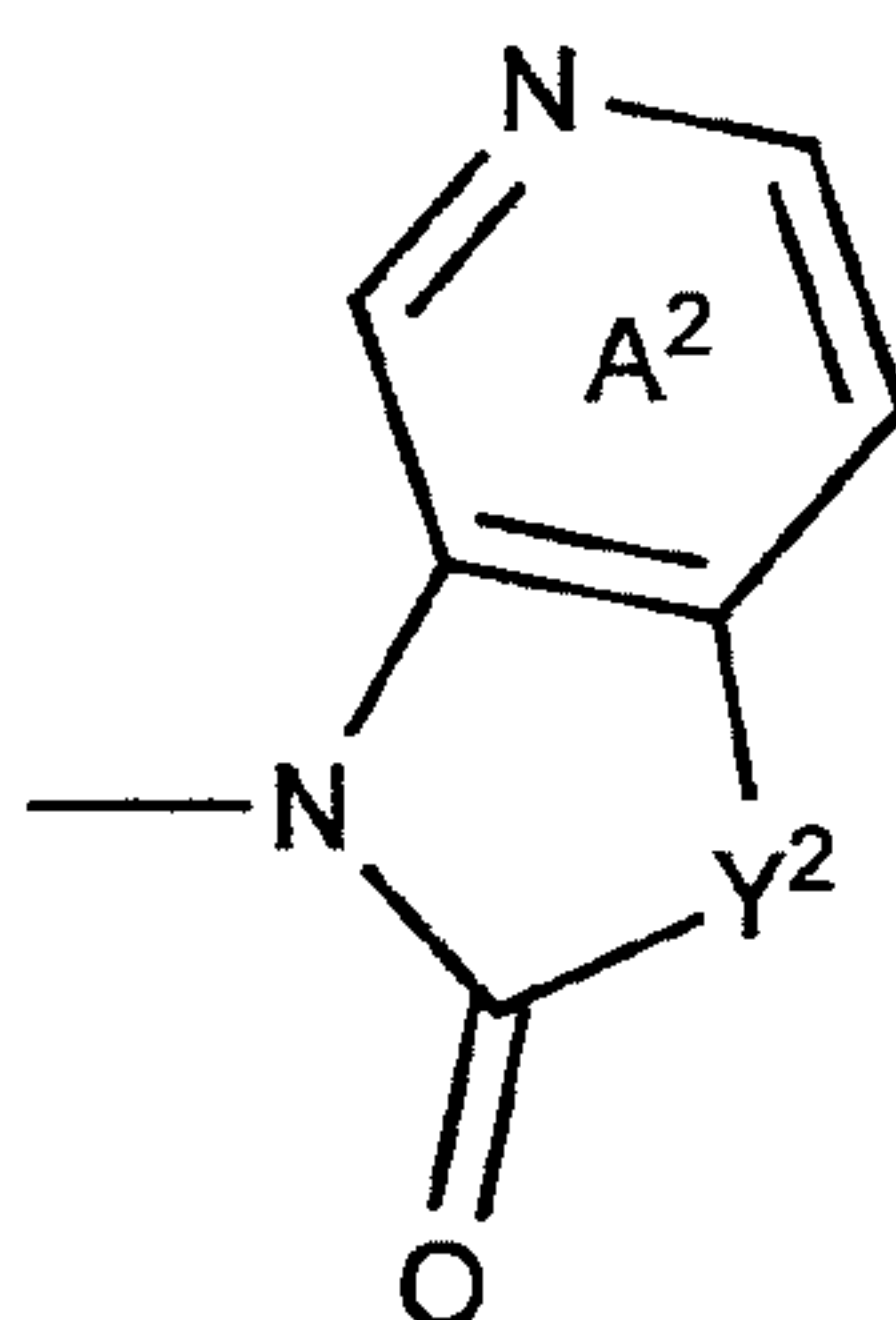
is a group represented by the formula:



wherein

20 Y¹ is an optionally substituted methylene group or -NR^c- wherein R^c is a hydrogen atom or a substituent, and

ring A¹ is an optionally substituted pyridine ring, or
a group represented by the formula:

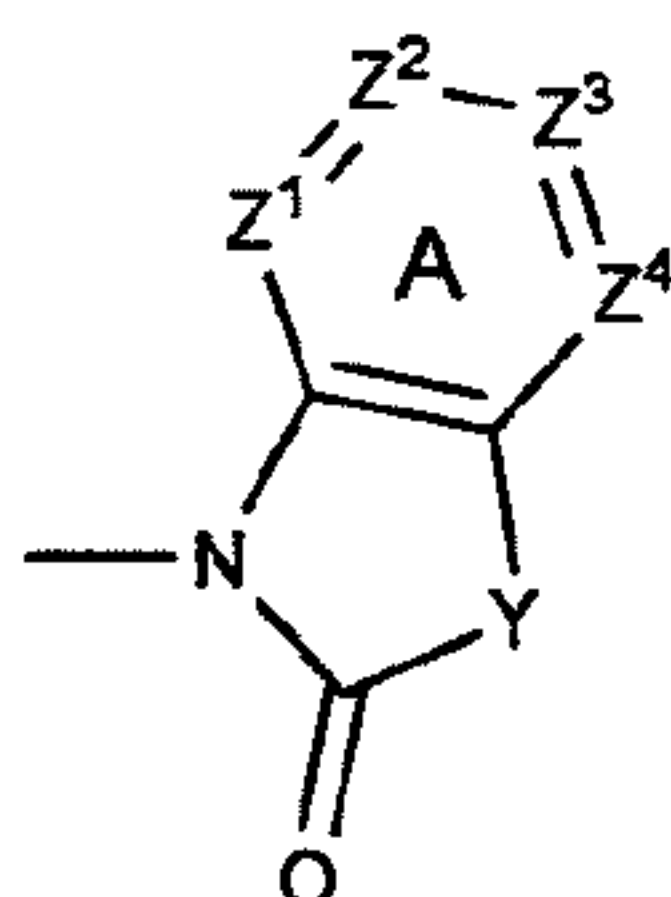


wherein

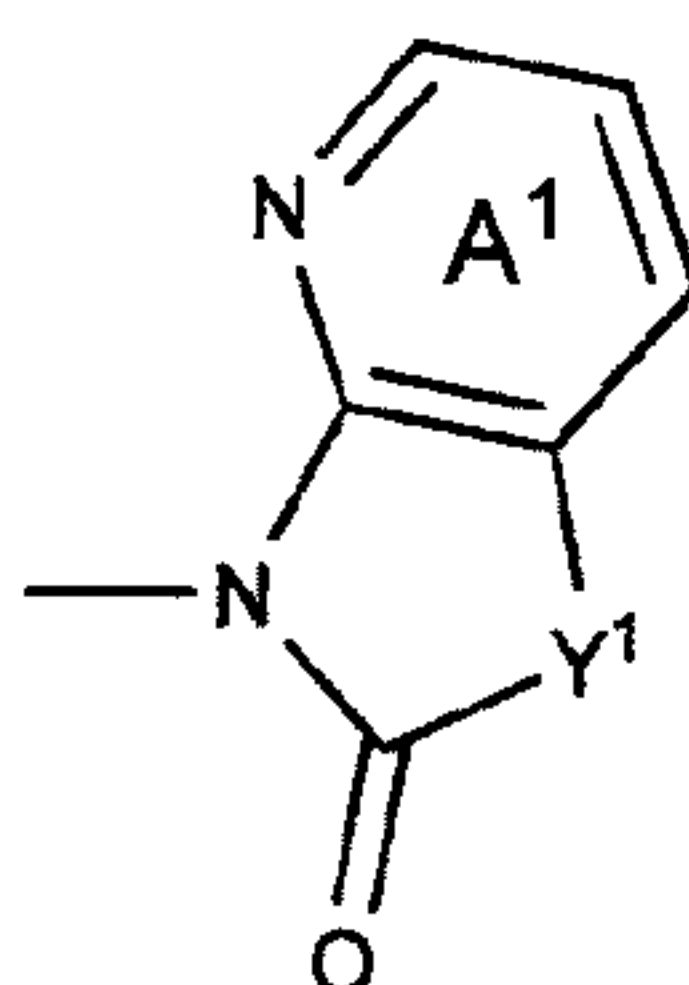
- 5 Y² is -NR^d- wherein R^d is a substituent, and
ring A² is an optionally substituted pyridine ring,
or a salt thereof.

[4] The compound of the aforementioned [1], wherein L is an
oxygen atom, or -NR^a- wherein R^a is a hydrogen atom or an
10 optionally substituted C₁₋₆ alkyl group, or
L and R¹ in combination optionally form an optionally
substituted bi- or tri-cyclic fused heterocyclic group,
or a salt thereof.

[5] The compound of the aforementioned [3], wherein the
15 partial structure of formula (I):

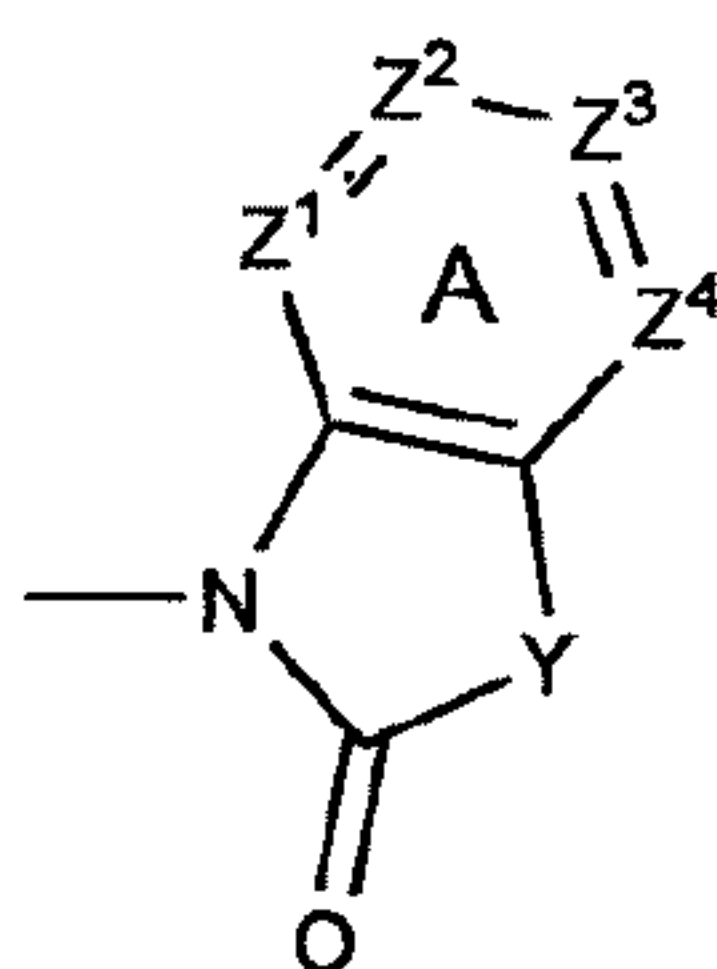


is a group represented by the formula:

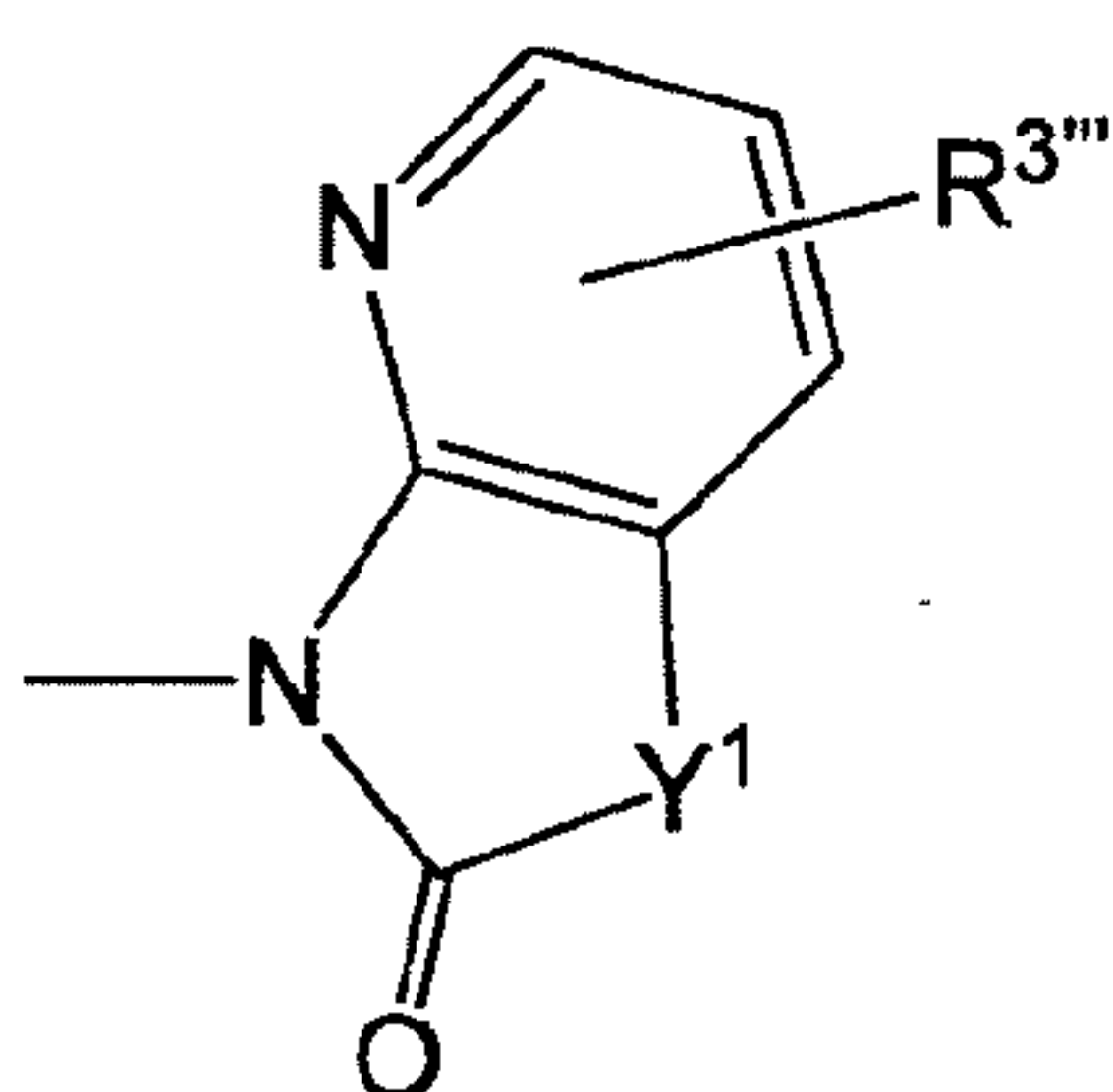


wherein ring A¹ and Y¹ are as defined in the aforementioned [3],
20 or a salt thereof.

[6] The compound of the aforementioned [3], wherein the partial structure of formula of formula (I):



is a group represented by the formula:



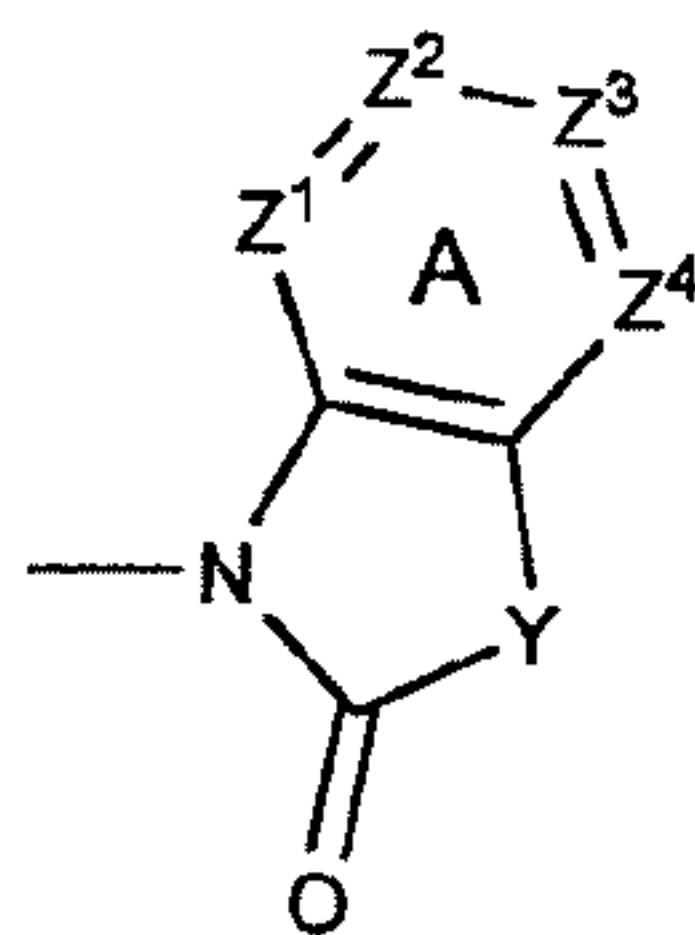
5

wherein

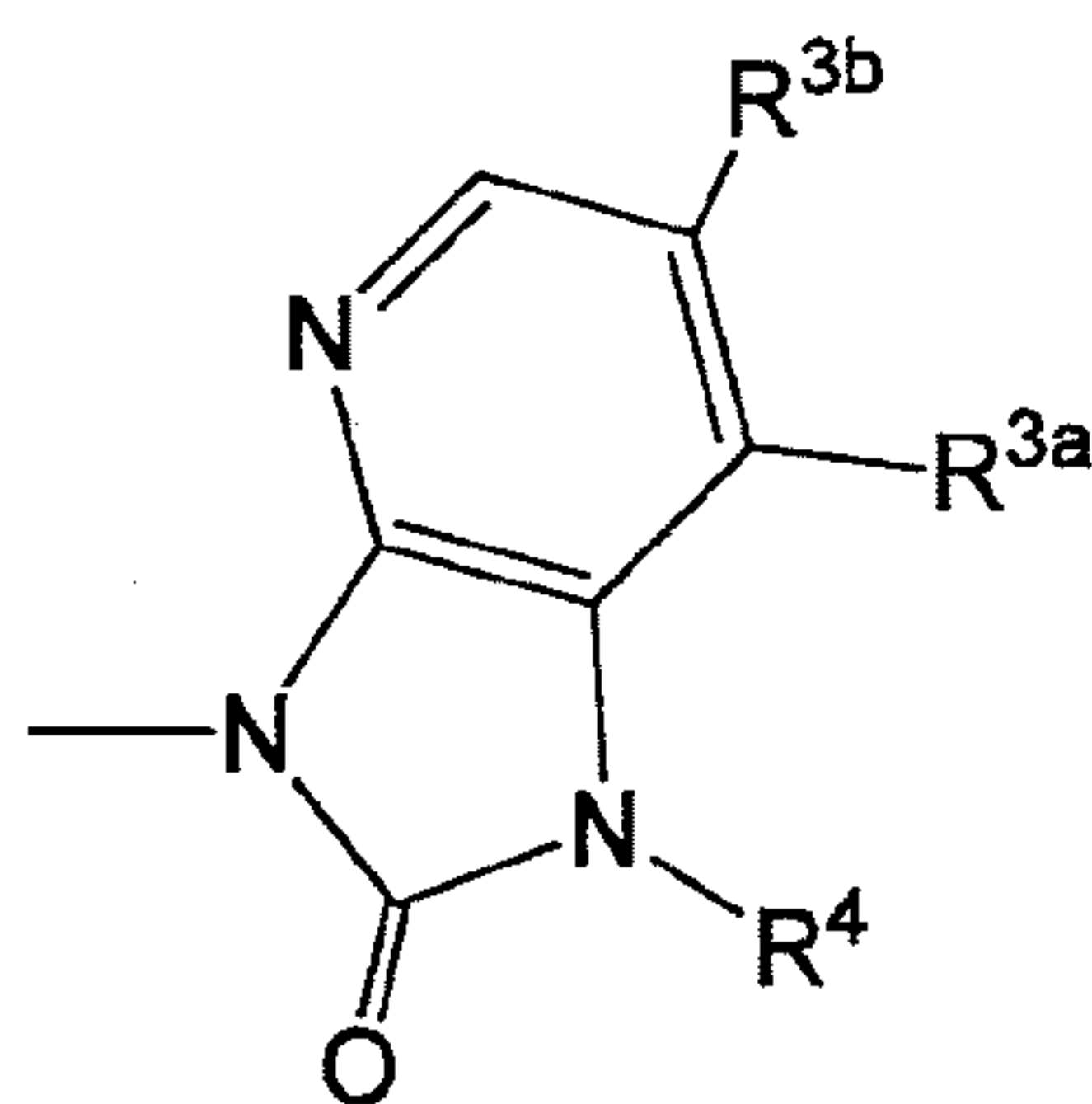
the $R^{3'''}$ represents a hydrogen atom, a halogen atom, an optionally substituted C_{1-4} alkyl group, or an optionally substituted C_{1-4} alkoxy group, and

10 Y^1 is as defined in the aforementioned [3],
or a salt thereof.

[7] The compound of the aforementioned [3], wherein the partial structure of formula (I):



15 is a group represented by the formula:



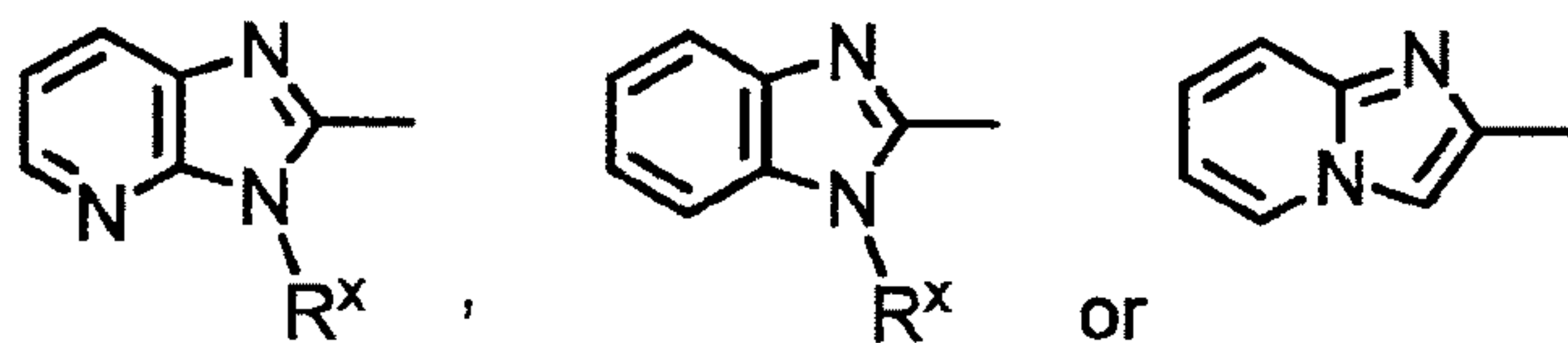
wherein

R^{3a} and R^{3b} represent the same or different a hydrogen atom, a halogen atom, cyano, an optionally substituted C_{1-4} alkyl group or an optionally substituted C_{1-4} alkoxy group, and R^4 represents an optionally substituted C_{1-4} alkyl group, provided that when one of R^{3a} and R^{3b} is a hydrogen atom, the other is not a hydrogen atom, or a salt thereof.

[8] The compound of the aforementioned [1], wherein ring B^1 is an optionally substituted benzene ring, or a salt thereof.

[9] The compound of the aforementioned [1], wherein R^1 is a 5- to 10-membered heterocyclic group which is optionally substituted, or a salt thereof.

[10] The compound of the aforementioned [9], wherein the 5- to 10-membered heterocyclic group which is optionally substituted is a group represented by the formula:



wherein R^x represents a hydrogen atom or an optionally substituted C_{1-6} alkyl group, or a salt thereof.

[11] 1-Ethyl-6-methyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

[12] 1-Ethyl-6-methoxy-3-{4-[(3-methyl-3H-imidazo[4,5-

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b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

[13] 1-Ethyl-7-methyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

[14] 6-Methyl-1-(1-methylethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

[15] 1-Ethyl-6-fluoro-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

[16] 1,7-Dimethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

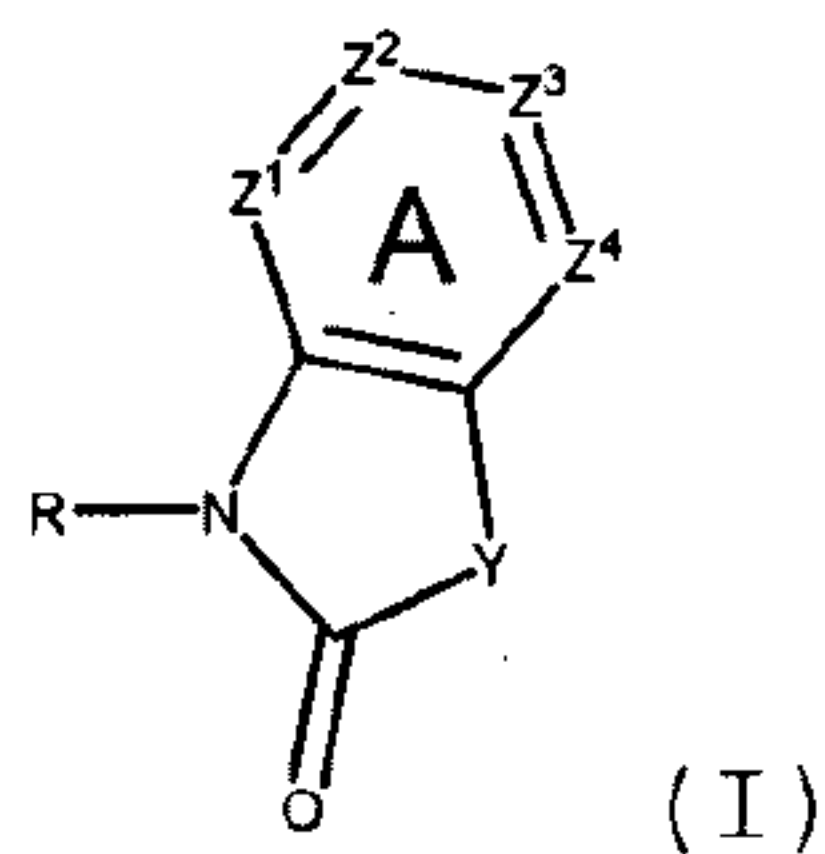
[17] 1-Ethyl-7-(hydroxymethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

[18] A medicament comprising the compound of the aforementioned [1], or a pharmacologically acceptable salt thereof.

[19] The medicament of the aforementioned [18], which is a phosphodiesterase 10A inhibitor.

[20] The medicament of the aforementioned [18], which is an agent for the prevention or treatment of schizophrenia, autism, Alzheimer's disease, a bipolar disorder, Parkinson's disease, Huntington's disease, obesity, drug addiction or attention deficit/hyperactivity disorder.

[21] Use of a compound represented by the formula (I):



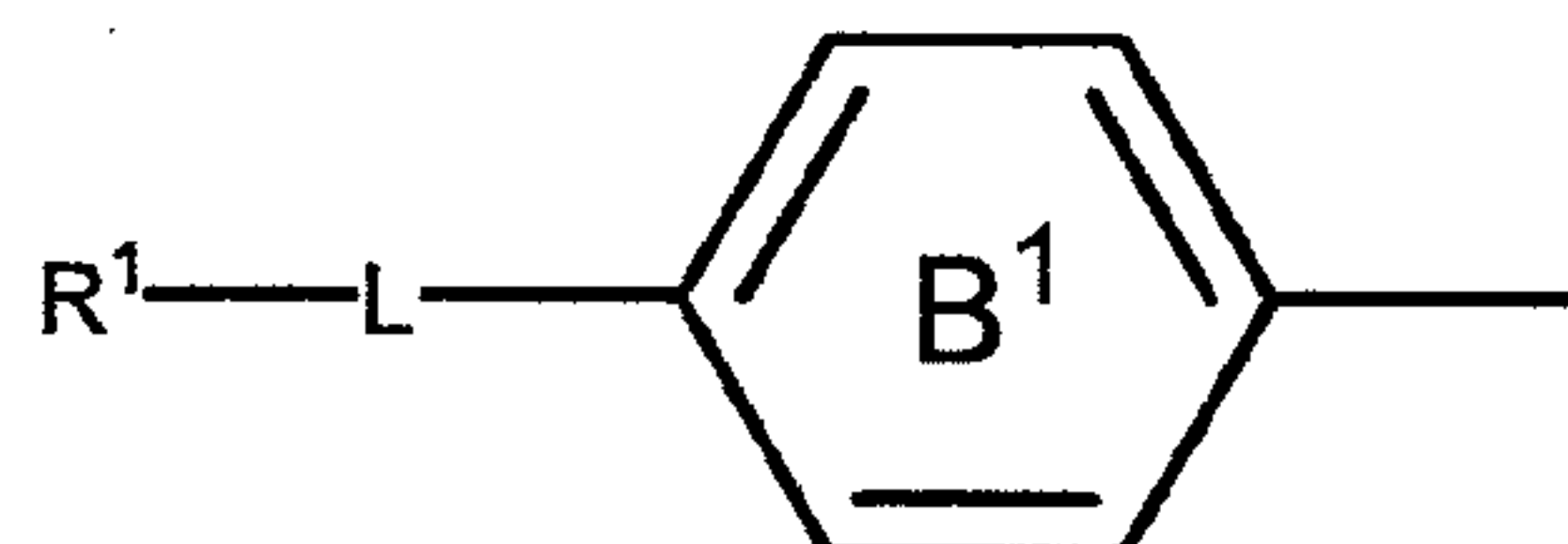
wherein

ring A represents an optionally substituted 6-membered ring,
any one or two of Z^1 to Z^4 represent $-N=$, and the others
represent $-CH=$,

Y represents an oxygen atom, a sulfur atom, an optionally
5 substituted methylene group, or $-NR^c-$ wherein R^c represents a
hydrogen atom or a substituent, and

R represents

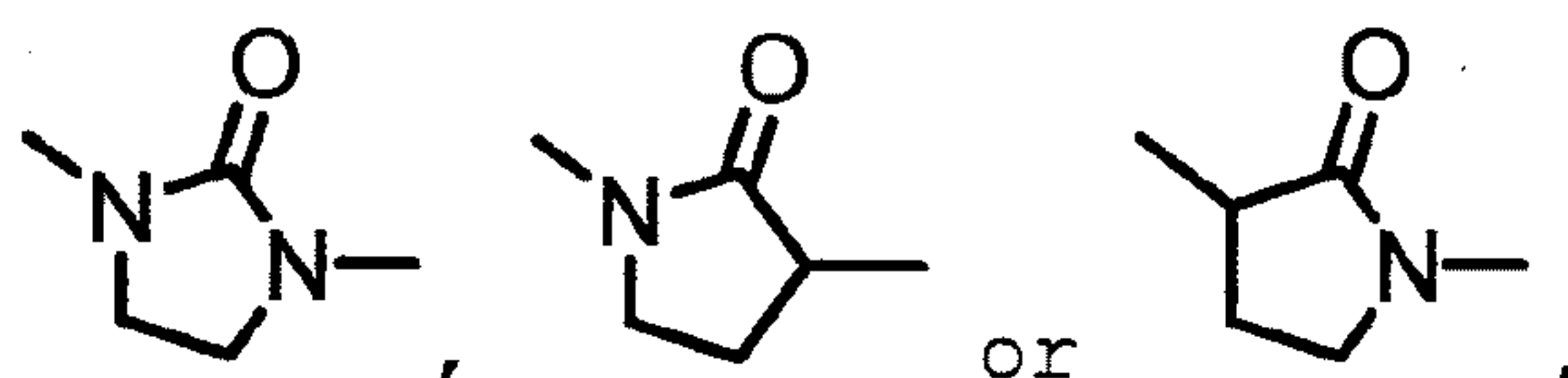
(1) a group represented by the formula:



10 wherein

R^1 is a phenyl group or a 5- to 10-membered heterocyclic
group, each of which is optionally substituted,

L is a sulfur atom, an oxygen atom, an optionally
substituted methylene group, $-CO-$, $-NR^a-$, $-CH_2O-$, $-OCH_2-$, $-$
15 NR^aCOO- , $-OCONR^a-$, $-NR^aCONR^b-$, $-NR^aCOCH_2-$, $-CH_2CONR^a-$, $-NR^aCO-$,
 $-CONR^a-$,

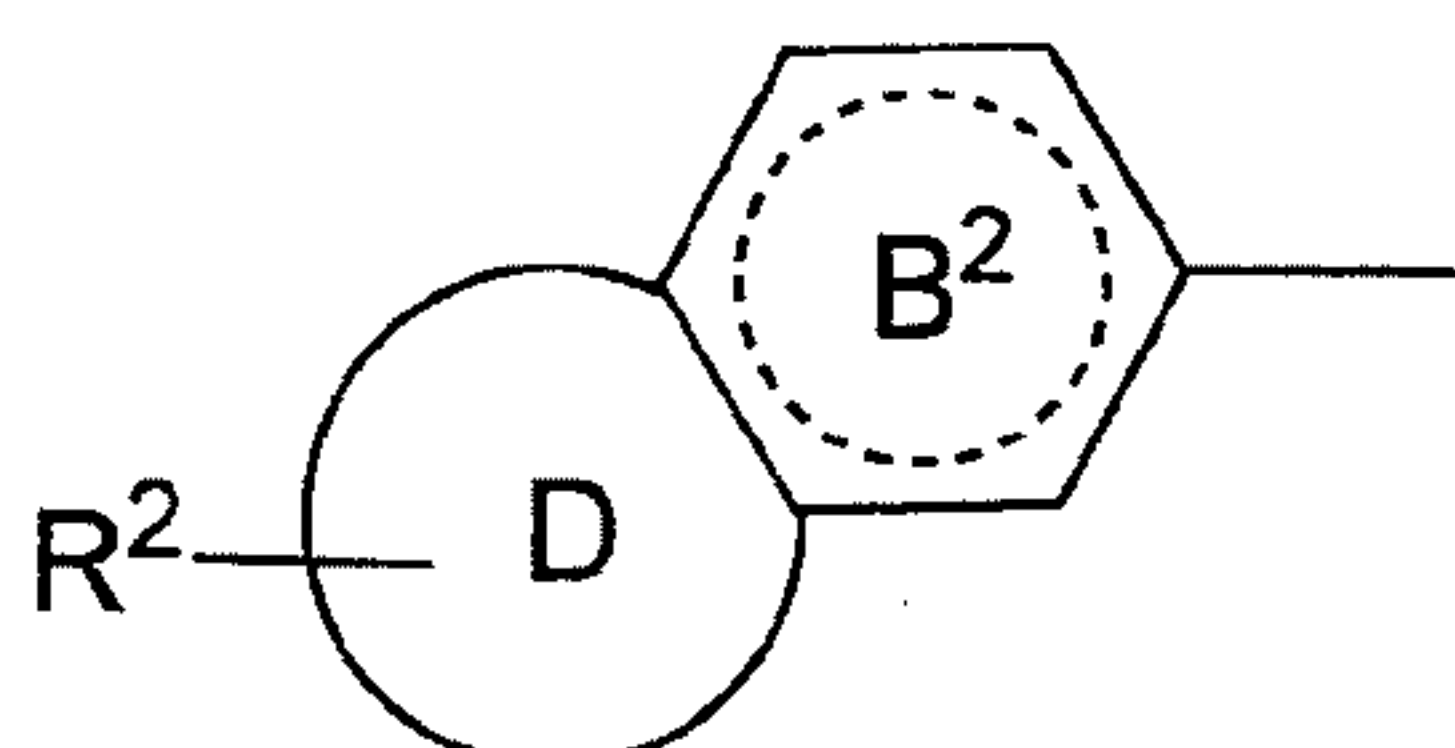


wherein

R^a and R^b are the same or different and each is a
20 hydrogen atom or an optionally substituted C_{1-6} alkyl
group, or

L and R^1 in combination optionally form an optionally
substituted bi- or tri-cyclic fused heterocyclic group, and
ring B^1 is a benzene ring, a pyridine ring, a pyrimidine
25 ring, a pyrazine ring or a pyridazine ring, each of which
is optionally substituted, or

(2) a group represented by the formula:



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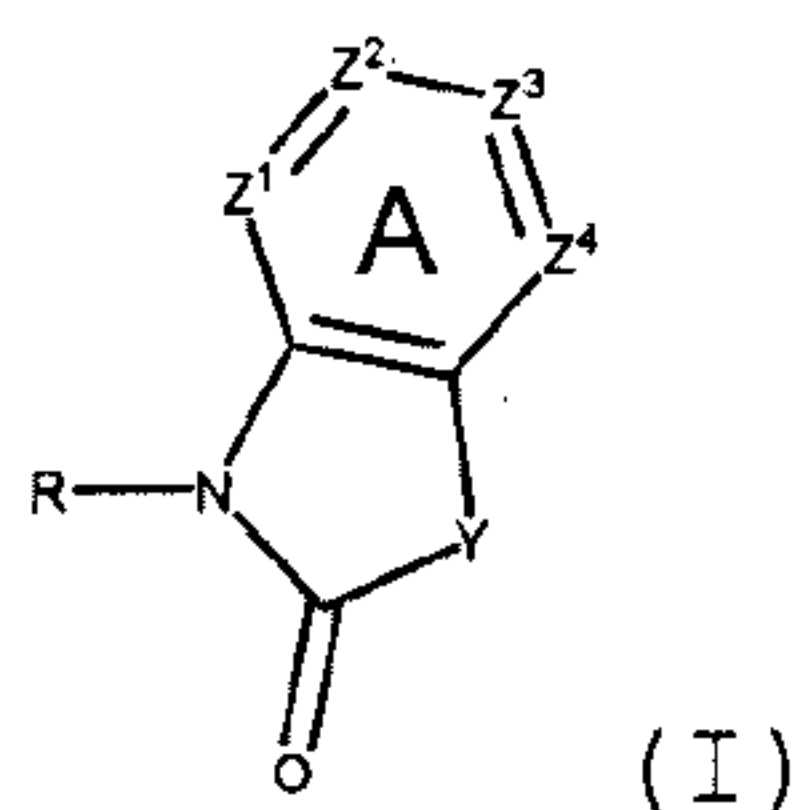
wherein

R^2 is a phenyl group or a 5- to 10-membered heterocyclic group, each of which is optionally substituted,

ring B^2 is a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted, and

ring D is an optionally further substituted 5- or 6-membered ring, or a pharmacologically acceptable salt thereof, for the prevention or treatment of schizophrenia, autism, Alzheimer's disease, a bipolar disorder, Parkinson's disease, Huntington's disease, obesity, drug addiction or attention deficit/hyperactivity disorder in a mammal.

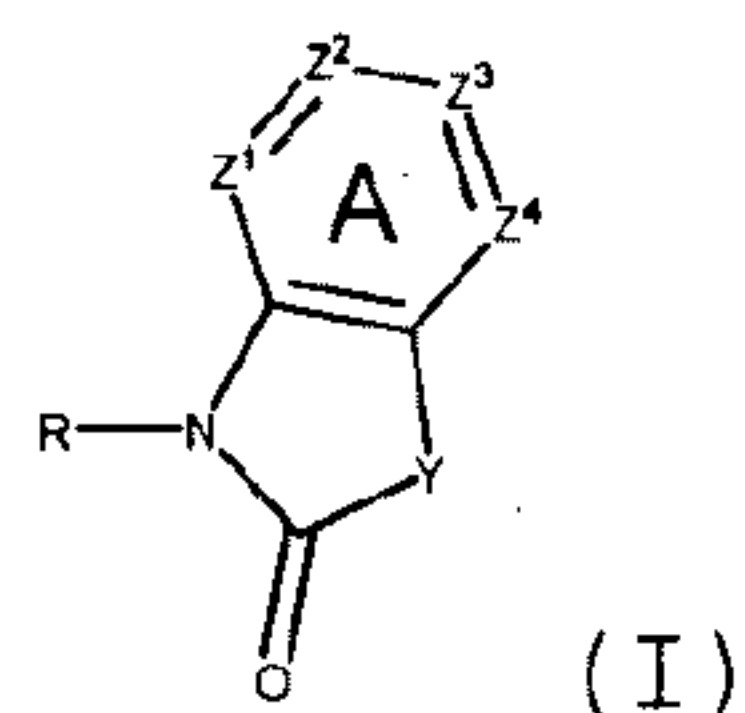
[22] Use of a compound represented by the formula (I):



wherein each symbol is as defined above,

or a pharmacologically acceptable salt thereof for the production of an agent for the prevention or treatment of schizophrenia, autism, Alzheimer's disease, a bipolar disorder, Parkinson's disease, Huntington's disease, obesity, drug addiction or attention deficit/hyperactivity disorder.

[23] A compound represented by the formula (I):



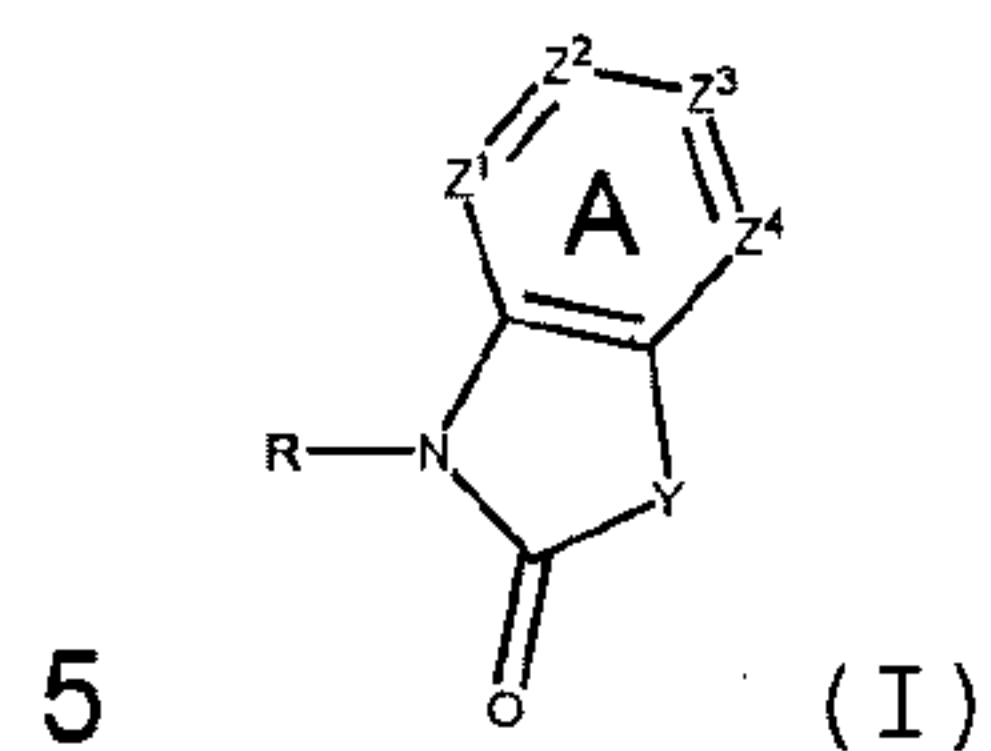
wherein each symbol is as defined above,

or a pharmacologically acceptable salt thereof for use in the prevention or treatment of schizophrenia, autism, Alzheimer's

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disease, a bipolar disorder, Parkinson's disease, Huntington's disease, obesity, drug addiction or attention deficit/hyperactivity disorder.

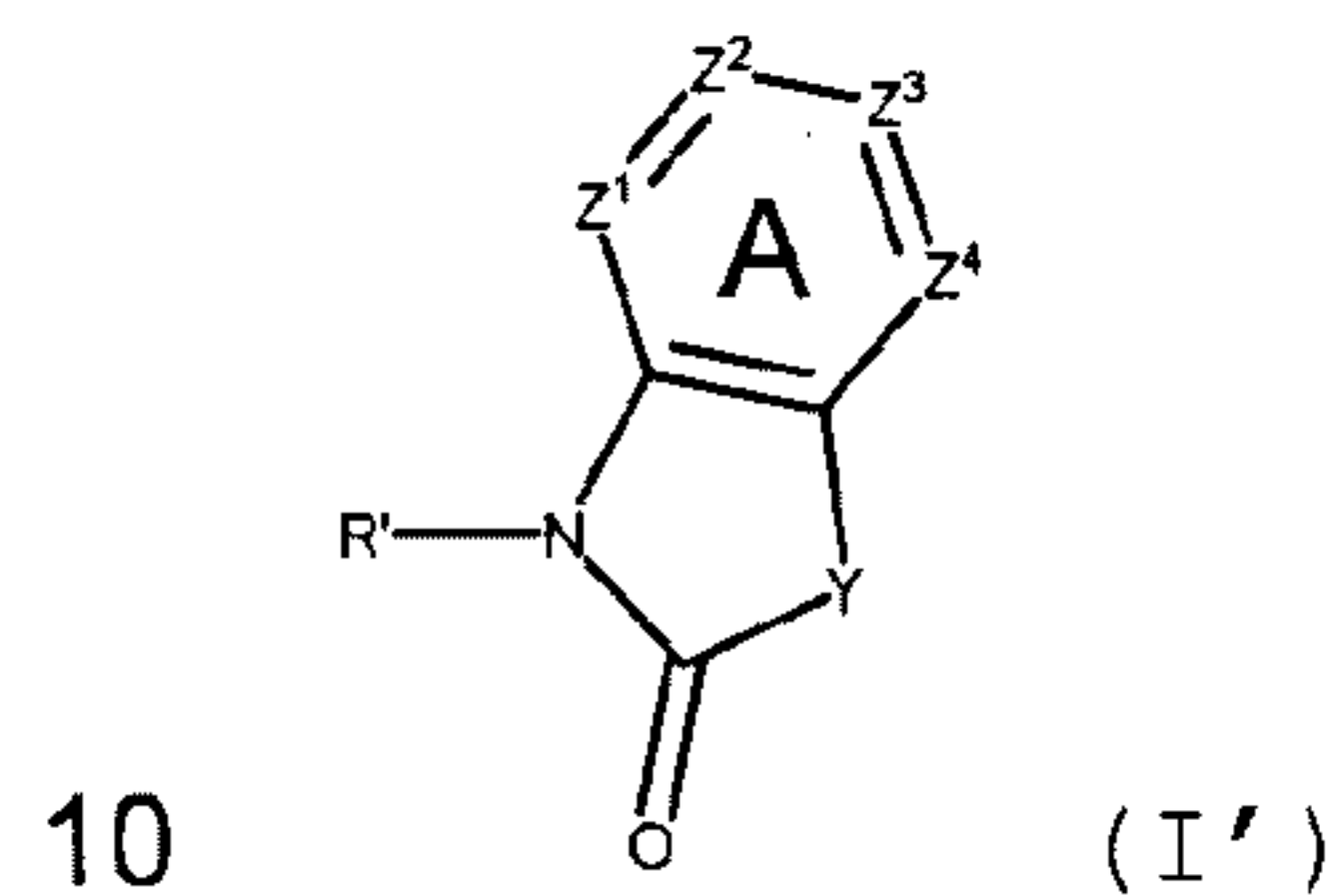
[24] Use of a compound represented by the formula (I):



wherein each symbol is as defined above,

or a pharmacologically acceptable salt thereof for use in the prophylaxis or treatment of schizophrenia.

[25] A compound represented by the formula (I'):



wherein

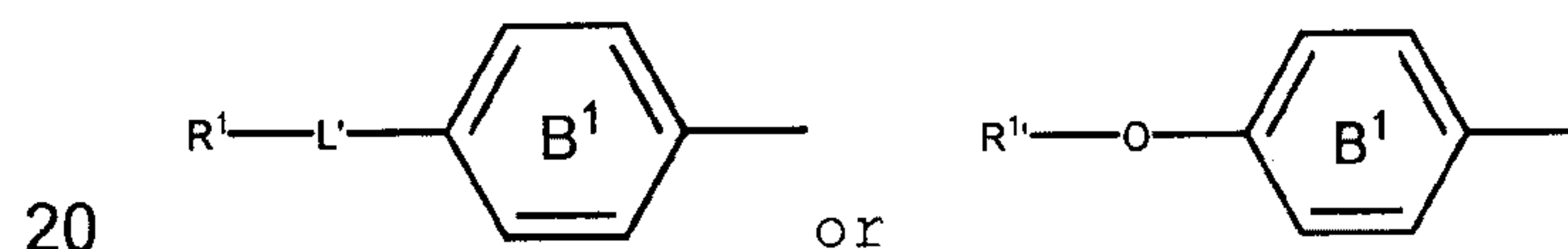
ring A represents an optionally substituted 6-membered ring,

any one or two of Z^1 to Z^4 represent $-N=$, and the others represent $-CH=$,

15 Y represents an oxygen atom, a sulfur atom, an optionally substituted methylene group, or $-NR^c-$ wherein R^c represents a hydrogen atom or a substituent, and

R' represents

(1) a group represented by the formula:



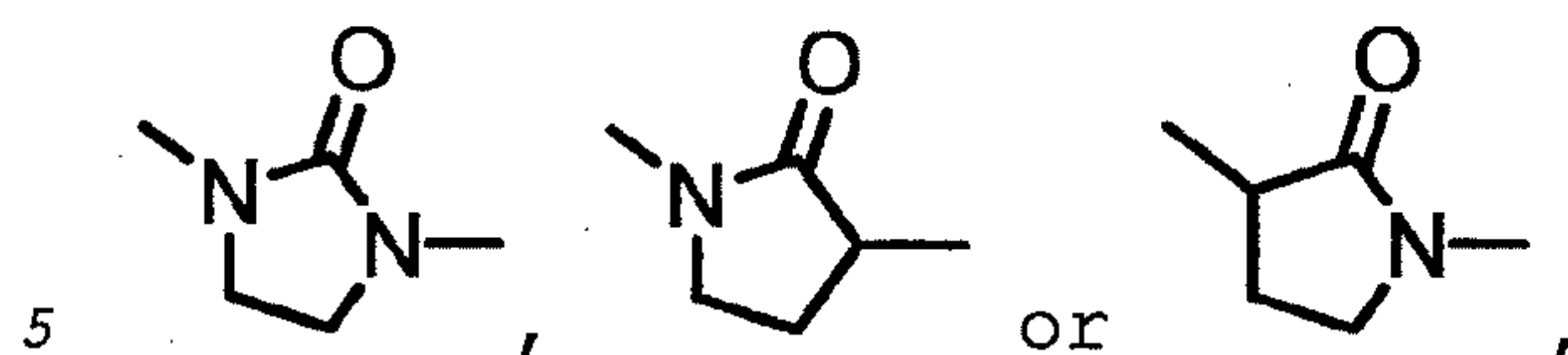
wherein

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R^1 is a phenyl group or a 5- to 10-membered heterocyclic group, each of which is optionally substituted,

L' is a sulfur atom, $-CO-$, $-NR^a-$, $-CH_2O-$, $-OCH_2-$, $-NR^aCOO-$, $-OCONR^a-$, $-NR^aCONR^b-$, $-NR^aCOCH_2-$, $-CH_2CONR^a-$, $-NR^aCO-$, $-CONR^a-$,



wherein

R^a and R^b are the same or different and each is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,

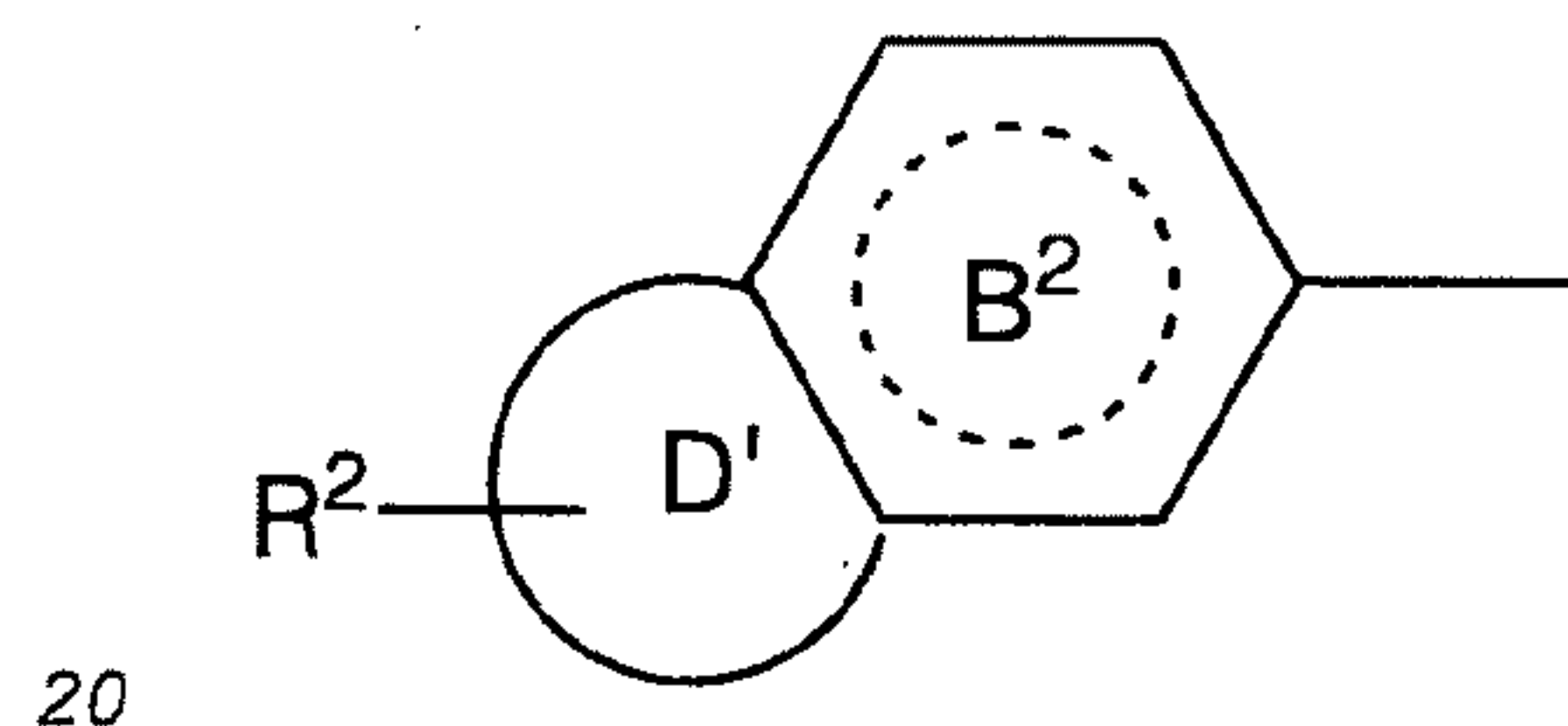
$R^{1'}$ is an optionally substituted 5- to 10-membered heterocyclic group, or

L and R^1 in combination optionally form a bi- or tri-cyclic fused heterocyclic group which is optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) an optionally esterified carboxy group, and

15 (c) an optionally substituted alkyl group, and

ring B^1 is a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted, or

(2) a group represented by the formula:



wherein

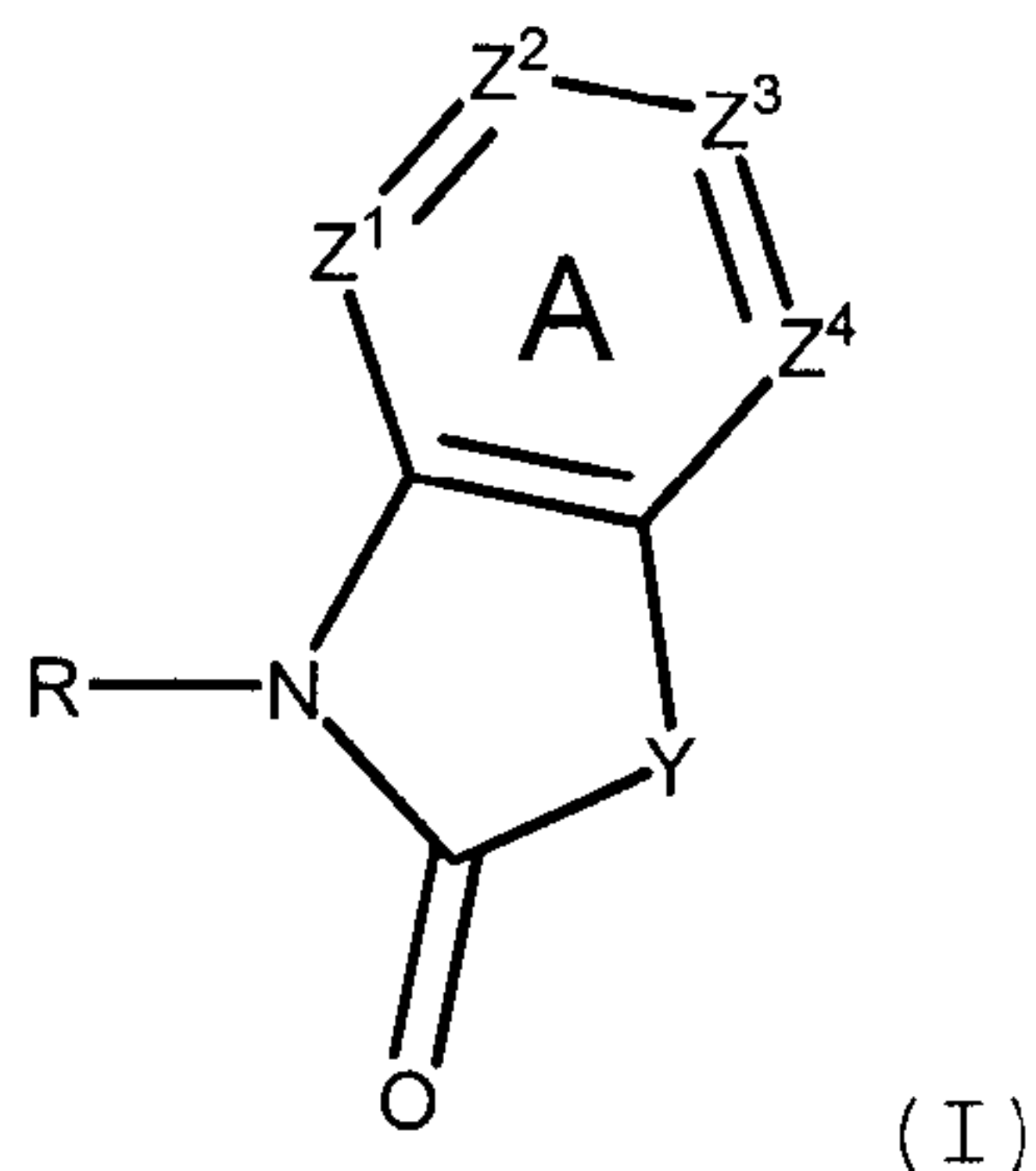
R^2 is a phenyl group or a 5- to 10-membered heterocyclic group, each of which is optionally substituted,

ring B^2 is a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted, and

ring D' is optionally further substituted 5- or 6-membered heterocycle,

or a salt thereof.

In an embodiment, there is provided a compound represented by the formula (I):



5 wherein

ring A represents a 6-membered ring optionally substituted by substituent(s) selected from the group consisting of

(1) a halogen atom,

(2) cyano,

10 (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carbonyloxy group, and

(4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen
15 atoms, any one or two of Z¹ to Z⁴ represent -N=, and the others represent -CH=;

Y represents

(1) an oxygen atom,

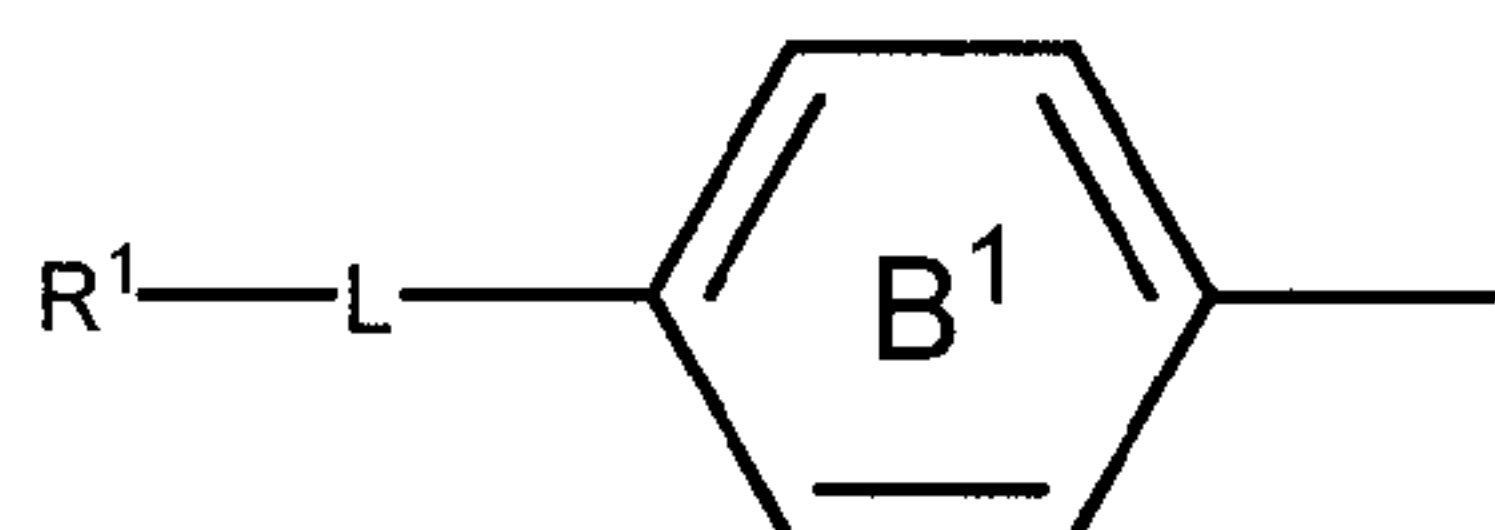
(2) a methylene group optionally substituted by 1 or 2 C₁₋₆
20 alkyl group(s), wherein the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane, or

(3) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected

from the group consisting of a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆ alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇ cycloalkyl group; and

5 R represents

a group represented by the formula:



wherein

R¹ represents a phenyl group or 5- to 10-membered heterocyclic

10 group, each of which is optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom,

(b) a C₁₋₆ alkoxy-carbonyl group,

(c) a C₁₋₆ alkyl group optionally substituted by one or more

15 substituents selected from the group consisting of

(i) a halogen atom,

(ii) a hydroxy group, and

(iii) a C₁₋₆ alkoxy group optionally substituted by trimethylsilyl,

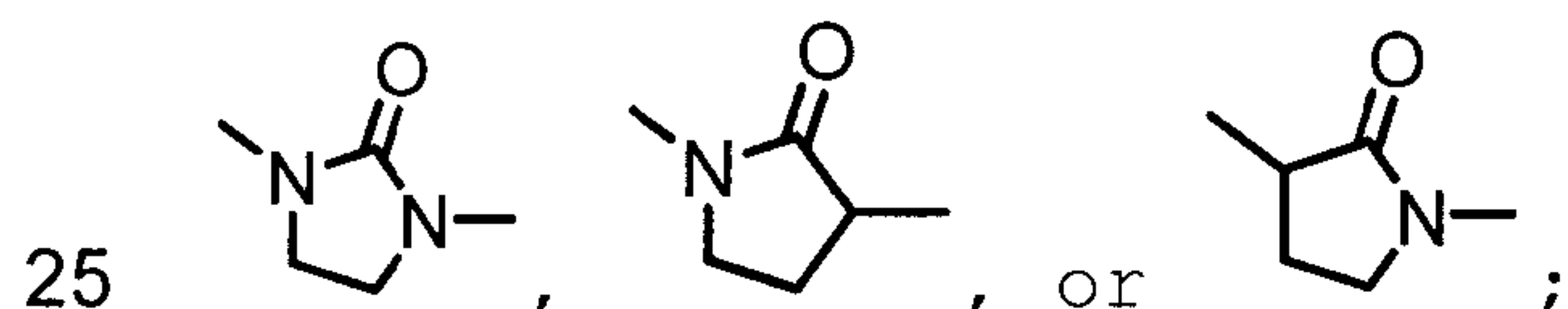
20 (d) a C₆₋₁₄ aryl group, and

(e) a C₁₋₆ alkyl-carbonyl group;

L represents a sulfur atom, an oxygen atom, a methylene group,

-CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-,

-NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



R^a and R^b are the same or different and each represents a hydrogen atom, or a C₁₋₆ alkyl group, or

L and R¹ in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom,

5 (b) a C₁₋₆ alkoxy-carbonyl group,

(c) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl group(s), and

(d) an oxo group; and

ring B¹ represents a benzene ring, a pyridine ring, a

10 pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom, and

(b) a C₁₋₆ alkyl group;

15 provided that

3,3'-benzene-1,4-diylbis(1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one),

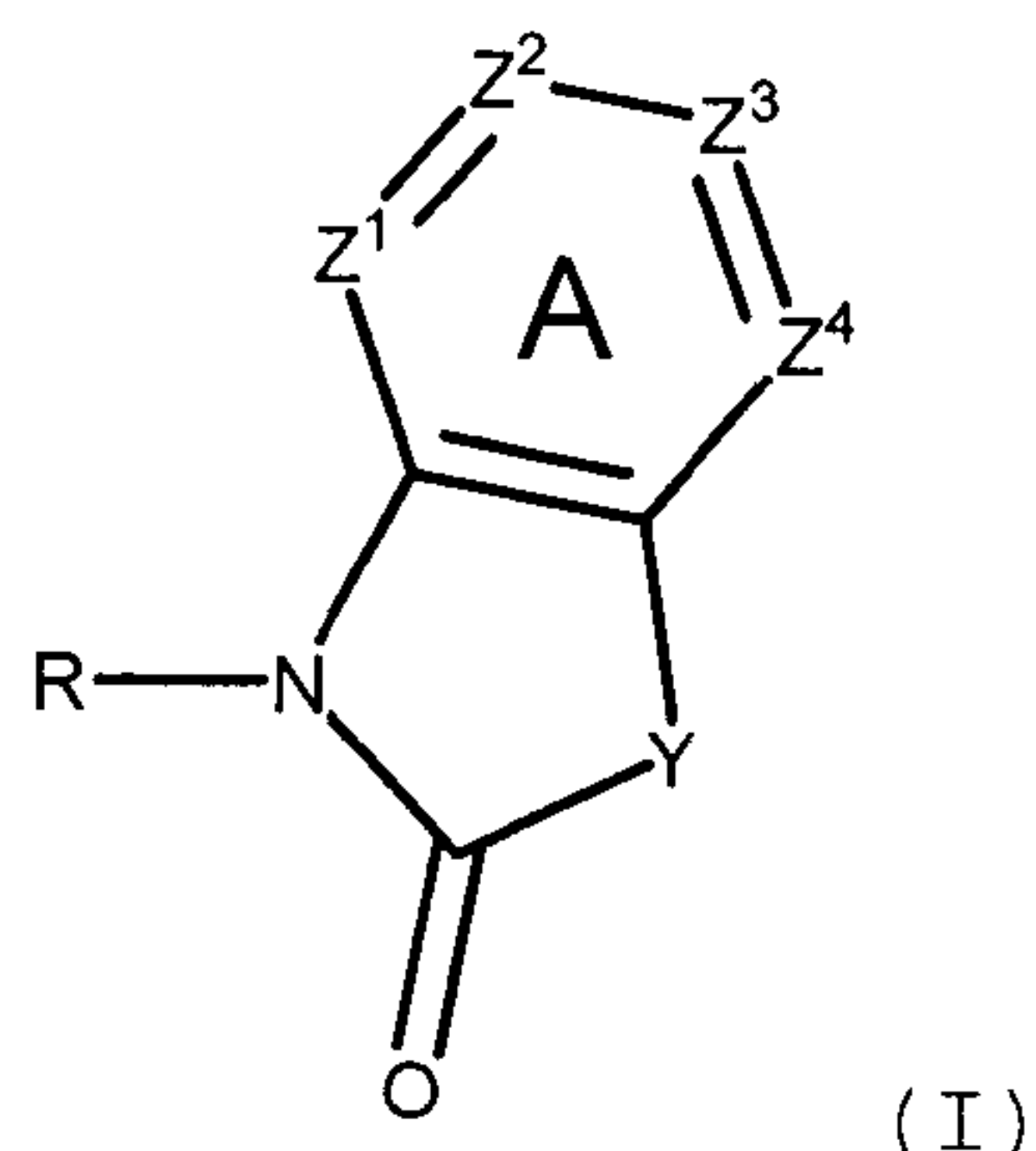
3-(4-phenoxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, and

20 3,3'-benzene-1,4-diylbis(1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one)

are excluded;

or a salt thereof.

In an embodiment, there is provided use of a compound
25 represented by the formula (I):



wherein

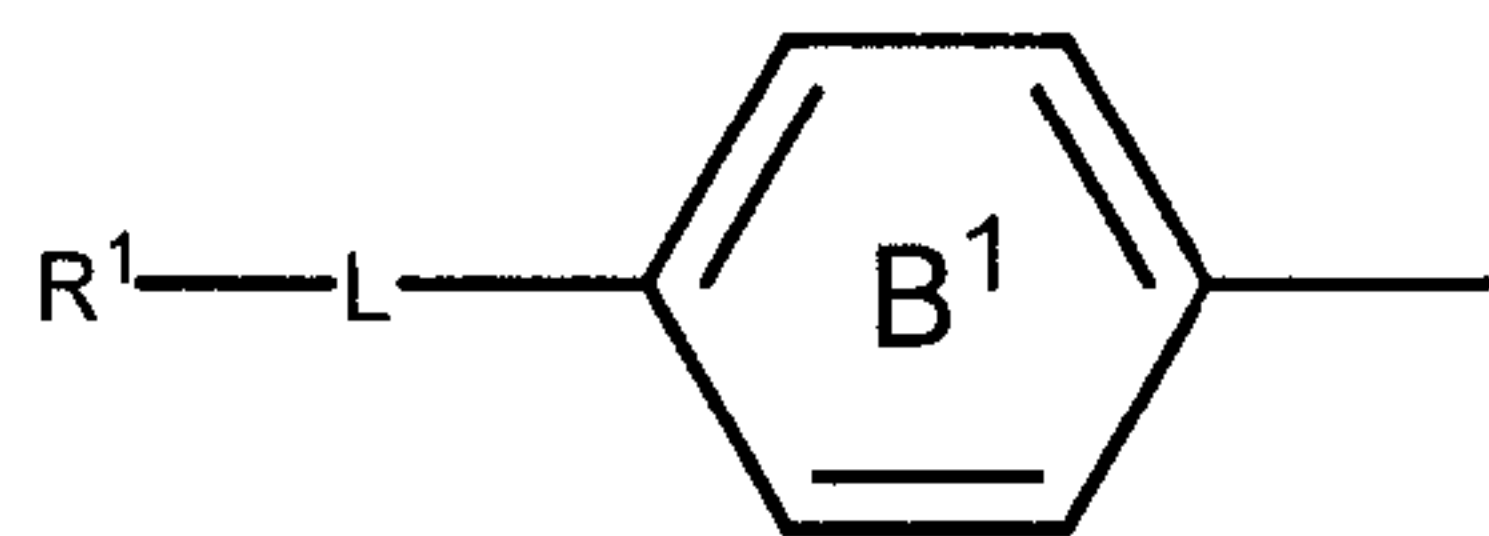
ring A represents a 6-membered ring optionally substituted by substituent(s) selected from the group consisting of

- 5 (1) a halogen atom,
 - (2) cyano,
 - (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carbonyloxy
 - 10 group, and
 - (4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, any one or two of Z¹ to Z⁴ represent -N=, and the others represent -CH=;
- Y represents
- 15 (1) an oxygen atom,
 - (2) a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl group(s), wherein the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane, or
 - 20 (3) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆

alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇ cycloalkyl group; and

R represents

a group represented by the formula:



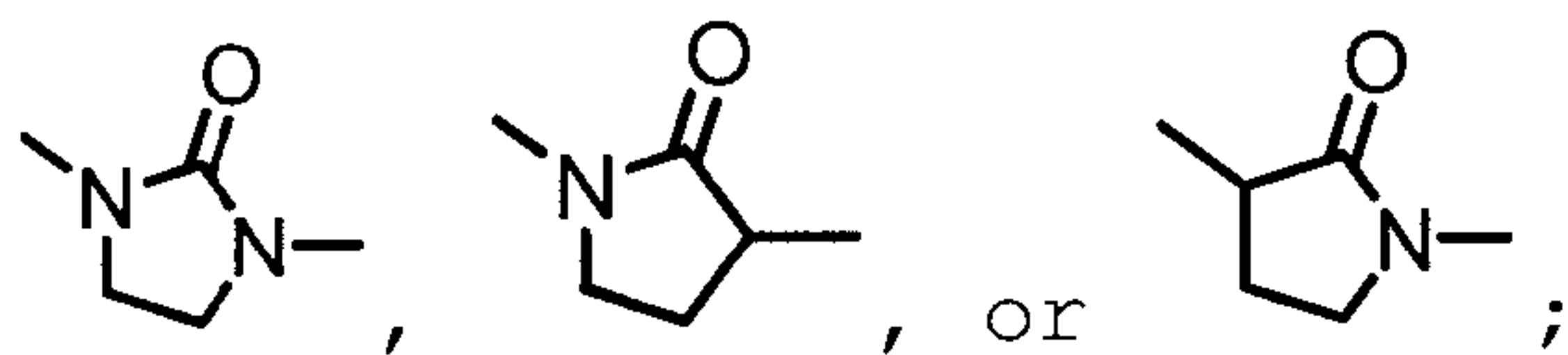
wherein

R¹ represents a phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted by substituent(s) selected from the group consisting of

- 10 (a) a halogen atom,
 (b) a C₁₋₆ alkoxy-carbonyl group,
 (c) a C₁₋₆ alkyl group optionally substituted by one or more substituents selected from the group consisting of

- (i) a halogen atom,
 15 (ii) a hydroxy group, and
 (iii) a C₁₋₆ alkoxy group optionally substituted by trimethylsilyl,
 (d) a C₆₋₁₄ aryl group, and
 (e) a C₁₋₆ alkyl-carbonyl group;

- 20 L represents a sulfur atom, an oxygen atom, a methylene group, -CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-, -NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



- R^a and R^b are the same or different and each represents a
 25 hydrogen atom, or a C₁₋₆ alkyl group, or

L and R¹ in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom,

5 (b) a C₁₋₆ alkoxy-carbonyl group,

(c) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl group(s), and

(d) an oxo group; and

ring B¹ represents a benzene ring, a pyridine ring, a

10 pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted by substituent(s) selected from the group consisting of

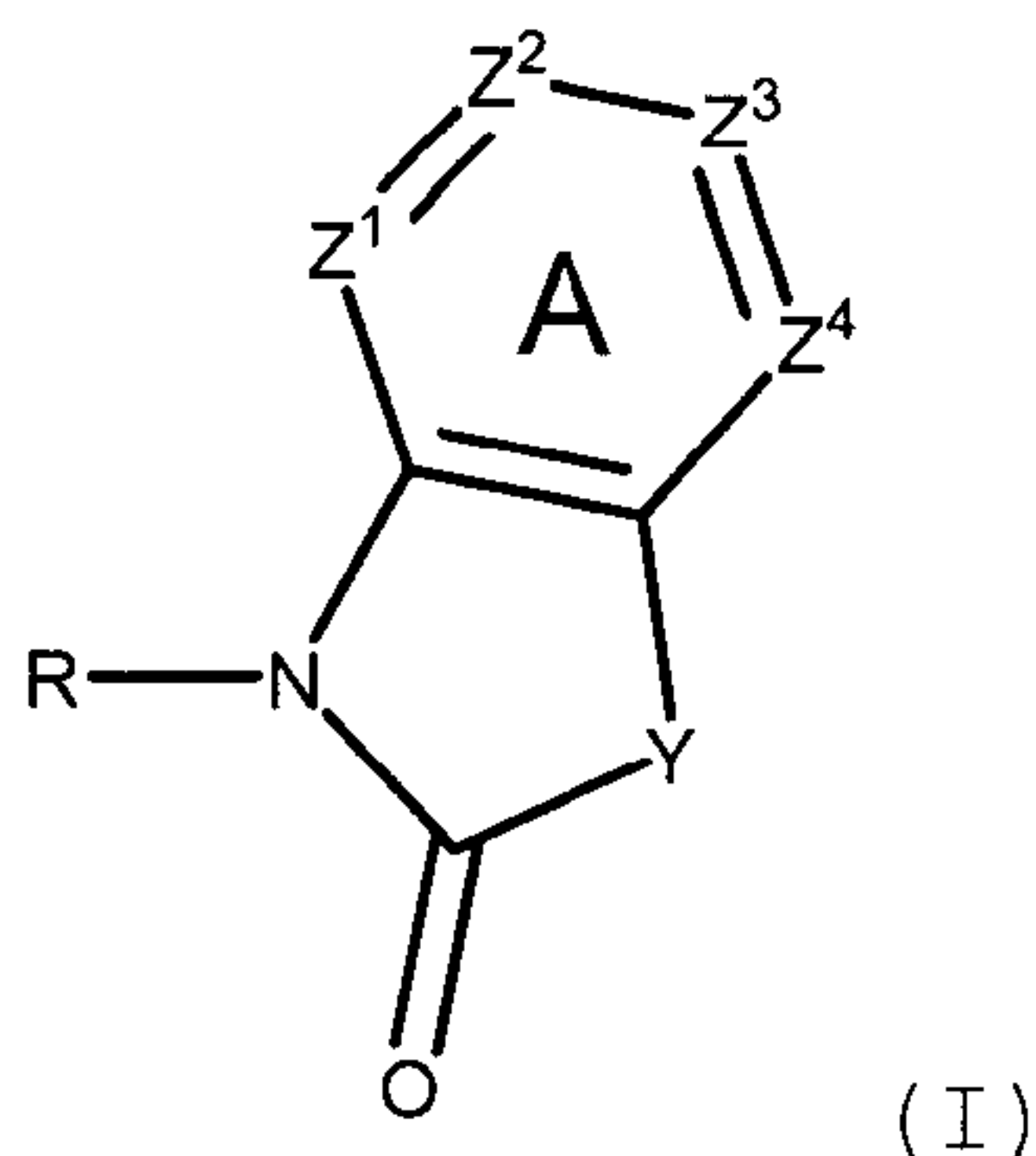
(a) a halogen atom, and

(b) a C₁₋₆ alkyl group;

15 or a pharmacologically acceptable salt thereof,

for the prevention or treatment of schizophrenia, autism, Alzheimer's disease, bipolar disorders, Parkinson's disease, Huntington's disease, obesity, drug addiction or attention deficit/hyperactivity disorder, in a mammal.

20 In an embodiment, there is provided use of a compound represented by the formula (I):



wherein

ring A represents a 6-membered ring optionally substituted by substituent(s) selected from the group consisting of

- (1) a halogen atom,
- (2) cyano,

- 5 (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carbonyloxy group, and

- (4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, any one or two of Z¹ to Z⁴ represent -N=, and the others represent -CH=;

Y represents

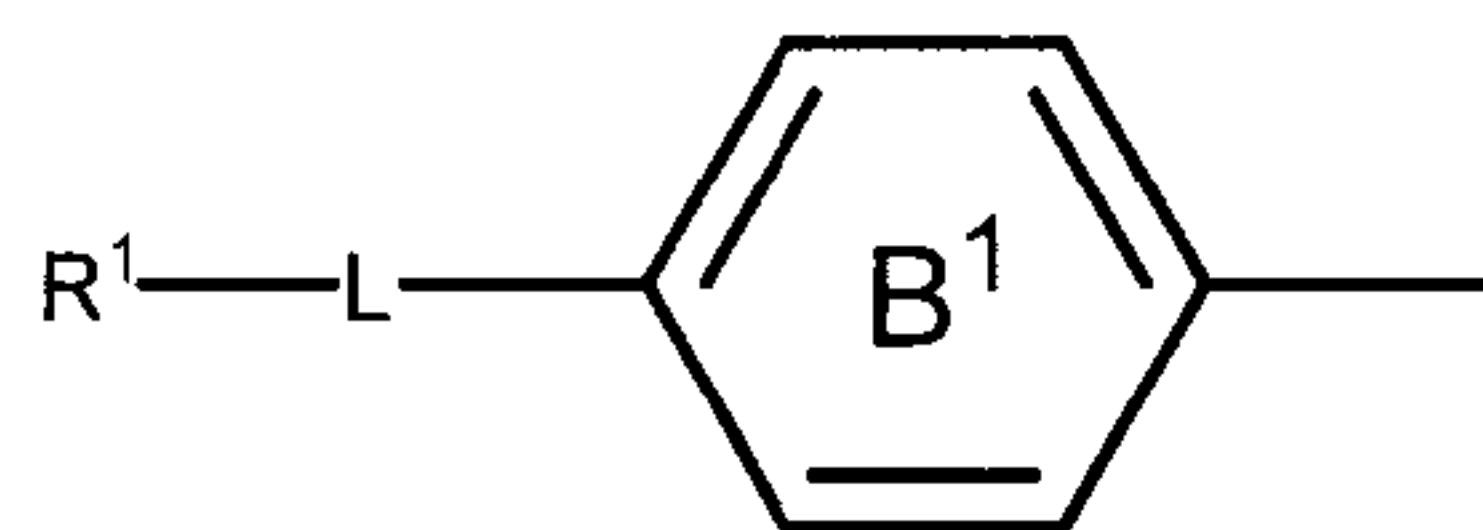
- (1) an oxygen atom,

- (2) a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl group(s), wherein the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane, or

- (3) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆ alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇ cycloalkyl group; and

R represents

- 25 a group represented by the formula:



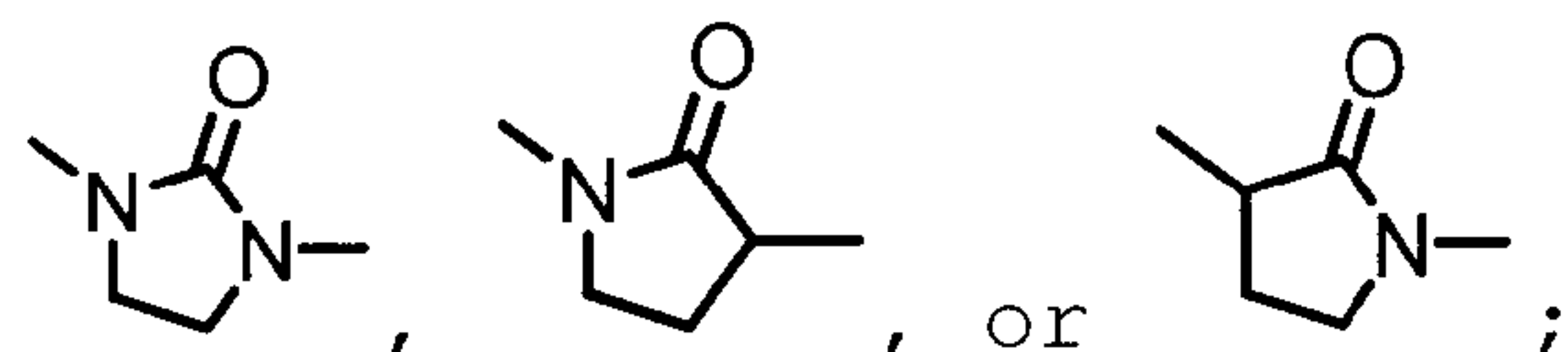
wherein

R^1 represents a phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted by substituent(s) selected from the group consisting of

- (a) a halogen atom,
- 5 (b) a C_{1-6} alkoxy-carbonyl group,
- (c) a C_{1-6} alkyl group optionally substituted by one or more substituents selected from the group consisting of
 - (i) a halogen atom,
 - (ii) a hydroxy group, and
 - 10 (iii) a C_{1-6} alkoxy group optionally substituted by trimethylsilyl,
- (d) a C_{6-14} aryl group, and
- (e) a C_{1-6} alkyl-carbonyl group;

L represents a sulfur atom, an oxygen atom, a methylene group,

- 15 -CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-,
-NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



R^a and R^b are the same or different and each represents a hydrogen atom, or a C_{1-6} alkyl group, or

- 20 L and R^1 in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by substituent(s) selected from the group consisting of
 - (a) a halogen atom,
 - (b) a C_{1-6} alkoxy-carbonyl group,
 - 25 (c) a C_{1-6} alkyl group optionally substituted by C_{6-14} aryl group(s), and
 - (d) an oxo group; and

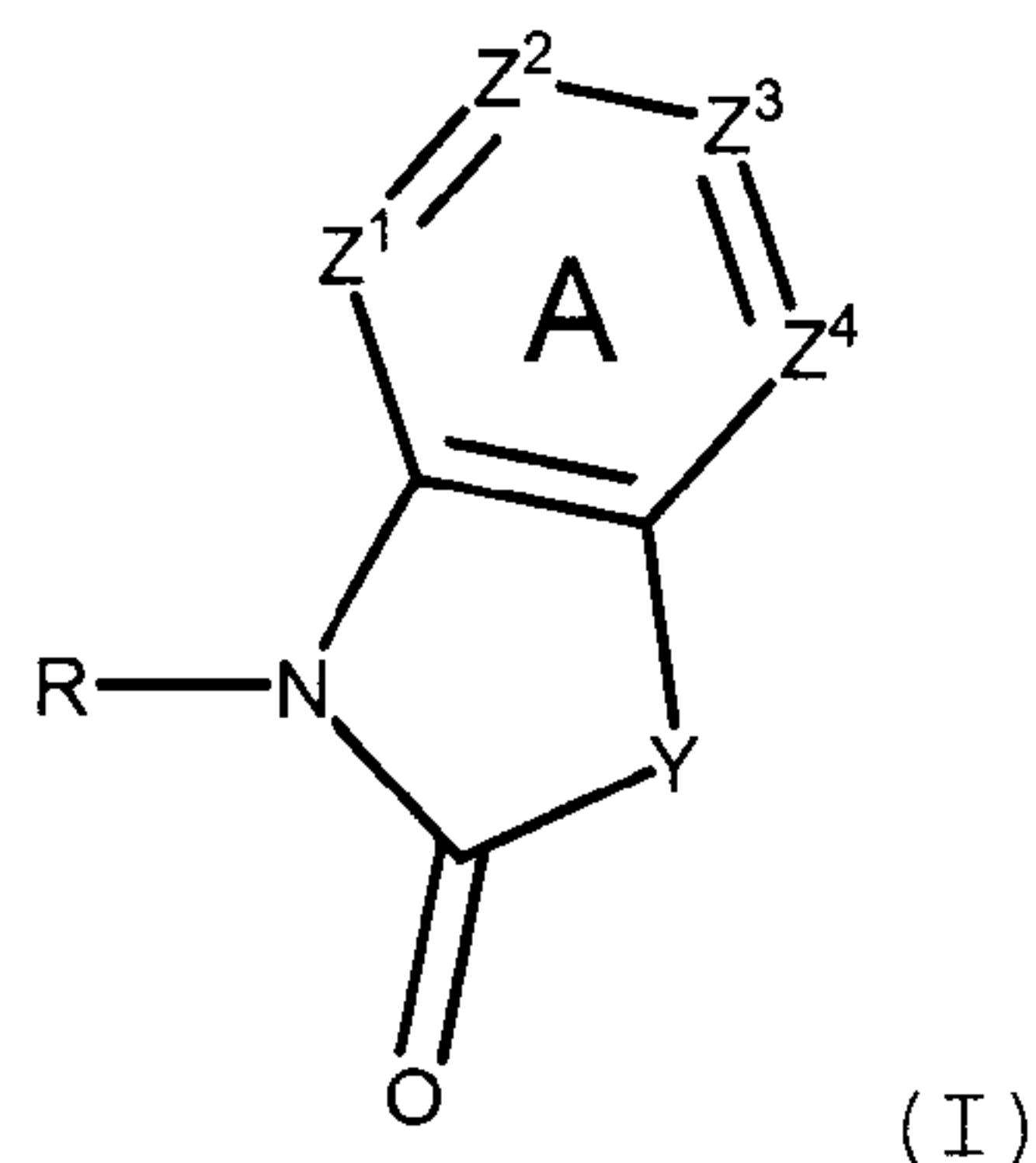
ring B^1 represents a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of

which is optionally substituted by substituent(s) selected from the group consisting of

- (a) a halogen atom, and
- (b) a C₁₋₆ alkyl group;

- 5 or a pharmacologically acceptable salt thereof,
for the production of a medicament for prevention or treatment of schizophrenia, autism, Alzheimer's disease, bipolar disorders, Parkinson's disease, Huntington's disease, obesity, drug addiction or attention deficit/hyperactivity disorder.

- 10 In an embodiment, there is provided a compound represented by the formula (I):



wherein

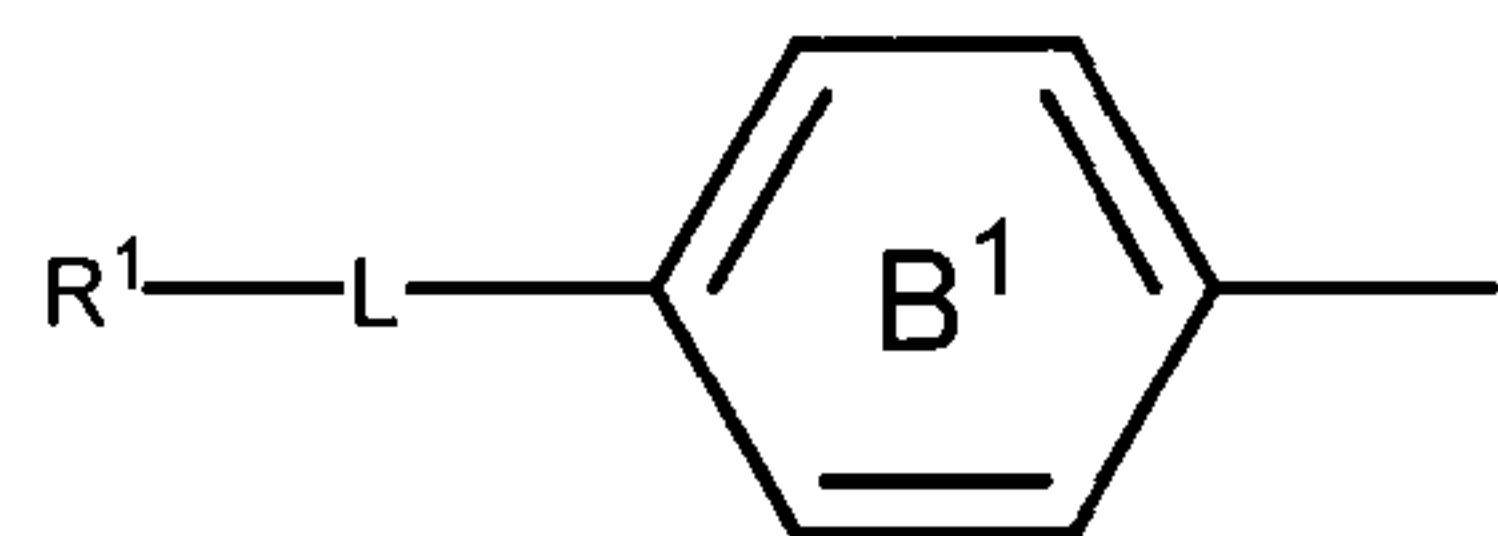
- ring A represents a 6-membered ring optionally substituted by
- 15 substituent(s) selected from the group consisting of
- (1) a halogen atom,
 - (2) cyano,
 - (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of (a) a
 - 20 halogen atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carbonyloxy group, and
 - (4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, any one or two of Z¹ to Z⁴ represent -N=, and the others represent -CH=;

Y represents

- (1) an oxygen atom,
- (2) a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl group(s), wherein the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane, or
- (3) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆ alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇ cycloalkyl group; and

R represents

a group represented by the formula:

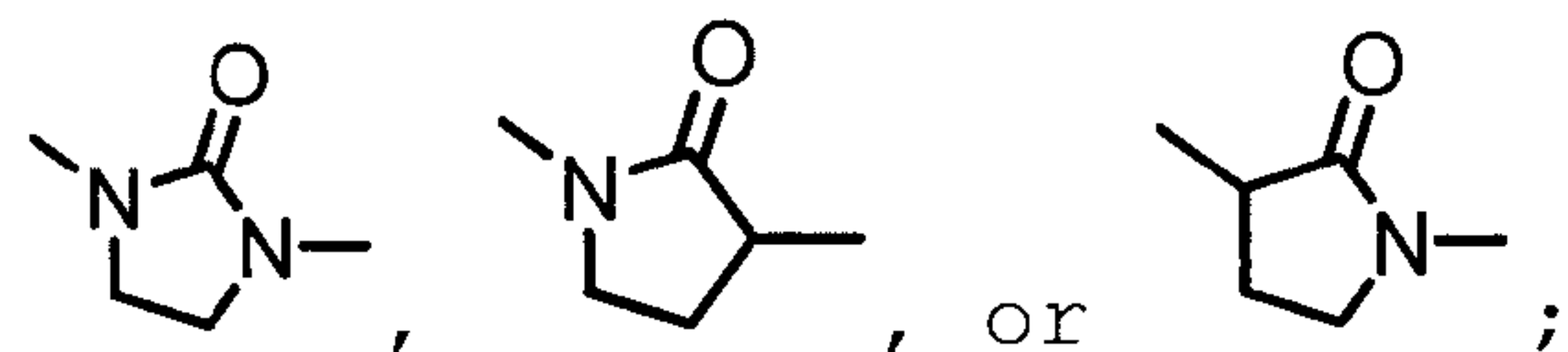


wherein

R¹ represents a phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted by substituent(s) selected from the group consisting of

- (a) a halogen atom,
- (b) a C₁₋₆ alkoxy-carbonyl group,
- (c) a C₁₋₆ alkyl group optionally substituted by one or more substituents selected from the group consisting of
 - (i) a halogen atom,
 - (ii) a hydroxy group, and
 - (iii) a C₁₋₆ alkoxy group optionally substituted by trimethylsilyl,
- (d) a C₆₋₁₄ aryl group, and
- (e) a C₁₋₆ alkyl-carbonyl group;

L represents a sulfur atom, an oxygen atom, a methylene group, -CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-, -NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



- 5 R^a and R^b are the same or different and each represents a hydrogen atom, or a C₁₋₆ alkyl group, or
- L and R¹ in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by substituent(s) selected from the group consisting of
- 10 (a) a halogen atom,
 (b) a C₁₋₆ alkoxy-carbonyl group,
 (c) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl group(s), and
 (d) an oxo group; and
- 15 ring B¹ represents a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted by substituent(s) selected from the group consisting of
- (a) a halogen atom, and
- 20 (b) a C₁₋₆ alkyl group;
 or a pharmacologically acceptable salt thereof,
 for use in prevention or treatment of schizophrenia, autism, Alzheimer's disease, bipolar disorders, Parkinson's disease, Huntington's disease, obesity, drug addiction or attention
- 25 deficit/hyperactivity disorder.

Brief Description of the Drawings

[0006]

Fig. 1 shows increase of cAMP (Fig. 1A) and cGMP (Fig. 1B) contents in the mouse striatum by oral administration of compounds. Sixty min after oral administration of the compounds, striatum was isolated from mice and then cAMP and cGMP contents were measured using EIA kits.

Fig. 2 shows inhibition of MK-801-induced hyperlocomotion by compounds in mice. By orally administered 60 min before MK-801 (0.3 mg/kg, s.c.) treatment, compounds produced the inhibition of MK-801-induced hyperlocomotion.

Detailed Description of the Invention

[0007]

In the present specification, unless otherwise specified, examples of the "halogen atom" include fluorine, chlorine, bromine and iodine.

In the present specification, unless otherwise specified, the term "optionally halogenated" or "halogeno" means the optionally presence of one or more (e.g., 1 to 3) halogen atoms as substituents.

[0008]

In the present specification, unless otherwise specified, examples of the "alkyl (group)" include a C₁₋₆ alkyl (group).

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkyl (group)" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl and the like.

In the present specification, unless otherwise specified, the "optionally halogenated C₁₋₆ alkyl (group)" means

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a C₁₋₆ alkyl (group) optionally substituted by halogen atom(s),
and examples thereof include trifluoromethyl and the like.

[0009]

In the present specification, unless otherwise specified, examples of the "alkenyl (group)" include a C₂₋₆ alkenyl (group).

In the present specification, unless otherwise specified, examples of the "C₂₋₆ alkenyl (group)" include vinyl, 1-propen-
5 1-yl, 2-propen-1-yl, isopropenyl, 2-buten-1-yl, 4-penten-1-yl, 5-hexen-1-yl and the like.

[0010]

In the present specification, unless otherwise specified, examples of the "alkynyl (group)" include a C₂₋₆ alkynyl group.
10 Examples of the "C₂₋₆ alkynyl (group)" include ethynyl, 1-propyn-1-yl, 2-propyn-1-yl, 4-pentyn-1-yl, 5-hexyn-1-yl and the like.

In the present specification, unless otherwise specified, examples of the "C₃₋₇ cycloalkyl-C₂₋₆ alkynyl (group)" include
15 cyclopropylethynyl and the like.

[0011]

In the present specification, unless otherwise specified, examples of the "C₃₋₇ cycloalkyl (group)" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

20 [0012]

In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ aryl (group)" include phenyl, 1-naphthyl, 2-naphthyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-anthryl and the like.

25 [0013]

In the present specification, unless otherwise specified, examples of the "C₇₋₁₆ aralkyl (group)" include benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-
30 phenylpentyl, 2-biphenylmethyl, 3-biphenylmethyl, 4-biphenylmethyl and the like.

[0014]

In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ aryl-C₂₋₆ alkenyl (group)" include styryl
35 and the like.

[0015]

In the present specification, unless otherwise specified, examples of the "carbocycle having 5 or 6 carbon atoms" include a C₅₋₆ cycloalkane (e.g., cyclopentane, cyclohexane), a
5 C₅₋₆ cycloalkene (e.g., cyclopentene, cyclohexene), a C₅₋₆ cycloalkadiene (e.g., cyclopentadiene, cyclohexadiene) and a benzene ring.

In the present specification, unless otherwise specified, examples of the "C₃₋₆ cycloalkane" include cyclopropane,
10 cyclobutane, cyclohexane and cyclopentane.

[0016]

In the present specification, unless otherwise specified, examples of the "5- or 6-membered heterocycle" include a 5- or 6-membered heterocycle containing, besides carbon atoms, 1 to
15 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

In the present specification, unless otherwise specified, examples of the "5- or 6-membered heterocycle containing, besides carbon atoms, 1 to 4 hetero atoms selected from a
20 nitrogen atom, a sulfur atom and an oxygen atom" include a pyrrolidine ring, a tetrahydrofuran ring, a tetrahydrothiophene ring, a piperidine ring, a tetrahydropyran ring, a morpholine ring, a thiomorpholine ring, a piperazine ring, a furan ring, a thiophene ring, a pyrrole ring, an
25 oxazole ring, an isoxazole ring, a thiazole ring, an isothiazole ring, an imidazole ring, a pyrazole ring, a 1,2,3-oxadiazole ring, a 1,2,4-oxadiazole ring, a 1,3,4-oxadiazole ring, a furazan ring, a 1,2,3-thiadiazole ring, a 1,2,4-thiadiazole ring, a 1,3,4-thiadiazole ring, a 1,2,3-triazole
30 ring, a 1,2,4-triazole ring, a tetrazole ring, a pyridine ring, a pyridazine ring, a pyrimidine ring, a pyrazine ring, a triazine ring and the like.

In the present specification, unless otherwise specified, "heterocyclic group" (and the heterocyclic moiety of the
35 substituent) is a non-aromatic heterocyclic group or a

heteroaryl group (i.e., an aromatic heterocyclic group), and examples thereof include a 3- to 14-membered heterocyclic group containing 1 to 5 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. The "heterocyclic group" can be monocyclic, bicyclic or tricyclic.

In the present specification, unless otherwise specified, examples of the "3- to 14-membered heterocyclic group" include 3- to 14-membered aromatic heterocyclic groups containing 1 to 5 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, such as pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), triazolyl (e.g., 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxadiazolyl (e.g., 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl), thiadiazolyl (e.g., 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl), tetrazolyl, pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyrazinyl, isoindolyl (e.g., 1-isoindolyl, 2-isoindolyl, 3-isoindolyl, 4-isoindolyl, 5-isoindolyl, 6-isoindolyl, 7-isoindolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), benzo[b]furanyl (e.g., 2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), benzo[c]furanyl (e.g., 1-benzo[c]furanyl, 4-benzo[c]furanyl, 5-benzo[c]furanyl), benzo[b]thienyl (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl, 4-benzo[b]thienyl, 5-benzo[b]thienyl, 6-benzo[b]thienyl, 7-benzo[b]thienyl), benzo[c]thienyl (e.g., 1-benzo[c]thienyl, 4-benzo[c]thienyl, 5-benzo[c]thienyl), indazolyl (e.g., 1-

indazolyl, 2-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (e.g., 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl), 1,2-benzisoxazolyl (e.g., 1,2-benzisoxazol-3-yl, 1,2-benzisoxazol-4-yl, 1,2-benzisoxazol-5-yl, 1,2-benzisoxazol-6-yl, 1,2-benzisoxazol-7-yl), benzoxazolyl (e.g., 2-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, 7-benzoxazolyl), 1,2-benzisothiazolyl (e.g., 1,2-benzisothiazol-3-yl, 1,2-benzisothiazol-4-yl, 1,2-benzisothiazol-5-yl, 1,2-benzisothiazol-6-yl, 1,2-benzisothiazol-7-yl), benzothiazolyl (e.g., 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), cinnolinyl (e.g., 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl), phthalazinyl (e.g., 1-phthalazinyl, 5-phthalazinyl, 6-phthalazinyl), quinazolinyl (e.g., 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl), quinoxalinyl (e.g., 2-quinoxalinyl, 5-quinoxalinyl, 6-quinoxalinyl), pyrazolo[1,5-a]pyridyl (e.g., pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-3-yl, pyrazolo[1,5-a]pyridin-4-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyridin-6-yl, pyrazolo[1,5-a]pyridine-7-yl), imidazo[1,2-a]pyridyl (e.g., imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-5-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyridin-7-yl, imidazo[1,2-a]pyridin-8-yl) and the like; and

3- to 14-membered saturated or unsaturated non-aromatic heterocyclic groups containing 1 to 5 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, such as tetrahydrofuryl, oxazolidinyl, imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), aziridinyl (e.g., 1-aziridinyl, 2-aziridinyl), azetidiny (e.g., 1-

azetidiny1, 2-azetidiny1), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), piperidyl (e.g., 1-piperidyl, 2-piperidyl, 3-piperidyl), azepanyl (e.g., 1-azepanyl, 2-azepanyl, 3-azepanyl, 4-azepanyl), azocanyl (e.g., 1-azocanyl, 2-azocanyl, 3-azocanyl, 4-azocanyl), azonanyl (e.g., 1-azonanyl, 2-azonanyl, 3-azonanyl, 4-azonanyl, 5-azonanyl), piperazinyl (e.g., 1,4-piperazin-1-yl, 1,4-piperazin-2-yl), diazepinyl (e.g., 1,4-diazepin-1-yl, 1,4-diazepin-2-yl, 1,4-diazepin-5-yl, 1,4-diazepin-6-yl), diazocanyl (e.g., 1,4-diazocan-1-yl, 1,4-diazocan-2-yl, 1,4-diazocan-5-yl, 1,4-diazocan-6-yl, 1,5-diazocan-1-yl, 1,5-diazocan-2-yl, 1,5-diazocan-3-yl), tetrahydropyranyl (e.g., tetrahydropyran-4-yl), morpholinyl (e.g., 4-morpholinyl), thiomorpholinyl (e.g., 4-thiomorpholinyl), 2-oxazolidinyl, dihydrofuryl, dihydropyranyl, dihydroquinolyl, dihydroisoquinolyl (e.g., 3,4-dihydroisoquinolin-2-yl) and the like.

[0017]

In the present specification, unless otherwise specified, examples of the "aromatic heterocyclic group" (and the aromatic heterocyclic moiety of the substituent) include those similar to the "3- to 14-membered aromatic heterocyclic group containing 1 to 5 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom" exemplified above as the aforementioned "heterocyclic group".

25 [0018]

In the present specification, unless otherwise specified, examples of the "non-aromatic heterocyclic group" (and the non-aromatic heterocyclic moiety of the substituent) include those similar to the "3- to 14-membered saturated or unsaturated non-aromatic heterocyclic group containing 1 to 5 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom" exemplified above as the aforementioned "heterocyclic group".

[0019]

35 In the present specification, unless otherwise specified,

examples of the "saturated heterocyclic group" (and the saturated heterocyclic moiety of the substituent) include a saturated heterocyclic group, from among the aforementioned "non-aromatic heterocyclic groups", and specific examples
5 thereof include tetrahydrofuryl, morpholinyl, thiomorpholinyl, piperidyl, pyrrolidinyl, piperazinyl and the like.

In the present specification, unless otherwise specified, examples of the "5- or 6-membered saturated heterocyclic group" (and the 5- or 6-membered saturated heterocyclic moiety
10 of the substituent) include a 5- or 6-membered saturated heterocyclic group, from among the aforementioned "saturated heterocyclic groups".

[0020]

In the present specification, unless otherwise specified, examples of the "alkoxy (group)" include a C₁₋₆ alkoxy (group).
15

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkoxy (group)" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy and the like.

20 [0021]

In the present specification, unless otherwise specified, examples of the "C₃₋₇ cycloalkyloxy (group)" include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like.

25 [0022]

In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ aryloxy (group)" include phenyloxy, 1-naphthyloxy, 2-naphthyloxy and the like.

[0023]

30 In the present specification, unless otherwise specified, examples of the "C₇₋₁₆ aralkyloxy (group)" include benzyloxy, phenethyloxy and the like.

[0024]

In the present specification, unless otherwise specified, examples of the "alkyl-carbonyloxy (group)" include a C₁₋₆
35

alkyl-carbonyloxy (group).

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkyl-carbonyloxy (group)" include acetoxy, propionyloxy and the like.

5 [0025]

In the present specification, unless otherwise specified, examples of the "alkoxy-carbonyloxy (group)" include a C₁₋₆ alkoxy-carbonyloxy (group).

In the present specification, unless otherwise specified, 10 examples of the "C₁₋₆ alkoxy-carbonyloxy (group)" include methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy and the like.

[0026]

In the present specification, unless otherwise specified, 15 examples of the "mono-alkyl-carbamoyloxy (group)" include a mono-C₁₋₆ alkyl-carbamoyloxy (group).

In the present specification, unless otherwise specified, examples of the "mono-C₁₋₆ alkyl-carbamoyloxy (group)" include methylcarbamoyloxy, ethylcarbamoyloxy and the like.

20 [0027]

In the present specification, unless otherwise specified, examples of the "di-alkyl-carbamoyloxy (group)" include a di-C₁₋₆ alkyl-carbamoyloxy (group).

In the present specification, unless otherwise specified, 25 examples of the "di-C₁₋₆ alkyl-carbamoyloxy (group)" include dimethylcarbamoyloxy, diethylcarbamoyloxy and the like.

[0028]

In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ aryl-carbonyloxy (group)" include 30 benzoyloxy, naphthylcarbonyloxy and the like.

[0029]

In the present specification, unless otherwise specified, examples of the "mono- or di-C₆₋₁₄ aryl-carbamoyl (group)" include phenylcarbamoyl, naphthylcarbamoyl and the like.

35 [0030]

In the present specification, unless otherwise specified, examples of the "mono- or di-C₆₋₁₄ aryl-carbamoyloxy (group)" include phenylcarbamoyloxy, naphthylcarbamoyloxy and the like.
[0031]

5 In the present specification, unless otherwise specified, examples of the heterocyclic moiety of the "heterocyclyl-oxy (group)" include those similar to the aforementioned "heterocyclic group". Specific examples of the "heterocyclyl-oxy (group)" include a 5- to 14-membered heterocyclyl-oxy
10 (group) containing 1 to 5 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.
[0032]

In the present specification, unless otherwise specified, examples of the aromatic heterocyclic moiety of the "aromatic
15 heterocyclyl-oxy (group)" include those similar to the "aromatic heterocyclic group" exemplified as the aforementioned "heterocyclic group". Specific examples of the "aromatic heterocyclyl-oxy (group)" include a 3- to 14-membered aromatic heterocyclyl-oxy containing 1 to 5 hetero
20 atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.
[0033]

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkylsulfonyloxy group" include
25 methylsulfonyloxy, ethylsulfonyloxy and the like.
[0034]

In the present specification, unless otherwise specified, examples of the "halogeno C₁₋₆ alkylsulfonyloxy group" include halogenomethylsulfonyloxy, halogenoethylsulfonyloxy and the
30 like.
[0035]

In the present specification, unless otherwise specified, examples of the "alkylsulfanyl (group)" include a C₁₋₆ alkylsulfanyl (group).

35 In the present specification, unless otherwise specified,

examples of the "C₁₋₆ alkylsulfanyl (group)" include methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, butylsulfanyl, sec-butylsulfanyl, tert-butylsulfanyl and the like.

5 [0036]

In the present specification, unless otherwise specified, examples of the "C₃₋₇ cycloalkylsulfanyl (group)" include cyclopropylsulfanyl, cyclobutylsulfanyl, cyclopentylsulfanyl, cyclohexylsulfanyl and the like.

10 [0037]

In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ arylsulfanyl (group)" include phenylsulfanyl, 1-naphthylsulfanyl, 2-naphthylsulfanyl and the like.

15 [0038]

In the present specification, unless otherwise specified, examples of the "C₇₋₁₆ aralkylsulfanyl (group)" include benzylsulfanyl, phenethylsulfanyl and the like.

[0039]

20 In the present specification, unless otherwise specified, examples of the heterocyclic moiety of the "heterocyclyl-sulfanyl (group)" include those similar to the aforementioned "heterocyclic group". Specific examples of the "heterocyclyl-sulfanyl (group)" include a 3- to 14-membered heterocyclyl-sulfanyl (group) containing 1 to 5 hetero atoms selected from
25 a nitrogen atom, a sulfur atom and an oxygen atom.

[0040]

In the present specification, unless otherwise specified, examples of the "alkyl-carbonyl (group)" include a C₁₋₆ alkyl-
30 carbonyl.

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkyl-carbonyl (group)" include acetyl, propionyl, pivaloyl and the like.

[0041]

35 In the present specification, unless otherwise specified,

examples of the "C₃₋₇ cycloalkyl-carbonyl (group)" include cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl and the like.

[0042]

5 In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ aryl-carbonyl (group)" include benzoyl, 1-naphthoyl, 2-naphthoyl and the like.

[0043]

In the present specification, unless otherwise specified,
10 examples of the "C₇₋₁₆ aralkyl-carbonyl (group)" include phenylacetyl, 3-phenylpropionyl and the like.

[0044]

In the present specification, unless otherwise specified, examples of the heterocyclic moiety of the "heterocyclyl-carbonyl (group)" include those similar to the above-mentioned
15 "heterocyclic group". Specific examples thereof include a 3- to 14-membered heterocyclyl-carbonyl (group) containing 1 to 5 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. More specific examples thereof include
20 picolinoyl, nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, 4-morpholinylcarbonyl, 4-thiomorpholinylcarbonyl, aziridin-1-ylcarbonyl, aziridin-2-ylcarbonyl, azetidin-1-ylcarbonyl, azetidin-2-ylcarbonyl, pyrrolidin-1-ylcarbonyl, pyrrolidin-2-ylcarbonyl, pyrrolidin-
25 3-ylcarbonyl, piperidin-1-ylcarbonyl, piperidin-2-ylcarbonyl, piperidin-3-ylcarbonyl, azepan-1-ylcarbonyl, azepan-2-ylcarbonyl, azepan-3-ylcarbonyl, azepan-4-ylcarbonyl, azocan-1-ylcarbonyl, azocan-2-ylcarbonyl, azocan-3-ylcarbonyl, azocan-4-ylcarbonyl, 1,4-piperazin-1-ylcarbonyl, 1,4-
30 piperazin-2-ylcarbonyl, 1,4-diazepan-1-ylcarbonyl, 1,4-diazepan-2-ylcarbonyl, 1,4-diazepan-5-ylcarbonyl, 1,4-diazepan-6-ylcarbonyl, 1,4-diazocan-1-ylcarbonyl, 1,4-diazocan-2-ylcarbonyl, 1,4-diazocan-5-ylcarbonyl, 1,4-diazocan-6-ylcarbonyl, 1,5-diazocan-1-ylcarbonyl, 1,5-
35 diazocan-2-ylcarbonyl, 1,5-diazocan-3-ylcarbonyl and the like.

[0045]

In the present specification, unless otherwise specified, examples of the "optionally esterified carboxy (group)" include carboxy, optionally substituted alkoxy-carbonyl, optionally substituted C₆₋₁₄ aryloxy-carbonyl, optionally substituted C₇₋₁₆ aralkyloxy-carbonyl, optionally substituted silyloxy-carbonyl (e.g., trimethylsilyloxycarbonyl (TMS-O-CO-), triethylsilyloxycarbonyl (TES-O-CO-, tert-butyl dimethylsilyloxycarbonyl (TBS-O-CO-), triisopropylsilyloxycarbonyl (TIPS-O-CO-), tert-butyl diphenylsilyloxycarbonyl (TBDPS-O-CO-)) and the like.

[0046]

In the present specification, unless otherwise specified, examples of the "alkoxy-carbonyl (group)" include a C₁₋₆ alkoxy-carbonyl (group).

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkoxy-carbonyl (group)" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like.

[0047]

In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ aryloxy-carbonyl (group)" include phenoxycarbonyl and the like.

In the present specification, unless otherwise specified, examples of the "C₇₋₁₆ aralkyloxy-carbonyl (group)" include benzyloxycarbonyl, phenethyloxycarbonyl and the like.

[0048]

In the present specification, unless otherwise specified, examples of the "alkylsulfonyl (group)" include a C₁₋₆ alkylsulfonyl (group).

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkylsulfonyl (group)" include methylsulfonyl, ethylsulfonyl and the like.

[0049]

In the present specification, unless otherwise specified,

examples of the "C₃₋₇ cycloalkylsulfonyl (group)" include cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl and the like.

[0050]

5 In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ arylsulfonyl (group)" include phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl and the like.

[0051]

10 In the present specification, unless otherwise specified, examples of the heterocyclic moiety of the "heterocyclyl-sulfonyl (group)" include those similar to the aforementioned "heterocyclic group". Specific examples of the "heterocyclyl-sulfonyl (group)" include a 3- to 14-membered heterocyclyl-sulfonyl (group) containing 1 to 5 hetero atoms selected from
15 a nitrogen atom, a sulfur atom and an oxygen atom.

[0052]

In the present specification, unless otherwise specified, examples of the "alkylsulfinyl (group)" include a C₁₋₆
20 alkylsulfinyl (group).

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkylsulfinyl (group)" include methylsulfinyl, ethylsulfinyl and the like.

[0053]

25 In the present specification, unless otherwise specified, examples of the "C₃₋₇ cycloalkylsulfinyl (group)" include cyclopropylsulfinyl, cyclobutylsulfinyl, cyclopentylsulfinyl, cyclohexylsulfinyl and the like.

[0054]

30 In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ arylsulfinyl (group)" include phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl and the like.

[0055]

35 In the present specification, unless otherwise specified,

examples of the heterocyclic moiety of the "heterocyclyl-sulfinyl (group)" include those similar to the aforementioned "heterocyclic group". Specific examples of the "heterocyclyl-sulfinyl (group)" include a 3- to 14-membered heterocyclyl-sulfinyl (group) containing 1 to 5 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0056]

In the present specification, unless otherwise specified, examples of the "alkyl-carbamoyl (group)" include a mono- or di-C₁₋₆ alkyl-carbamoyl.

In the present specification, unless otherwise specified, examples of the "mono- or di-C₁₋₆ alkyl-carbamoyl (group)" include methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl and the like.

15 [0057]

In the present specification, unless otherwise specified, examples of the "mono- or di-alkylamino (group)" include a mono- or di-C₁₋₆ alkylamino (group).

In the present specification, unless otherwise specified, examples of the "mono- or di-C₁₋₆ alkylamino (group)" include methylamino, ethylamino, propylamino, dimethylamino, diethylamino and the like.

[0058]

In the present specification, unless otherwise specified, examples of the "alkyl-carbonylamino (group)" include a mono- or di-C₁₋₆ alkyl-carbonylamino.

In the present specification, unless otherwise specified, examples of the "mono- or di-C₁₋₆ alkyl-carbonylamino (group)" include acetylamino, propionylamino, pivaloylamino and the like.

30 [0059]

In the present specification, unless otherwise specified, examples of the "heterocyclyl (group)" of the "heterocyclyl-amino (group)" include those similar to the above-mentioned "heterocyclic group". Examples of the "heterocyclyl-amino

(group)" include 2-pyridyl-amino and the like.

[0060]

In the present specification, unless otherwise specified, examples of the "heterocyclyl-carbonyl" of the "heterocyclyl-carbonylamino (group)" include those similar to the above-mentioned "heterocyclyl-carbonyl". Examples of the "heterocyclyl-carbonylamino (group)" include pyridyl-carbonylamino.

[0061]

10 In the present specification, unless otherwise specified, examples of the "heterocyclyl (group)" of the "heterocyclyl-oxycarbonylamino (group)" include those similar to the above-mentioned "heterocyclic group". Examples of the "heterocyclyl-oxycarbonylamino (group)" include 2-pyridyl-oxycarbonylamino.

15 [0062]

In the present specification, unless otherwise specified, examples of the "heterocyclyl (group)" of the "heterocyclyl-sulfonylamino (group)" include those similar to the above-mentioned "heterocyclic group". Examples of the "heterocyclyl-sulfonylamino (group)" include 2-pyridyl-sulfonylamino and the like.

[0063]

In the present specification, unless otherwise specified, examples of the "alkoxy-carbonylamino (group)" include a C₁₋₆ alkoxy-carbonylamino (group).

In the present specification, unless otherwise specified, examples of the "C₁₋₆ alkoxy-carbonylamino (group)" include methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino and the like.

30 [0064]

In the present specification, unless otherwise specified, examples of the "alkylsulfonylamino (group)" include a C₁₋₆ alkylsulfonylamino (group).

In the present specification, unless otherwise specified, 35 examples of the "C₁₋₆ alkylsulfonylamino (group)" include

methysulfonylamino, ethylsulfonylamino and the like.

[0065]

In the present specification, unless otherwise specified, examples of the "mono- or di-C₃₋₇ cycloalkylamino (group)" include cyclopropylamino, cyclopentylamino, cyclohexylamino and the like.

[0066]

In the present specification, unless otherwise specified, examples of the "C₃₋₇ cycloalkyl-carbonylamino (group)" include cyclopropylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino and the like.

[0067]

In the present specification, unless otherwise specified, examples of the "C₃₋₈ cycloalkoxy-carbonylamino (group)" include cyclopropoxycarbonylamino, cyclopentyloxycarbonylamino, cyclohexyloxycarbonylamino and the like.

[0068]

In the present specification, unless otherwise specified, examples of the "C₃₋₈ cycloalkylsulfonylamino (group)" include cyclopropylsulfonylamino, cyclopentylsulfonylamino, cyclohexylsulfonylamino and the like.

[0069]

In the present specification, unless otherwise specified, examples of the "mono- or di-C₆₋₁₄ arylamino (group)" include phenylamino, diphenylamino and the like.

[0070]

In the present specification, unless otherwise specified, examples of the "mono- or di-C₇₋₁₆ aralkylamino (group)" include benzylamino and the like.

[0071]

In the present specification, unless otherwise specified, examples of the "C₆₋₁₄ aryl-carbonylamino (group)" include benzoylamino, naphthoylamino and the like.

[0072]

In the present specification, unless otherwise specified,

examples of the "C₆₋₁₄ arylsulfonylamino (group)" include phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino and the like.

[0073]

5 [Substituent Group A]

- (1) a halogen atom;
- (2) nitro;
- (3) cyano;
- (4) an optionally esterified carboxy group;
- 10 (5) an optionally substituted alkyl group;
- (6) an optionally substituted alkenyl group;
- (7) an optionally substituted alkynyl group (e.g., an optionally substituted C₃₋₇ cycloalkyl-C₂₋₆ alkynyl group);
- (8) an optionally substituted C₃₋₇ cycloalkyl group;
- 15 (9) an optionally substituted C₆₋₁₄ aryl group;
- (10) an optionally substituted C₇₋₁₆ aralkyl group;
- (11) an optionally substituted C₆₋₁₄ aryl-C₂₋₆ alkenyl group;
- (12) an optionally substituted heterocyclic group;
- (13) a hydroxy group;
- 20 (14) an optionally substituted alkoxy group;
- (15) an optionally substituted C₃₋₇ cycloalkyloxy group;
- (16) an optionally substituted C₆₋₁₄ aryloxy group;
- (17) an optionally substituted C₇₋₁₆ aralkyloxy group;
- (18) an optionally substituted alkyl-carbonyloxy group;
- 25 (19) an optionally substituted alkoxy-carbonyloxy group;
- (20) an optionally substituted mono-alkyl-carbamoyloxy group;
- (21) an optionally substituted di-alkyl-carbamoyloxy group;
- (22) an optionally substituted C₆₋₁₄ aryl-carbonyloxy group;
- (23) an optionally substituted mono- or di-C₆₋₁₄ aryl-
- 30 carbamoyloxy group;
- (24) an optionally substituted heterocyclyl-oxy group (e.g., an optionally substituted aromatic heterocyclyl-oxy group);
- (25) an optionally substituted C₁₋₆ alkylsulfonyloxy group (e.g., an optionally substituted halogeno C₁₋₆ alkylsulfonyloxy group);
- 35 (26) a mercapto group;

- (27) an optionally substituted alkylsulfanyl group;
(28) an optionally substituted C₃₋₇ cycloalkylsulfanyl group;
(29) an optionally substituted C₆₋₁₄ arylsulfanyl group;
(30) an optionally substituted C₇₋₁₆ aralkylsulfanyl group;
5 (31) an optionally substituted heterocyclyl-sulfanyl group;
(32) a formyl group;
(33) an optionally substituted alkyl-carbonyl group;
(34) an optionally substituted C₃₋₇ cycloalkyl-carbonyl group;
(35) an optionally substituted C₆₋₁₄ aryl-carbonyl group;
10 (36) an optionally substituted C₇₋₁₆ aralkyl-carbonyl group;
(37) an optionally substituted heterocyclyl-carbonyl group;
(38) an optionally substituted alkylsulfonyl group;
(39) an optionally substituted C₃₋₇ cycloalkylsulfonyl group;
(40) an optionally substituted C₆₋₁₄ arylsulfonyl group;
15 (41) an optionally substituted heterocyclyl-sulfonyl group;
(42) an optionally substituted alkylsulfinyl group;
(43) an optionally substituted C₃₋₇ cycloalkylsulfinyl group;
(44) an optionally substituted C₆₋₁₄ arylsulfinyl group;
(45) an optionally substituted heterocyclyl-sulfinyl group;
20 (46) a sulfo group;
(47) a sulfamoyl group;
(48) a sulfinamoyl group;
(49) a sulfenamoyl group;
(50) a thiocarbamoyl group;
25 (51) an optionally substituted carbamoyl group [e.g., an optionally substituted alkyl-carbamoyl and the like];
(52) an optionally substituted amino group
[e.g.,
amino,
30 an optionally substituted mono- or di-alkylamino group,
an optionally substituted mono- or di-C₃₋₇ cycloalkylamino group,
an optionally substituted mono- or di-C₆₋₁₄ arylamino group,
an optionally substituted mono- or di-C₇₋₁₆ aralkylamino group,
an optionally substituted heterocyclyl-amino group,
35 an optionally substituted C₆₋₁₄ aryl-carbonylamino group,

a formylamino group,
 an optionally substituted alkyl-carbonylamino group (e.g., a
 mono-(C₁₋₆ alkyl-carbonyl)-amino group),
 an optionally substituted C₃₋₇ cycloalkyl-carbonylamino group,
 5 an optionally substituted heterocyclyl-carbonylamino group,
 an optionally substituted alkoxy-carbonylamino group,
 an optionally substituted C₃₋₈ cycloalkoxy-carbonylamino group,
 an optionally substituted heterocyclyl-oxycarbonylamino group,
 an optionally substituted carbamoylamino group,
 10 an optionally substituted alkylsulfonylamino group,
 an optionally substituted C₃₋₈ cycloalkylsulfonylamino group,
 an optionally substituted heterocyclyl-sulfonylamino group,
 an optionally substituted C₆₋₁₄ arylsulfonylamino group];
 (53) an optionally substituted alkoxy-carbonyl group;
 15 (54) an optionally substituted C₆₋₁₄ aryloxy-carbonyl group;
 (55) an optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group.
 [0074]

The number of the substituents is preferably 0 (i.e., unsubstituted), or 1 or 2.

20 The number of the substituents is more preferably 0 (i.e., unsubstituted).
 [0075]

Among Substituent Group A, examples of the substituent of
 the "optionally substituted alkoxy-carbonyl group",
 25 "optionally substituted alkyl group",
 "optionally substituted alkenyl group",
 "optionally substituted alkynyl group",
 "optionally substituted alkoxy group",
 "optionally substituted alkyl-carbonyloxy group",
 30 "optionally substituted alkoxy-carbonyloxy group",
 "optionally substituted mono-alkyl-carbamoyloxy group",
 "optionally substituted di-alkyl-carbamoyloxy group",
 "optionally substituted C₁₋₆ alkylsulfonyloxy group"
 "optionally substituted halogeno C₁₋₆ alkylsulfonyloxy group",
 35 "optionally substituted alkylsulfanyl group",

"optionally substituted alkyl-carbonyl group",
 "optionally substituted alkylsulfonyl group",
 "optionally substituted alkylsulfinyl group",
 "optionally substituted alkyl-carbamoyl group",
 5 "optionally substituted mono- or di-alkylamino group",
 "optionally substituted alkyl-carbonylamino group",
 "optionally substituted mono-(C₁₋₆ alkyl-carbonyl)-amino group",
 "optionally substituted alkoxy-carbonylamino group" and
 "optionally substituted alkylsulfonylamino group" include
 10 substituents selected from the following Substituent Group B.
 The number of the substituents is 1 to the maximum
 substitutable number, more preferably 1 to 3.

[0076]

Among Substituent Group A, examples of the substituent of
 15 the "optionally substituted C₆₋₁₄ aryloxy-carbonyl group",
 "optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group",
 "optionally substituted C₃₋₇ cycloalkyl-C₂₋₆ alkynyl group",
 "optionally substituted C₃₋₇ cycloalkyl group",
 "optionally substituted C₆₋₁₄ aryl group",
 20 "optionally substituted C₇₋₁₆ aralkyl group",
 "optionally substituted C₆₋₁₄ aryl-C₂₋₆ alkenyl group",
 "optionally substituted heterocyclic group",
 "optionally substituted C₃₋₇ cycloalkyloxy group",
 "optionally substituted C₆₋₁₄ aryloxy group",
 25 "optionally substituted C₇₋₁₆ aralkyloxy group",
 "optionally substituted C₆₋₁₄ aryl-carbonyloxy group",
 "optionally substituted mono- or di-C₆₋₁₄ aryl-carbamoyloxy
 group",
 "optionally substituted heterocyclyl-oxy group",
 30 "optionally substituted aromatic heterocyclyl-oxy group",
 "optionally substituted C₃₋₇ cycloalkylsulfanyl group",
 "optionally substituted C₆₋₁₄ arylsulfanyl group",
 "optionally substituted C₇₋₁₆ aralkylsulfanyl group",
 "optionally substituted heterocyclyl-sulfanyl group",
 35 "optionally substituted C₃₋₇ cycloalkyl-carbonyl group",

"optionally substituted C₆₋₁₄ aryl-carbonyl group",
 "optionally substituted C₇₋₁₆ aralkyl-carbonyl group",
 "optionally substituted heterocyclyl-carbonyl group",
 "optionally substituted C₃₋₇ cycloalkylsulfonyl group",
 5 "optionally substituted C₆₋₁₄ arylsulfonyl group",
 "optionally substituted heterocyclyl-sulfonyl group",
 "optionally substituted C₃₋₇ cycloalkylsulfinyl group",
 "optionally substituted C₆₋₁₄ arylsulfinyl group",
 "optionally substituted heterocyclyl-sulfinyl group",
 10 "optionally substituted carbamoyl group",
 "optionally substituted amino group",
 "optionally substituted mono- or di-C₃₋₇ cycloalkylamino group",
 "optionally substituted mono- or di-C₆₋₁₄ arylamino group",
 "optionally substituted mono- or di-C₇₋₁₆ aralkylamino group",
 15 "optionally substituted heterocyclyl-amino group",
 "optionally substituted C₆₋₁₄ aryl-carbonylamino group",
 "optionally substituted C₃₋₈ cycloalkyl-carbonylamino group",
 "optionally substituted heterocyclyl-carbonylamino group",
 "optionally substituted C₃₋₈ cycloalkoxy-carbonylamino group",
 20 "optionally substituted heterocyclyl-oxycarbonylamino group",
 "optionally substituted carbamoylamino group",
 "optionally substituted C₃₋₈ cycloalkylsulfonylamino group",
 "optionally substituted heterocyclyl-sulfonylamino group" and
 "optionally substituted C₆₋₁₄ arylsulfonylamino group" include
 25 substituents selected from the following Substituent Group B
 and the following Substituent Group B'. The number of the
 substituents is 1 to the maximum substitutable number, more
 preferably 1 to 3, further more preferably 1.

[0077]

30 In the present specification, Substituent Group B
 consists of

- (a) a halogen atom;
- (b) a hydroxy group;
- (c) a nitro group;
- 35 (d) a cyano group;

(e) an optionally substituted C₆₋₁₄ aryl group (the C₆₋₁₄ aryl group is optionally substituted by 1 to 5 (preferably 1 to 3, more preferably 1) substituents selected from a halogen atom, hydroxy, cyano, amino, optionally halogenated C₁₋₆ alkyl by 1 to 3 halogen atoms, mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, mono- or di-C₇₋₁₆ aralkylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ alkylsulfanyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamoyl, thiocarbamoyl, mono- or di-C₁₋₆ alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl and the like);

(f) an optionally substituted C₆₋₁₄ aryloxy group (the C₆₋₁₄ aryloxy group is optionally substituted by 1 to 5 (preferably 1 to 3, more preferably 1) substituents selected from a halogen atom, hydroxy, cyano, amino, optionally halogenated C₁₋₆ alkyl by 1 to 3 halogen atoms, mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, mono- or di-C₇₋₁₆ aralkylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ alkylsulfanyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamoyl, thiocarbamoyl, mono- or di-C₁₋₆ alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl and the like);

(g) an optionally substituted C₇₋₁₆ aralkyloxy group (the C₇₋₁₆ aralkyloxy group is optionally substituted by 1 to 5 (preferably 1 to 3, more preferably 1) substituents selected from a halogen atom, hydroxy, cyano, amino, optionally halogenated C₁₋₆ alkyl by 1 to 3 halogen atoms, mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, mono- or di-C₇₋₁₆ aralkylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ alkylsulfanyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamoyl, thiocarbamoyl, mono- or di-C₁₋₆

alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl and the like);

(h) an optionally substituted 5- to 10-membered heterocyclic group containing 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom (e.g., furyl, pyridyl, thienyl, 1-pyrrolidinyl, 1-piperidyl, 4-piperidyl, piperazinyl, 1-morpholinyl, 4-thiomorpholinyl, 1-azepanyl, 1-azocanyl, 1-azonanyl, 3,4-dihydroisoquinolin-2-yl and the like) (the heterocyclic group is optionally substituted by 1 to 5 (preferably 1 to 3, more preferably 1) substituents selected from a halogen atom, hydroxy, cyano, amino, optionally halogenated C₁₋₆ alkyl by 1 to 3 halogen atoms, mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, mono- or di-C₇₋₁₆ aralkylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ alkylsulfanyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamoyl, thiocarbamoyl, mono- or di-C₁₋₆ alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl and the like);

(i) an optionally substituted amino group [e.g., an amino group optionally substituted by 1 or 2 substituent(s) selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₆₋₁₄ aryl, C₇₋₁₆ aralkyl, a heterocyclic group and heterocyclyl-alkyl (the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₆₋₁₄ aryl, C₇₋₁₆ aralkyl, heterocyclic group and heterocyclyl-alkyl are each optionally substituted by 1 to 5 (preferably 1 to 3, more preferably 1) substituents selected from a halogen atom, hydroxy, cyano, amino, C₁₋₆ alkyl optionally halogenated by 1 to 3 halogen atoms (which is not a substituent for alkyl and alkenyl), mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, mono- or di-C₇₋₁₆ aralkylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, C₃₋₇ cycloalkyloxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ alkylsulfanyl, C₃₋₇ cycloalkylsulfanyl, C₁₋₆ alkylsulfinyl, C₃₋₇ cycloalkylsulfinyl, C₁₋₆ alkylsulfonyl, C₃₋₇ cycloalkylsulfonyl, carbamoyl,

thiocarbamoyl, mono- or di-C₁₋₆ alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl and the like). Examples of the "heterocyclic group" and the "heterocyclyl-" of the "heterocyclyl-alkyl" include those similar to the above-mentioned "heterocyclic group"];

(j) C₃₋₇ cycloalkyl;

(k) an optionally substituted C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted by 1 to 5 (preferably 1 to 3, more preferably 1) substituents selected from a halogen atom, hydroxy, amino, mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ alkylsulfanyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamoyl, thiocarbamoyl, mono- or di-C₁₋₆ alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl, trimethylsilyl (TMS) and the like);

(l) a formyl group;

(m) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl);

(n) a C₃₋₇ cycloalkyl-carbonyl group;

(o) a C₆₋₁₄ aryl-carbonyl group;

(p) a C₇₋₁₆ aralkyl-carbonyl group;

(q) a C₁₋₆ alkoxy-carbonyl group;

(r) a C₆₋₁₄ aryloxy-carbonyl group;

(s) a C₇₋₁₆ aralkyloxy-carbonyl group;

(t) a C₁₋₆ alkylsulfanyl group;

(u) a C₁₋₆ alkylsulfinyl group;

(v) a C₁₋₆ alkylsulfonyl group;

(w) a carbamoyl group;

(x) a thiocarbamoyl group;

(y) a mono-C₁₋₆ alkyl-carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl and the like);

(z) a di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl and the like);

(aa) a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g.,

phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl and the like);

(bb) a mono- or di-(5- to 7-membered heterocyclyl containing 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom)-carbamoyl group (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl and the like); and

(cc) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetoxy and the like).
[0078]

10 In the present specification, Substituent Group B' consists of

(a) an optionally substituted C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted by 1 to 5 (preferably 1 to 3, more preferably 1) substituents selected from a halogen atom, 15 hydroxy, cyano, amino, mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, mono- or di-C₇₋₁₆ aralkylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ 20 alkylsulfanyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamoyl, thiocarbamoyl, mono- or di-C₁₋₆ alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl and the like);

(b) an optionally substituted C₂₋₆ alkenyl group (the C₂₋₆ alkenyl group is optionally substituted by 1 to 5 (preferably 1 to 3, more preferably 1) substituents selected from a 25 halogen atom, hydroxy, cyano, amino, mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, mono- or di-C₇₋₁₆ aralkylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, 30 C₁₋₆ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ alkylsulfanyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamoyl, thiocarbamoyl, mono- or di-C₁₋₆ alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl and the like); and

(c) an optionally substituted C₂₋₆ alkynyl group (the C₂₋₆ alkynyl group is optionally substituted by 1 to 5 (preferably 35

1 to 3, more preferably 1) substituents selected from a halogen atom, hydroxy, cyano, amino, mono- or di-C₁₋₆ alkylamino, mono- or di-C₆₋₁₄ arylamino, mono- or di-C₇₋₁₆ aralkylamino, C₃₋₇ cycloalkyl, C₁₋₆ alkoxy, formyl, C₁₋₆ alkyl-carbonyl, C₃₋₇ cycloalkyl-carbonyl, C₆₋₁₄ aryl-carbonyl, C₇₋₁₆ aralkyl-carbonyl, C₁₋₆ alkoxy-carbonyl, C₆₋₁₄ aryloxy-carbonyl, C₇₋₁₆ aralkyloxy-carbonyl, C₁₋₆ alkylsulfanyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamoyl, thiocarbamoyl, mono- or di-C₁₋₆ alkyl-carbamoyl, mono- or di-C₆₋₁₄ aryl-carbamoyl and the like).

10 [0079]

Each symbol in formula (I) is explained in the following.

[0080]

Ring A is an optionally substituted 6-membered ring.

Any one or two of Z¹ to Z⁴, which are ring A-constituting
 15 atoms, is(are) -N=, and the others are -CH=. That is, the "6-membered ring" of the "optionally substituted 6-membered ring" for ring A is a pyridine ring, a pyridazine ring, a pyrimidine ring or a pyrazine ring, preferably a pyridine ring or a pyrimidine ring.

20 Preferably, Z¹ or Z² is -N= and the others are -CH=; or Z¹ and Z³ are -N= and the others are -CH=.

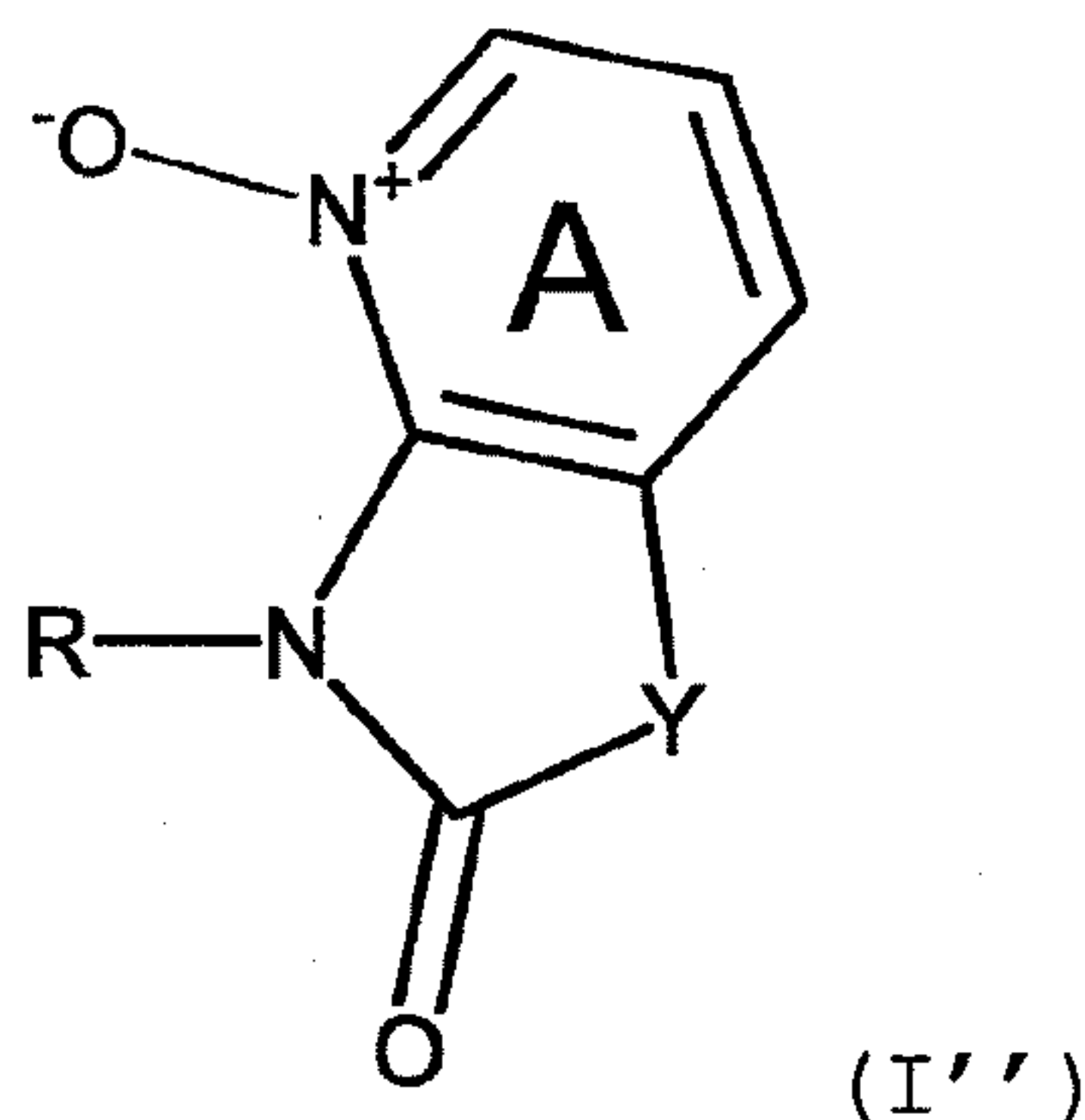
More preferably, Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=; or Z¹ and Z³ are -N= and the others (i.e., Z² and Z⁴) are -CH=.

25 Particularly preferably, Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=.

[0081]

The nitrogen atom of -N= for Z¹ to Z⁴ may be oxidized.

For example, when Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴)
 30 are each -CH=, a compound represented by the formula:



wherein each symbol is as defined above, is also encompassed in the compound represented by the formula (I). Particularly, when Z^1 is $-N=$, the nitrogen atom of $-N=$ for Z^1 is preferably
 5 oxidized.

[0082]

Examples of the substituent of the "optionally substituted 6-membered ring" for ring A include substituents selected from the above-mentioned Substituent Group A.

10 Among them, a halogen atom, cyano, an optionally substituted alkyl group, an optionally substituted alkoxy group and the like are preferable,
 a halogen atom, cyano, an optionally substituted C_{1-6} alkyl group and an optionally substituted C_{1-6} alkoxy group are more
 15 preferable,
 a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, a C_{1-6} alkyl group (preferably methyl) optionally substituted by 1 to 3 substituents selected from the group consisting of (1) a halogen atom (preferably a fluorine atom),
 20 (2) hydroxy and (3) a C_{1-6} alkyl-carboxyloxy group (preferably acetoxy), and a C_{1-6} alkoxy group (preferably methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom) are further more preferable, and
 a halogen atom (preferably a chlorine atom, a fluorine atom),
 25 cyano, methyl, hydroxymethyl, acetoxymethyl, trifluoromethyl, methoxy, difluoromethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy are particularly preferable.

The number of the substituents of the "optionally

substituted 6-membered ring" for ring A is 0 (i.e., unsubstituted), or 1 to 3, preferably 0, or 1 to 2, more preferably 0 or 1. When the number of the substituents is not less than 2, the respective substituents may be the same or
5 different.

[0083]

Ring A is preferably a pyridine ring or a pyrimidine ring, each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom, cyano, an optionally substituted
10 alkyl group and an optionally substituted alkoxy group [preferably a halogen atom, cyano, an optionally substituted C₁₋₆ alkyl group and an optionally substituted C₁₋₆ alkoxy group, more preferably a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, a C₁₋₆ alkyl group (preferably methyl)
15 optionally substituted by 1 to 3 substituents selected from the group consisting of (1) a halogen atom (preferably a fluorine atom), (2) hydroxy, and (3) a C₁₋₆ alkyl-carbonyloxy group (preferably acetoxy), and a C₁₋₆ alkoxy group (preferably methoxy, ethoxy) optionally substituted by 1 to 3 halogen
20 atoms (preferably a fluorine atom), further more preferably a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, methyl, trifluoromethyl, hydroxymethyl, acetoxymethyl, methoxy, difluoromethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy, further more preferably a fluorine atom,
25 methyl, hydroxymethyl and methoxy].

[0084]

In another embodiment, ring A is preferably
(1) a pyridine ring which is optionally substituted by one substituent selected from (i) a C₁₋₆ alkyl group optionally
30 substituted by 1 to 3 substituents selected from a halogen atom, hydroxy and a C₁₋₆ alkyl-carbonyloxy group (preferably methyl, trifluoromethyl, acetoxymethyl, hydroxymethyl), (ii) a halogen atom (preferably chlorine, fluorine), (iii) cyano, and (iv) a C₁₋₄ alkoxy group optionally substituted by 1 to 3
35 halogen atoms (preferably methoxy, difluoromethoxy,

difluoroethoxy, trifluoroethoxy)

[preferably a pyridine ring which is optionally substituted by
(1) a pyridine ring which is optionally substituted by one
substituent selected from (i) a C₁₋₆ alkyl group optionally
5 substituted by 1 to 3 substituents selected from a halogen
atom and hydroxy (preferably methyl, trifluoromethyl,
hydroxymethyl), (ii) a halogen atom (preferably chlorine,
fluorine), (iii) cyano, and (iv) a C₁₋₄ alkoxy optionally
substituted by 1 to 3 halogen atoms (preferably methoxy,
10 difluoromethoxy, difluoroethoxy, trifluoroethoxy)], or
(2) a pyrimidine ring.

[0085]

Y is an oxygen atom, a sulfur atom, an optionally
substituted methylene group or -NR^C-.

15 [0086]

Examples of the substituent of the "optionally
substituted methylene group" for Y include substituents
selected from the above-mentioned Substituent Group A.

Among them, an optionally substituted alkyl group and the
20 like are preferable.

The number of the substituents of the "optionally
substituted methylene group" for Y is 0 (i.e., unsubstituted),
1 or 2. When the number of the substituents is 2, the
respective substituents may be the same or different.

25 The "alkyl group" of the "optionally substituted alkyl
group" exemplified as the substituent of the "optionally
substituted methylene group" for Y is preferably a C₁₋₆ alkyl
group (preferably methyl) or the like.

As the substituent of the "optionally substituted alkyl
30 group" exemplified as the substituent of the "optionally
substituted methylene group" for Y, a halogen atom, a hydroxy
group, a C₃₋₇ cycloalkyl group, an optionally substituted C₁₋₆
alkoxy group (e.g., a trimethylsilyl-C₁₋₆ alkoxy group), a C₁₋₆
alkoxy-carbonyl group and the like are preferable.

35 The number of the substituents of the "optionally

substituted alkyl group" exemplified as the substituent of the "optionally substituted methylene group" for Y is preferably 0 (i.e., unsubstituted), or 1 to 5, particularly preferably 0 (i.e., unsubstituted). When the number of the substituents is not less than 2, the respective substituents may be the same or different.

When the number of the substituents of the "optionally substituted methylene group" for Y is 2, these two substituents optionally form, together with the adjacent carbon atom, an optionally substituted C₃₋₆ cycloalkane (preferably cyclobutane).

As the substituent of the "optionally substituted C₃₋₆ cycloalkane", a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, an optionally substituted C₁₋₆ alkoxy group (e.g., a trimethylsilyl-C₁₋₆ alkoxy group), a C₁₋₆ alkoxy-carbonyl group and the like are preferable.

The number of the substituents of the "optionally substituted C₃₋₆ cycloalkane" is preferably 0 (i.e., unsubstituted), or 1 to 5, particularly preferably 0 (i.e., unsubstituted). When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0087]

R^c is a hydrogen atom or a substituent.

[0088]

Examples of the substituent for R^c include substituents selected from the above-mentioned Substituent Group A.

Among them, an optionally substituted alkyl group, an optionally substituted C₃₋₇ cycloalkyl group and the like are preferable.

The "alkyl group" of the "optionally substituted alkyl group" exemplified as the substituent for R^c is preferably a C₁₋₆ alkyl group (preferably methyl, ethyl, propyl, isopropyl, isobutyl) or the like.

As the substituent of the "optionally substituted alkyl

group" exemplified as the substituent for R^c , a halogen atom (preferably a fluorine atom), a hydroxy group, a C_{3-7} cycloalkyl group (preferably cyclopropyl), an optionally substituted C_{1-6} alkoxy group (e.g., methoxy, ethoxy, a trimethylsilyl- C_{1-6} alkoxy group (preferably trimethylsilyl-ethoxy)), a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl) and the like are preferable.

The number of the substituents of the "optionally substituted alkyl group" exemplified as the substituent for R^c is preferably 0 (i.e., unsubstituted), or 1 to 5, more preferably 0 (i.e., unsubstituted), or 1 to 3. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

The "optionally substituted C_{3-7} cycloalkyl group" exemplified as the substituent for R^c is preferably cyclopropyl or the like.

As the substituent of the "optionally substituted C_{3-7} cycloalkyl group" exemplified as the substituent for R^c , a halogen atom, a hydroxy group, a C_{3-7} cycloalkyl group, an optionally substituted C_{1-6} alkoxy group (e.g., methoxy, ethoxy, a trimethylsilyl- C_{1-6} alkoxy group), a C_{1-6} alkoxy-carbonyl group and the like are preferable.

The number of the substituents of the "optionally substituted C_{3-7} cycloalkyl group" is preferably 0 (i.e., unsubstituted), or 1 to 5, particularly preferably 0 (i.e., unsubstituted). When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0089]

Y is preferably an oxygen atom, an optionally substituted methylene group, or $-NR^c-$ wherein R^c is preferably a hydrogen atom, an optionally substituted alkyl group or an optionally substituted C_{3-7} cycloalkyl group, more preferably an oxygen atom, a methylene group optionally substituted by 1 or 2 C_{1-6} alkyl group(s) (preferably methyl)

(the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane (preferably cyclobutane)), or -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group (preferably methyl, ethyl, propyl, isopropyl, isobutyl) optionally substituted by 1 to 3 (preferably 1 or 2) substituents selected from the group consisting of a halogen atom (preferably a fluorine atom), a hydroxy group, a C₃₋₇ cycloalkyl group (preferably cyclopropyl), an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, a trimethylsilyl-C₁₋₆ alkoxy group (preferably trimethylsilyl-ethoxy)) and a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl), or (iii) a C₃₋₇ cycloalkyl group (preferably cyclopropyl), particularly preferably -NR^c- wherein R^c is preferably a C₁₋₆ alkyl group (preferably methyl, ethyl, propyl, isopropyl, isobutyl), a diC₁₋₆ alkylmethylene group (preferably dimethylmethylene group) or the like, more preferably -NR^c- wherein R^c is preferably a C₁₋₆ alkyl group (preferably methyl, ethyl, isopropyl).

In another embodiment, Y is preferably -NR^c- wherein R^c is preferably an optionally substituted C₁₋₆ alkyl group, more preferably a C₁₋₆ alkyl group (preferably methyl, ethyl, propyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom (preferably a fluorine atom), a hydroxy group, a C₃₋₇ cycloalkyl group (preferably cyclopropyl), an optionally substituted C₁₋₆ alkoxy group (e.g., a trimethylsilyl-C₁₋₆ alkoxy group (preferably trimethylsilyl-ethoxy)) and a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl).

[0090]

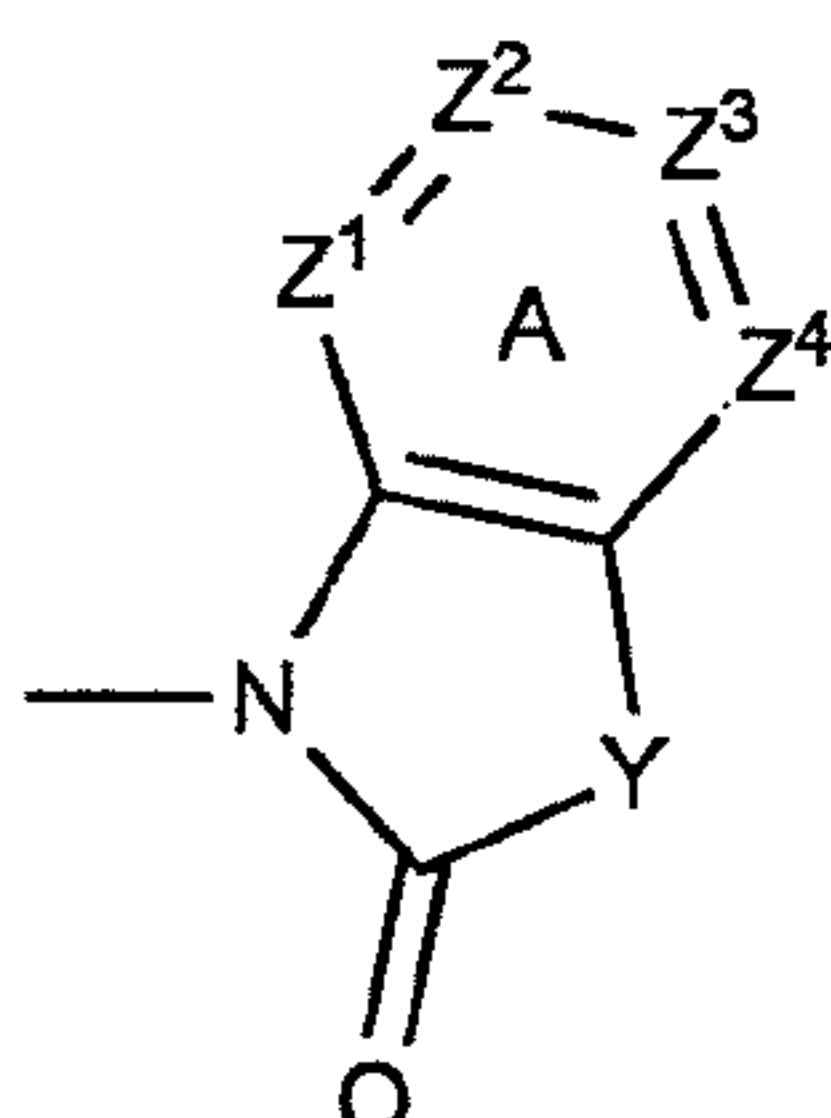
In another embodiment, Y is preferably -NR^c- wherein R^c is preferably an optionally substituted C₁₋₆ alkyl group, more preferably an optionally substituted C₁₋₄ alkyl group (preferably methyl, ethyl, propyl, isopropyl, isobutyl).

[0091]

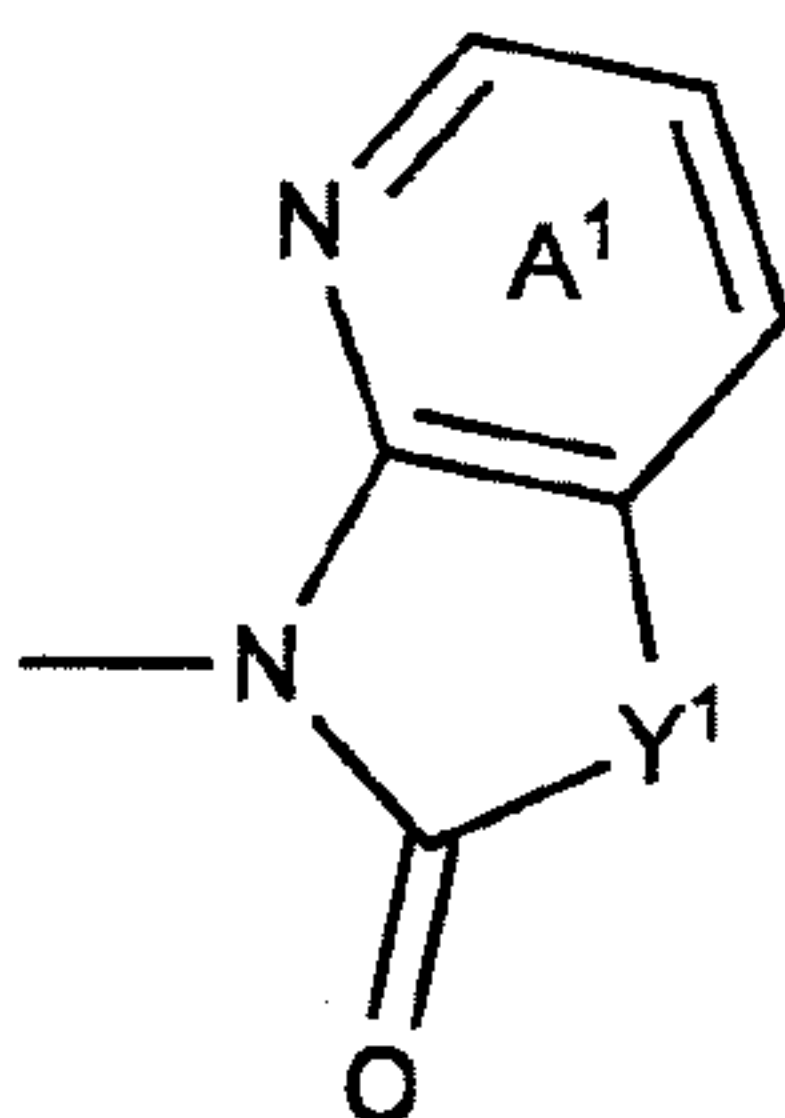
In another embodiment, Y is preferably a methylene group which is optionally substituted by 1 to 2 C₁₋₆ alkyl group(s) (preferably methyl), or -NR^c- wherein R^c is (1) a hydrogen atom, (2) a C₁₋₆ alkyl which is optionally substituted by 1 to 3 substituents selected from the group consisting of hydroxy and a halogen atom (preferably methyl, ethyl, propyl, isopropyl, hydroxymethyl, difluoromethyl), or (3) a C₃₋₇ cycloalkyl (preferably cyclopropyl).

[0092]

10 The partial structure of the formula (I):

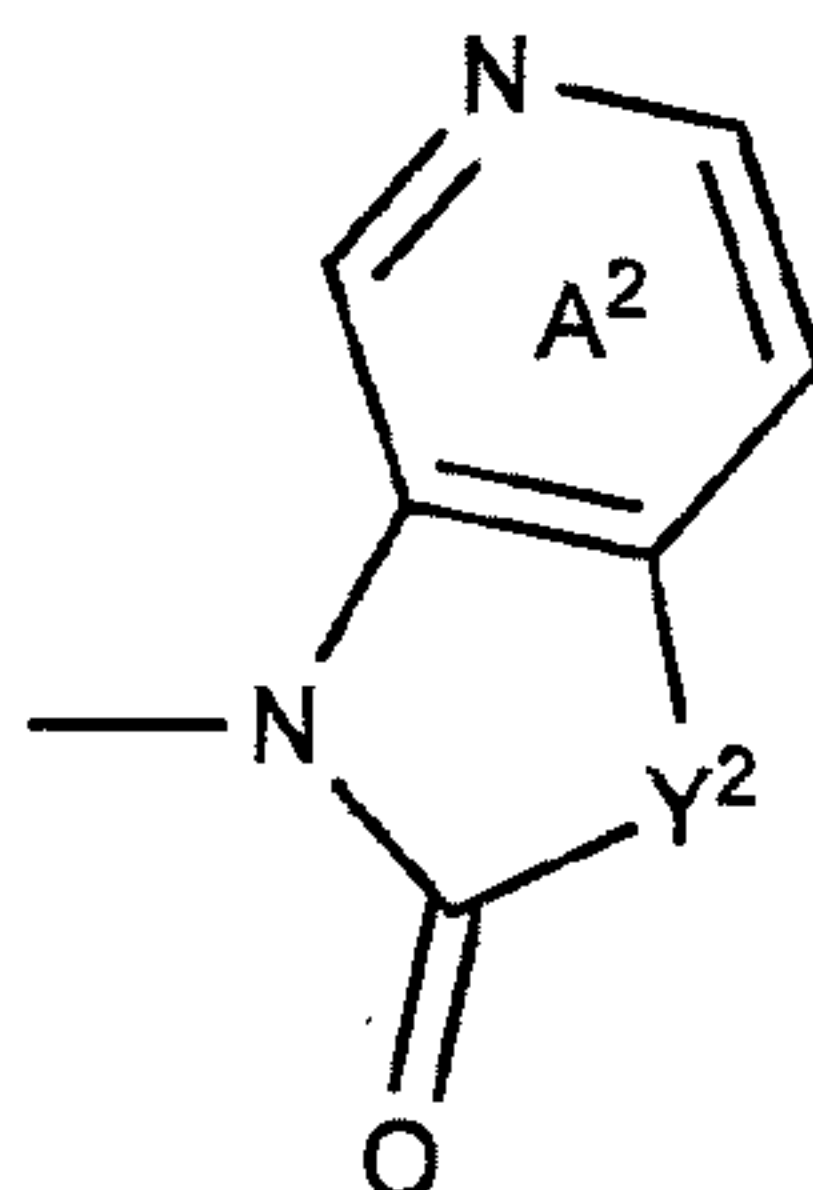


is preferably, for example, a group represented by the formula:



15 wherein

Y¹ is an optionally substituted methylene group, or -NR^c- wherein R^c is a hydrogen atom or a substituent, and ring A¹ is an optionally substituted pyridine ring, or a group represented by the formula:



20

wherein

Y^2 is $-NR^d-$ wherein R^d is a substituent, and

ring A^2 is an optionally substituted pyridine ring.

[0093]

5 Examples of the "optionally substituted methylene group" for Y^1 include those similar to the "optionally substituted methylene group" for Y .

[0094]

10 Examples of the "substituent" of the "optionally substituted pyridine ring" for ring A^1 include those similar to the "substituent" of the "optionally substituted 6-membered ring" for ring A .

[0095]

15 Examples of the "substituent" for R^d include those similar to the "substituent" for R^c .

Among them, an optionally substituted alkyl group and the like are preferably.

20 The "alkyl group" of the "optionally substituted alkyl group" exemplified as the substituent for R^d is preferably a C_{1-6} alkyl group (preferably a C_{1-4} alkyl group, more preferably methyl, ethyl, propyl, isopropyl, isobutyl) or the like.

As the substituent of the "optionally substituted alkyl group" exemplified as the substituent for R^d , a halogen atom (preferably a fluorine atom), a hydroxy group, a C_{3-7} cycloalkyl group (preferably cyclopropyl), an optionally substituted C_{1-6} alkoxy group (e.g., a trimethylsilyl- C_{1-6} alkoxy group (preferably trimethylsilyl-ethoxy)), a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl) and the like are preferable, and a halogen atom (preferably a fluorine atom), a hydroxy group, an optionally substituted C_{1-6} alkoxy group (e.g., methoxy, ethoxy, a trimethylsilyl- C_{1-6} alkoxy group (preferably trimethylsilyl-ethoxy)), a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl) and the like are more preferable.

35 The number of the substituents of the "optionally substituted alkyl group" exemplified as the substituent for R^d

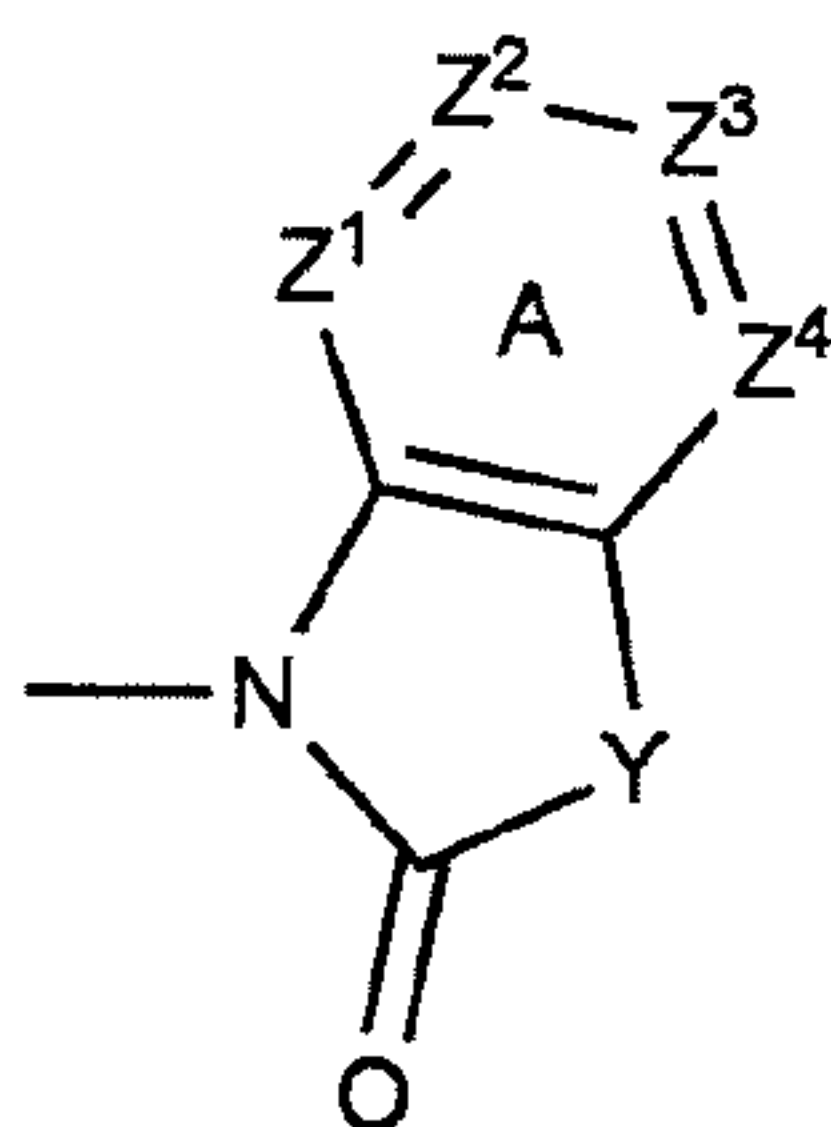
is preferably 0 (i.e., unsubstituted), or 1 to 5, more preferably 0 (i.e., unsubstituted), or 1 to 3. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

5 [0096]

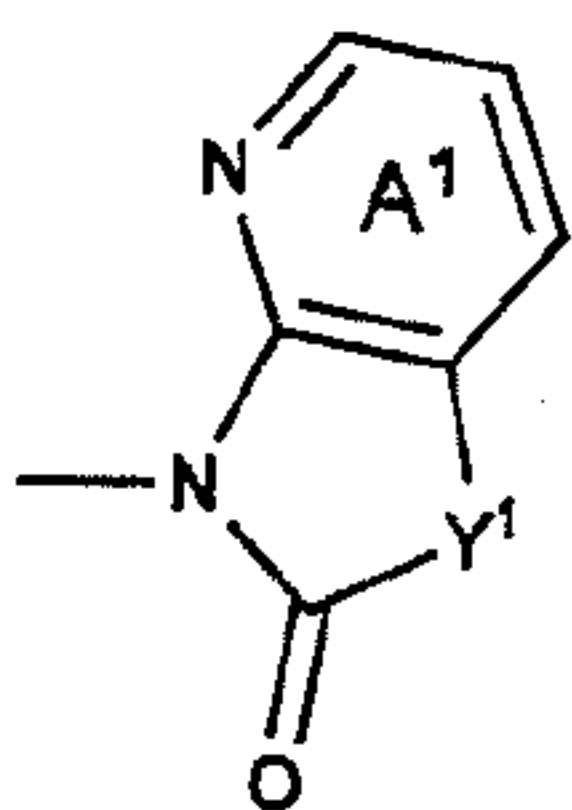
Examples of the "substituent" of the "optionally substituted pyridine ring" for ring A² include those similar to the "substituent" of the "optionally substituted 6-membered ring" for ring A.

10 [0097]

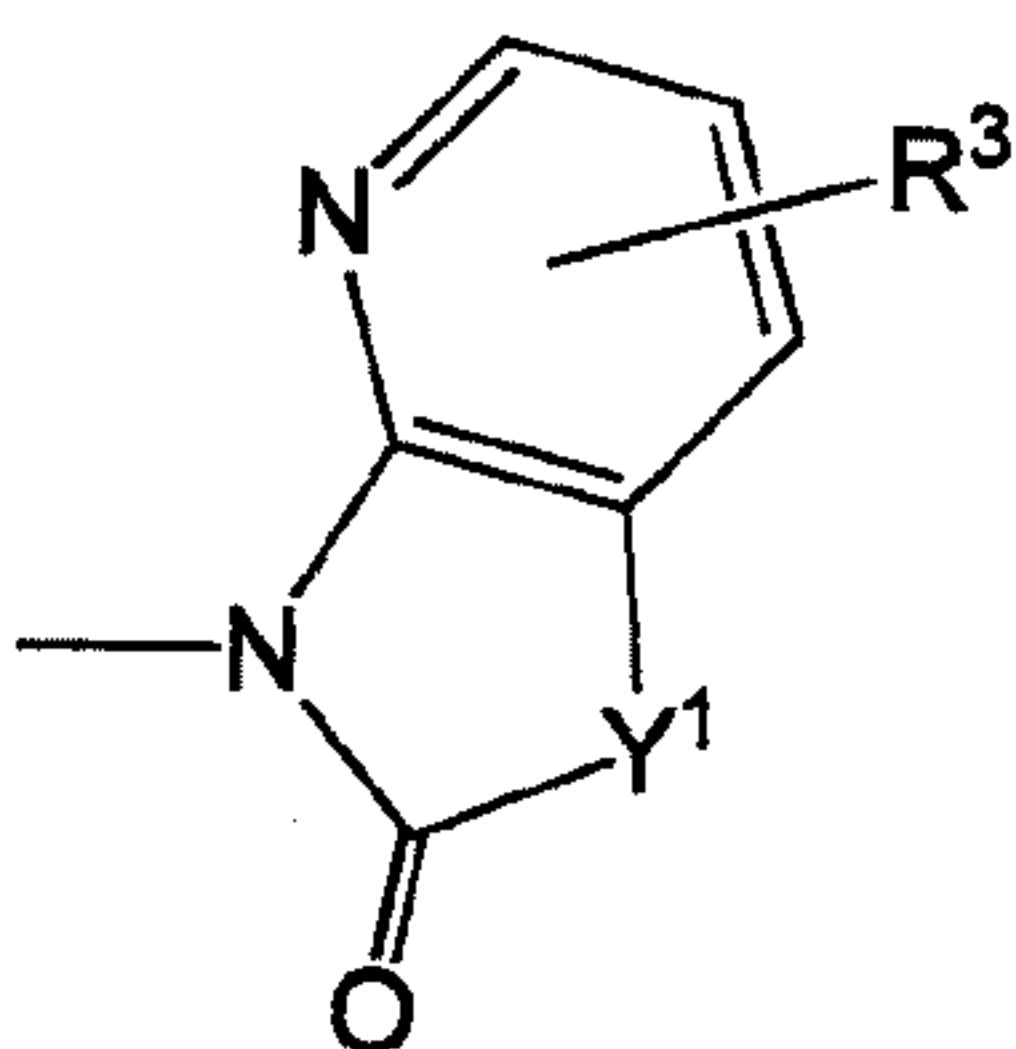
The partial structure of the formula (I):



is more preferably a group represented by the formula:



15 wherein each symbol is as defined above, further more preferably a group represented by the formula:



wherein

R³ is a hydrogen atom, a halogen atom, cyano, an optionally substituted C₁₋₆ alkyl group or an optionally substituted C₁₋₆ alkoxy group, and
 20 Y¹ is as defined above.

[0098]

The "optionally substituted C₁₋₆ alkyl group" for R³ is preferably an optionally substituted C₁₋₄ alkyl group, more preferably a C₁₋₄ alkyl group (preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom).

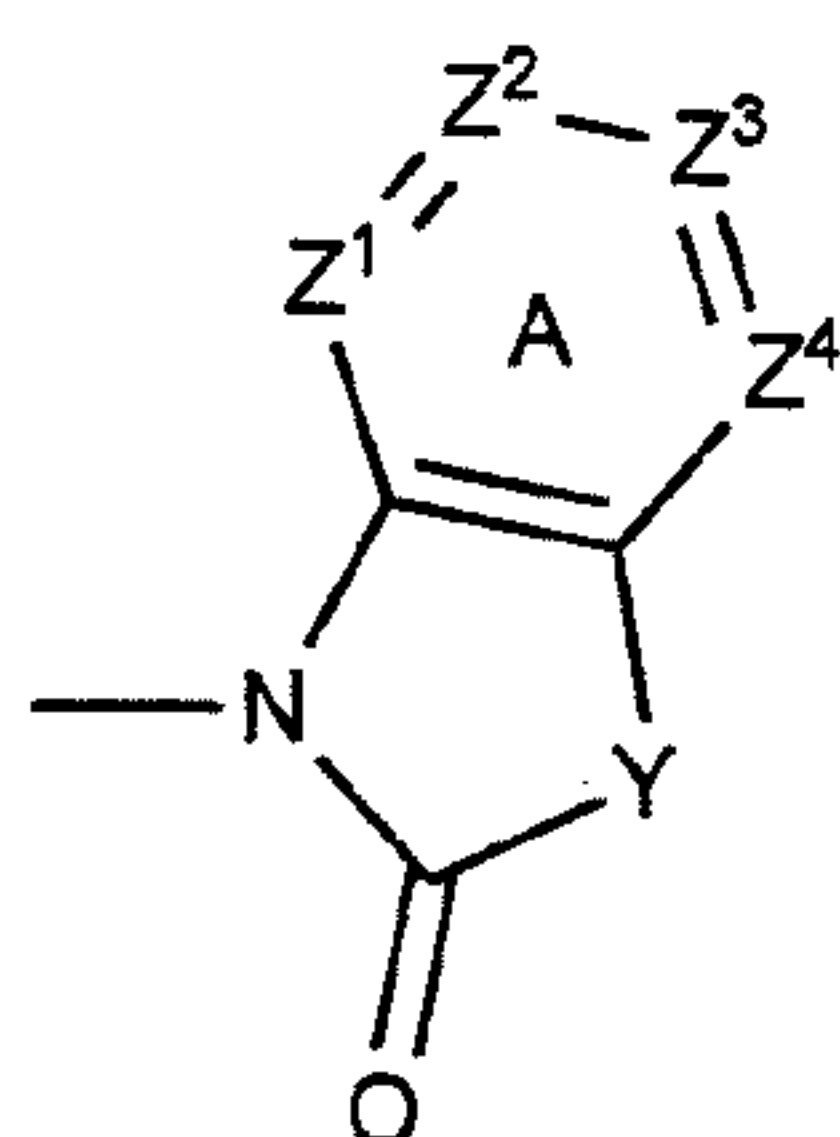
The "optionally substituted C₁₋₆ alkoxy group" for R³ is preferably an optionally substituted C₁₋₄ alkoxy group, more preferably a C₁₋₄ alkoxy group (preferably methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom).

R³ is preferably a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, C₁₋₆ alkyl (preferably C₁₋₄ alkyl, more preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom), or C₁₋₆ alkoxy (preferably C₁₋₄ alkoxy, more preferably methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom), particularly preferably a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, trifluoromethyl, difluoromethoxy, 2,2-difluoroethoxy or 2,2,2-trifluoroethoxy.

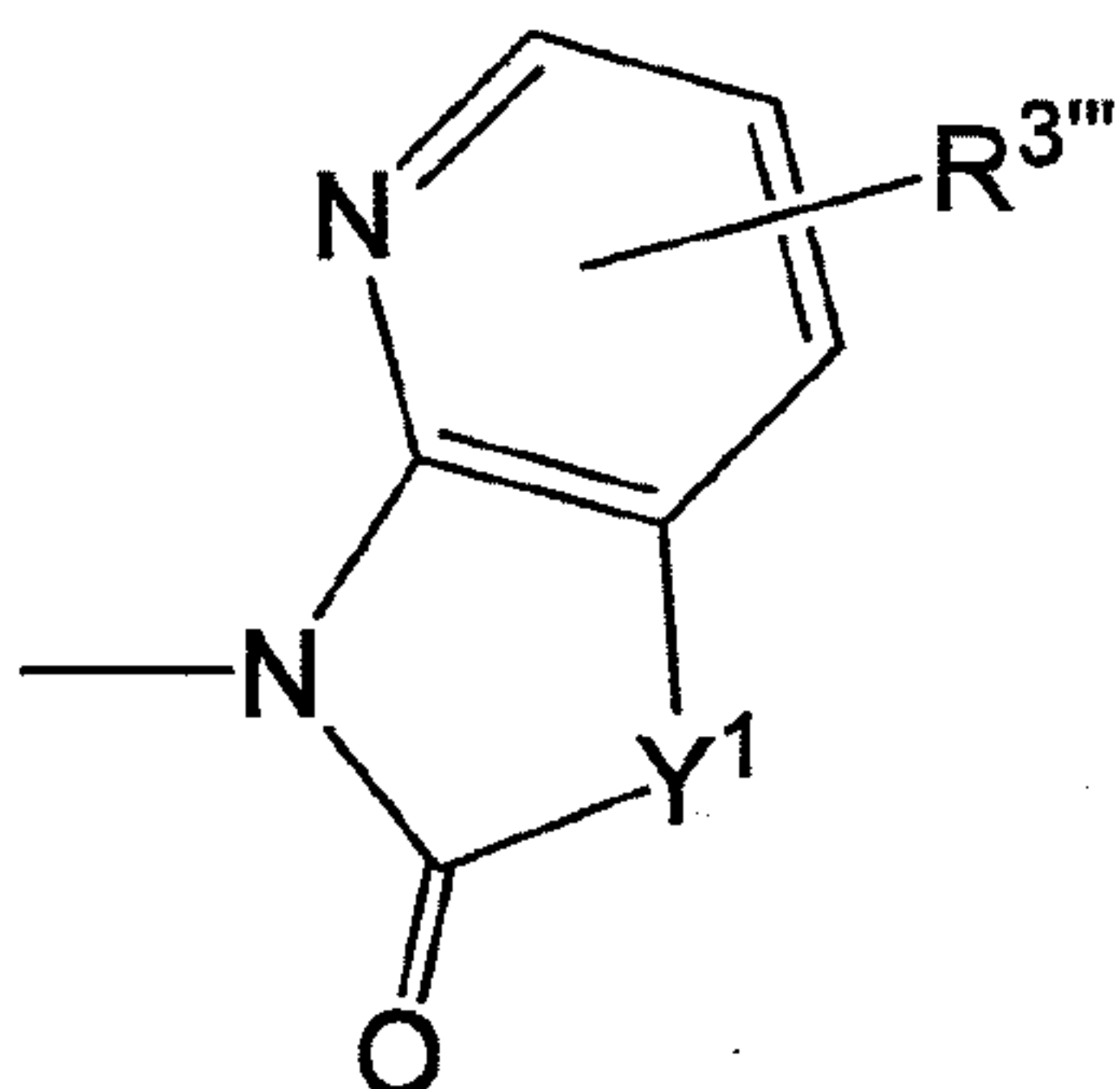
In another embodiment, R³ is preferably a hydrogen atom, a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, an optionally substituted C₁₋₄ alkyl group or an optionally substituted C₁₋₄ alkoxy group, more preferably a hydrogen atom, a halogen atom (preferably a chlorine atom, a fluorine atom), an optionally substituted C₁₋₄ alkyl group or an optionally substituted C₁₋₄ alkoxy group.

[0099]

The partial structure of the formula (I):



is particularly preferably a group represented by the formula:

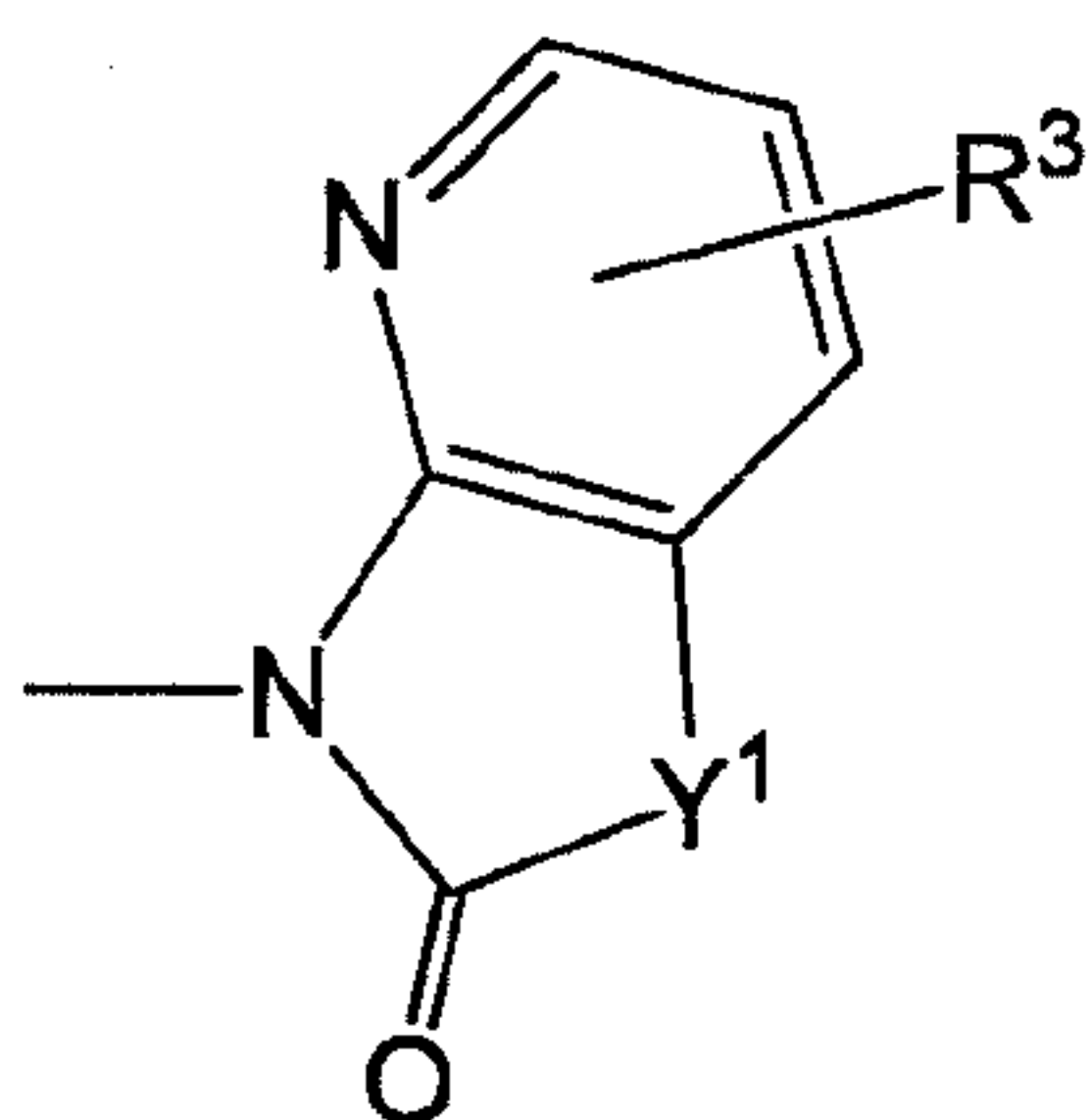


wherein

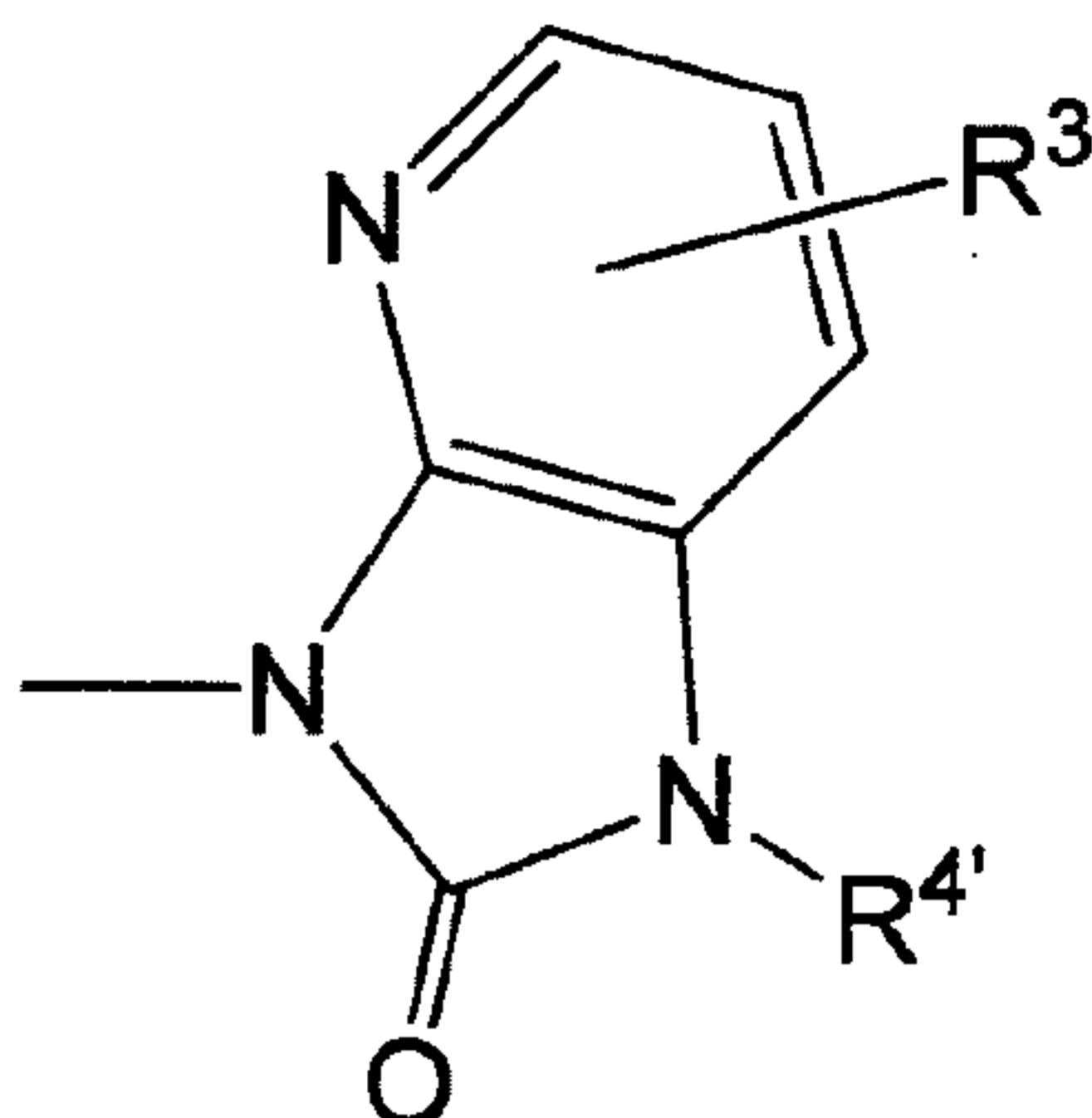
R³''' is a hydrogen atom, a halogen atom, an optionally substituted C₁₋₆ alkyl group (preferably an optionally substituted C₁₋₄ alkyl group) or an optionally substituted C₁₋₆ alkoxy group (preferably an optionally substituted C₁₋₄ alkoxy group), and Y¹ is as defined above.

10 [0100]

In another embodiment, the group represented by the formula:



is preferably



15

wherein

R⁴' is an optionally substituted C₁₋₆ alkyl group, and R³ is as defined above.

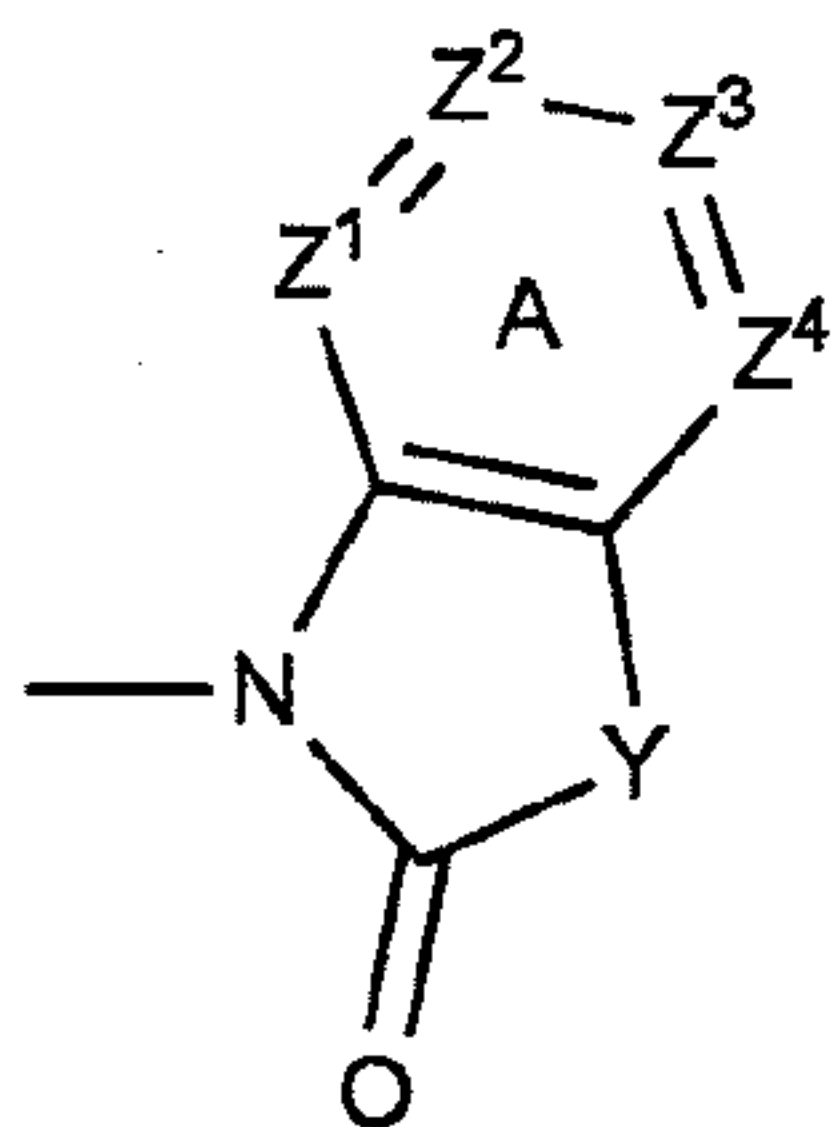
[0101]

The "optionally substituted C₁₋₆ alkyl group" for R^{4'} is preferably an optionally substituted C₁₋₄ alkyl group, more preferably a C₁₋₄ alkyl group (preferably methyl, ethyl, propyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom (preferably a fluorine atom), a hydroxy group, a C₃₋₇ cycloalkyl group (preferably cyclopropyl), an optionally substituted C₁₋₆ alkoxy group (preferably C₁₋₄ alkoxy) (e.g., methoxy, ethoxy, a trimethylsilyl-C₁₋₆ alkoxy group (preferably trimethylsilyl-ethoxy)), and a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl).

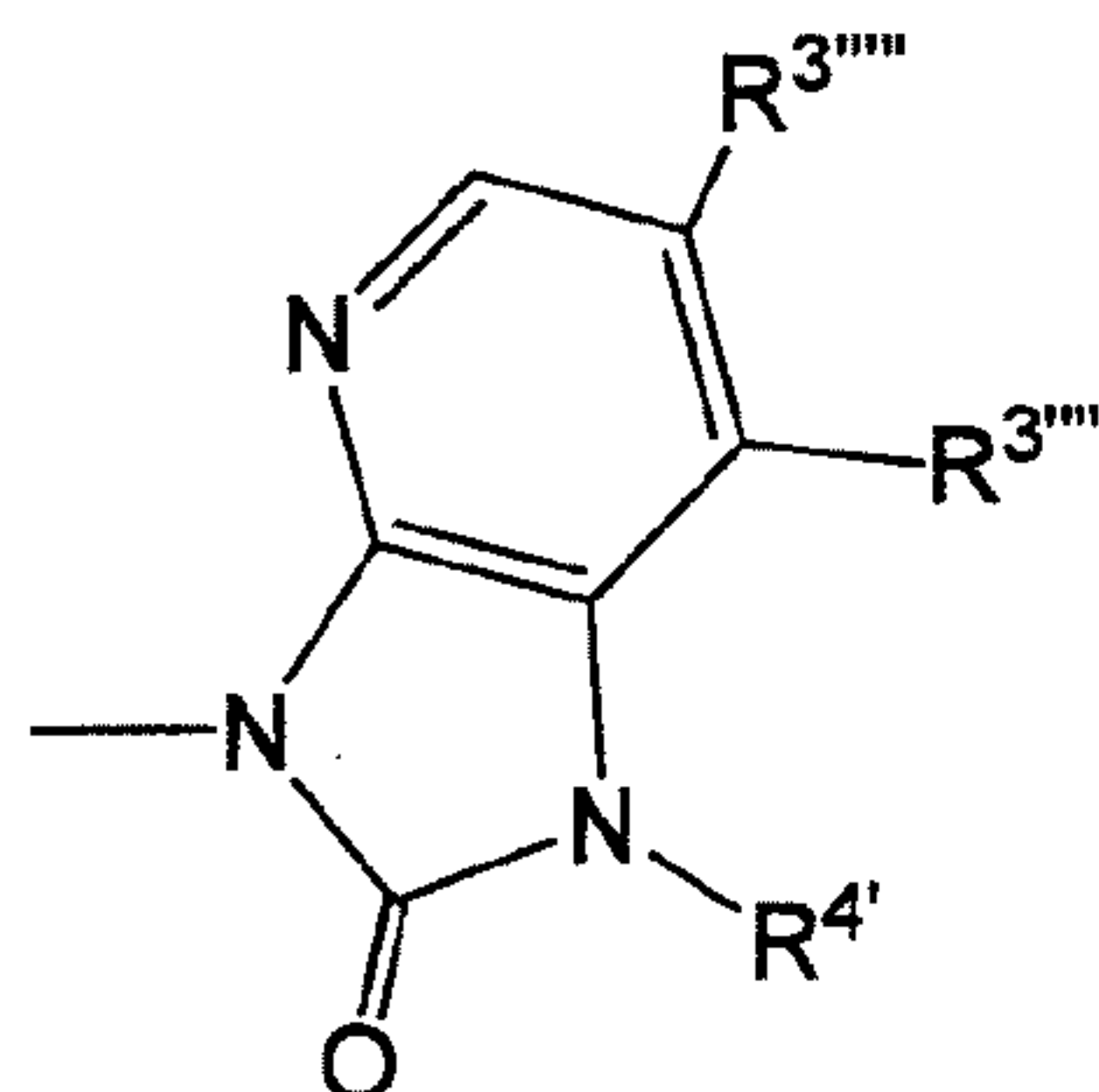
R^{4'} is preferably an optionally substituted C₁₋₆ alkyl group, more preferably an optionally substituted C₁₋₄ alkyl group.

[0102]

In another embodiment, the partial structure of the formula (I):



is preferably a group represented by the formula:



wherein

R^{3''''} and R^{3'''''} represent the same or different a hydrogen atom, a halogen atom, cyano, an optionally substituted C₁₋₆ alkyl group or an optionally substituted C₁₋₆

alkoxy group, and

R^{4'} is as defined above.

[0103]

The "optionally substituted C₁₋₆ alkyl group" for R^{3''''} or R^{3'''''} is preferably an optionally substituted C₁₋₄ alkyl group, more preferably a C₁₋₄ alkyl group (preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom).

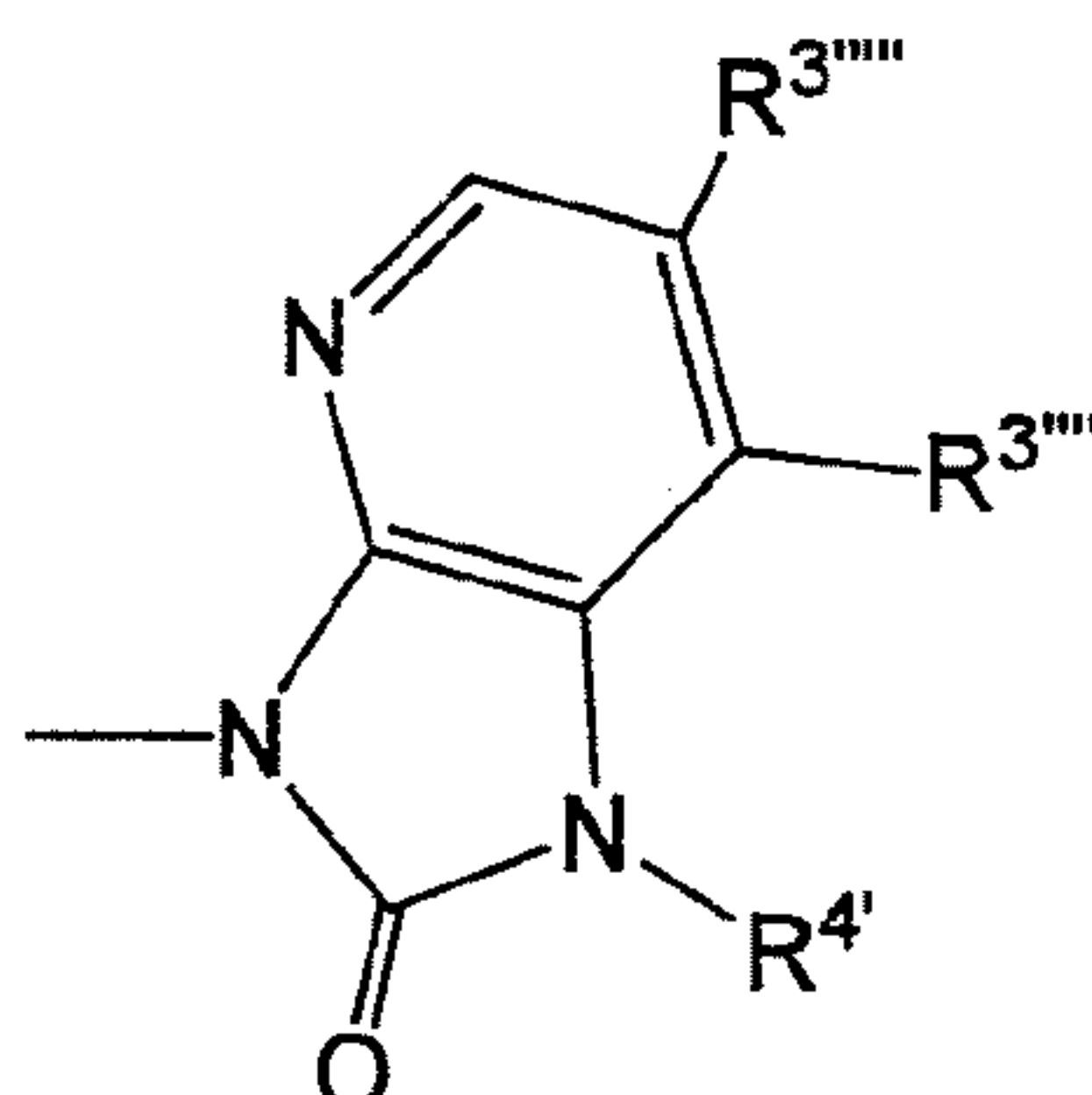
The "optionally substituted C₁₋₆ alkoxy group" for R^{3''''} or R^{3'''''} is preferably an optionally substituted C₁₋₄ alkoxy group, more preferably a C₁₋₄ alkoxy group (preferably methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom).

R^{3''''} is preferably a hydrogen atom, a halogen atom, an optionally substituted C₁₋₆ alkyl group or an optionally substituted C₁₋₆ alkoxy group, more preferably a hydrogen atom or an optionally substituted C₁₋₆ alkyl group, further more preferably a hydrogen atom or an optionally substituted C₁₋₄ alkyl group (preferably methyl, hydroxymethyl).

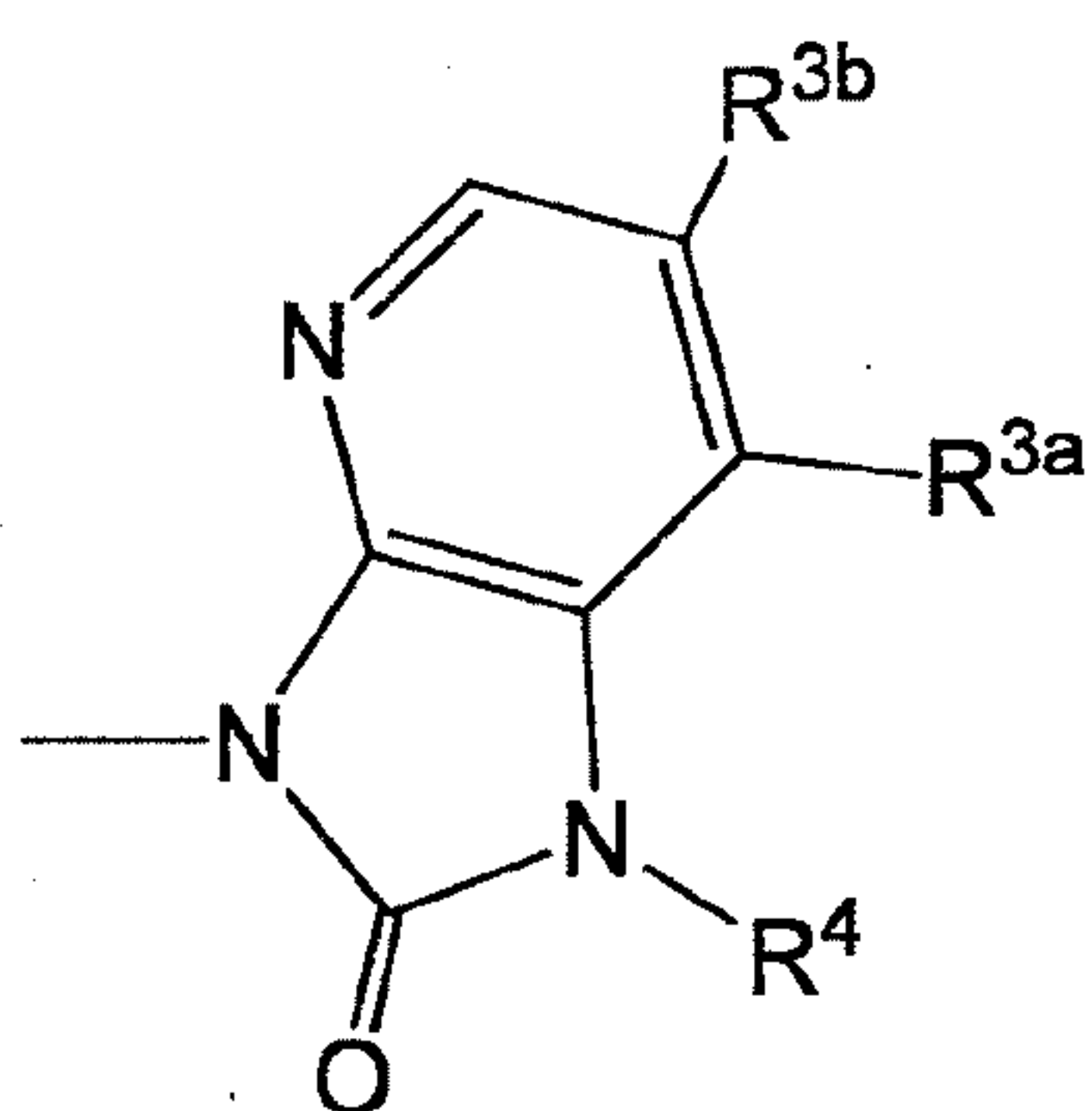
R^{3'''''} is preferably a hydrogen atom, a halogen atom, cyano, an optionally substituted C₁₋₆ alkyl group or an optionally substituted C₁₋₆ alkoxy group, more preferably a hydrogen atom, a halogen atom, cyano, an optionally substituted C₁₋₄ alkyl group or an optionally substituted C₁₋₄ alkoxy group.

[0104]

The group represented by the formula:



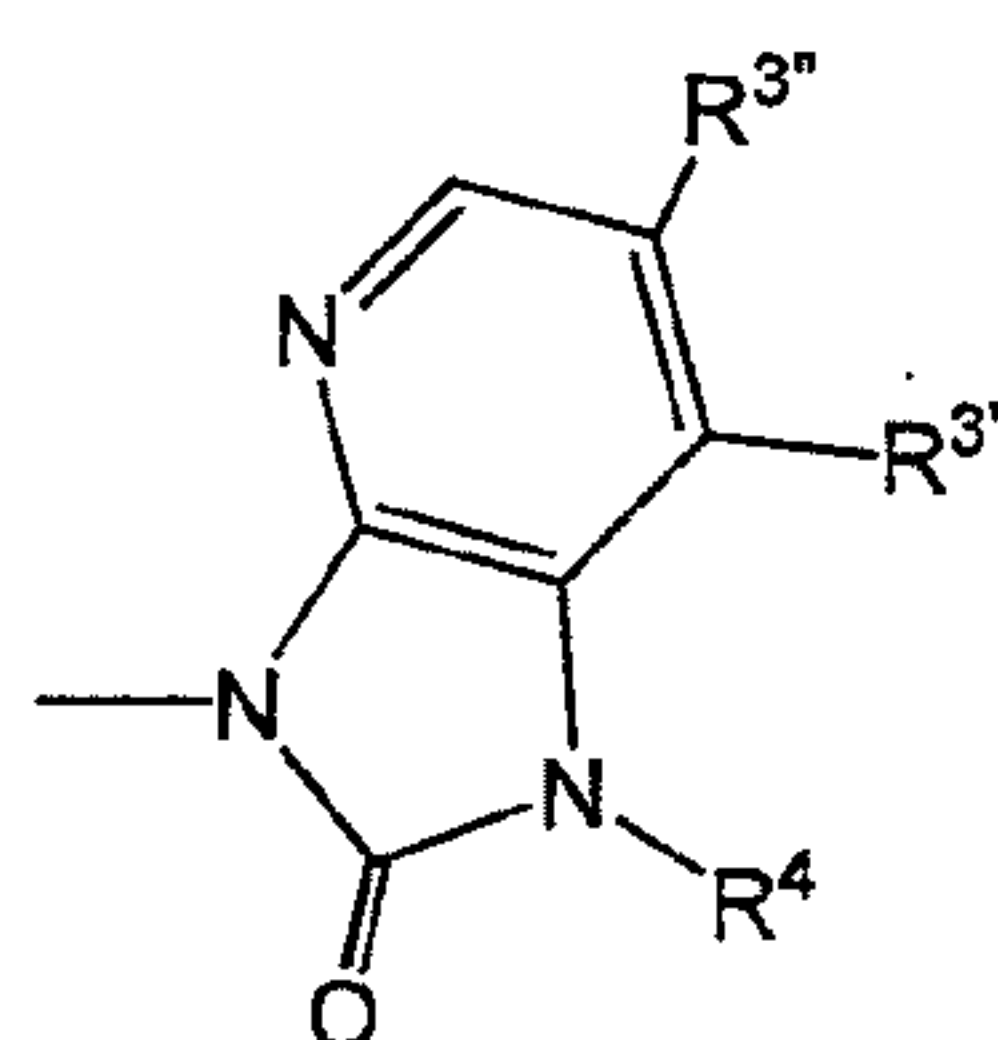
is preferably a group represented by the formula:



wherein

R^{3a} and R^{3b} represent the same or different a hydrogen atom, a halogen atom, cyano, an optionally substituted C_{1-4} alkyl group or an optionally substituted C_{1-4} alkoxy group, and R^4 represents an optionally substituted C_{1-4} alkyl group, provided that when one of R^{3a} and R^{3b} is a hydrogen atom, the other is not a hydrogen atom, and

more preferably a group represented by the formula:



wherein

$R^{3'}$ represents a hydrogen atom, or an optionally substituted C_{1-4} alkyl group (preferably, methyl, hydroxymethyl), $R^{3''}$ represents a hydrogen atom, a halogen atom, cyano, an optionally substituted C_{1-4} alkyl group or an optionally substituted C_{1-4} alkoxy group, and R^4 represents an optionally substituted C_{1-4} alkyl group, provided that when one of $R^{3'}$ and $R^{3''}$ is a hydrogen atom, the other is not a hydrogen atom.

[0105]

$R^{3''}$ is preferably a hydrogen atom, a halogen atom, an optionally substituted C_{1-4} alkyl group (preferably, methyl) or an optionally substituted C_{1-4} alkoxy group (preferably,

WO 2011/163355

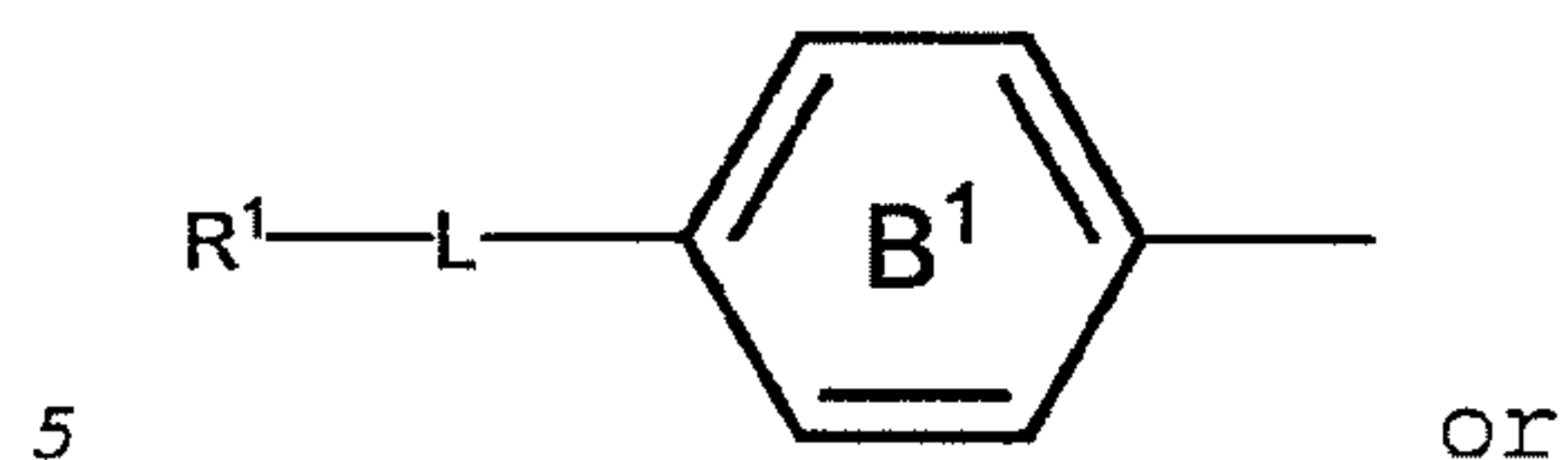
PCT/US2011/041443

methoxy).

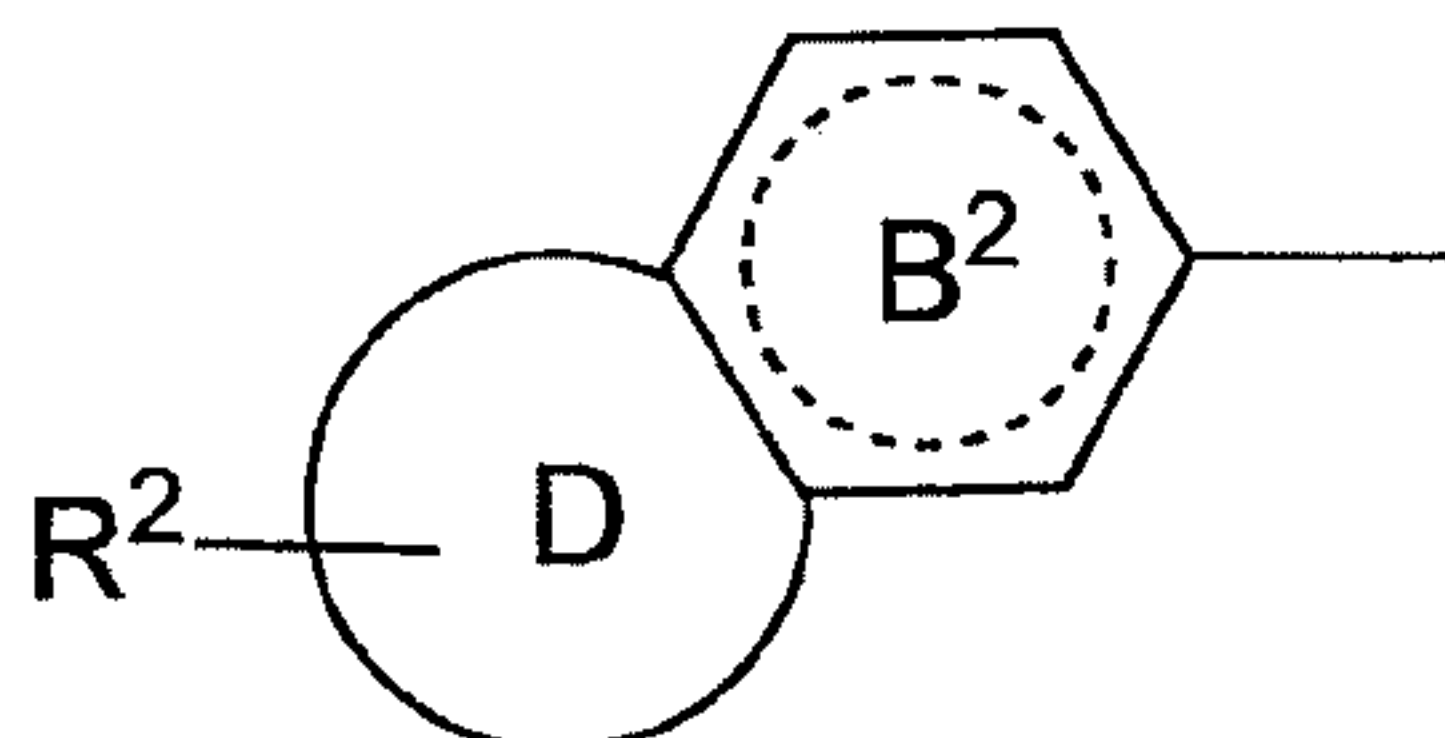
[0106]

R is

(1) a group represented by the formula:

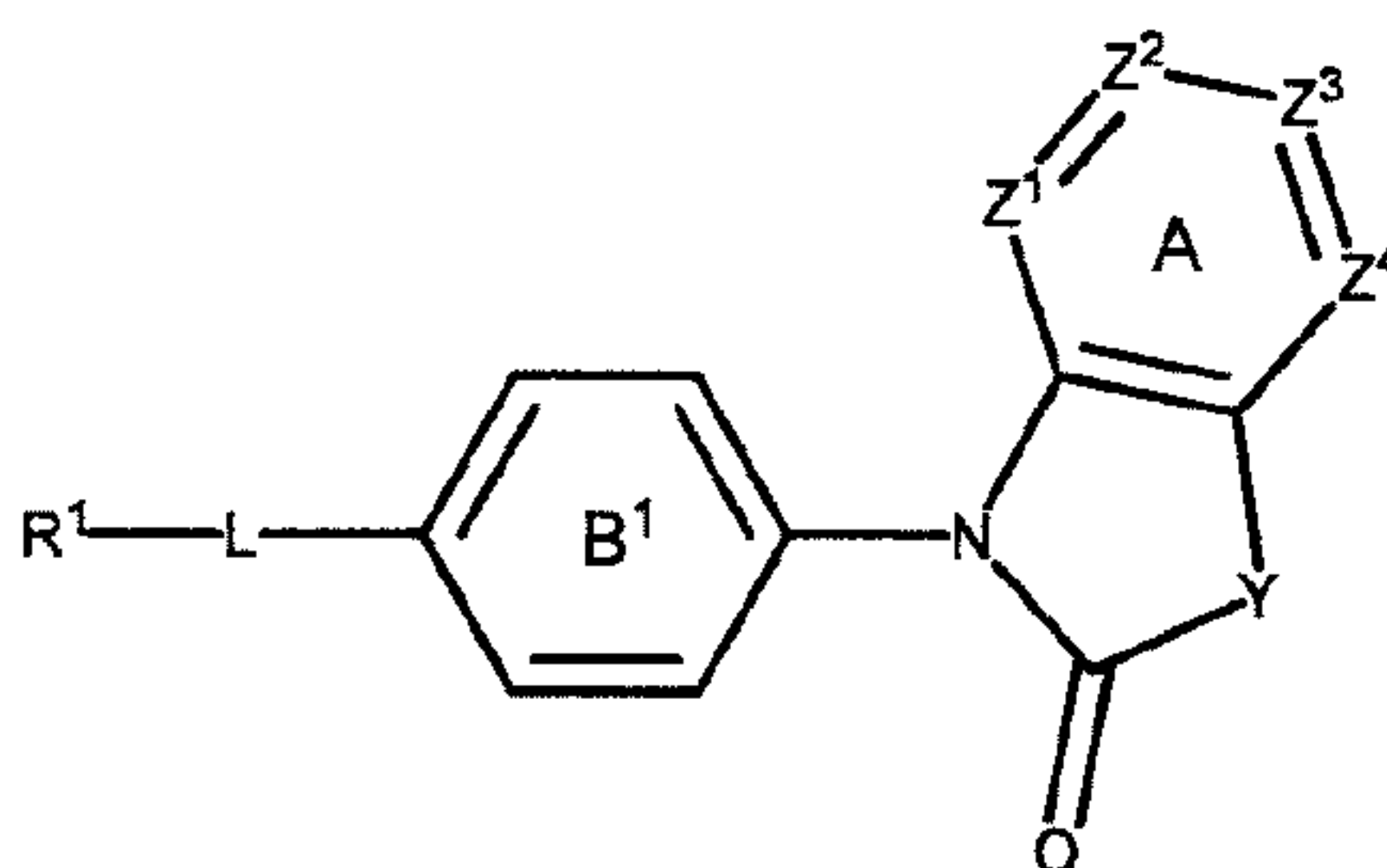


(2) a group represented by the formula:

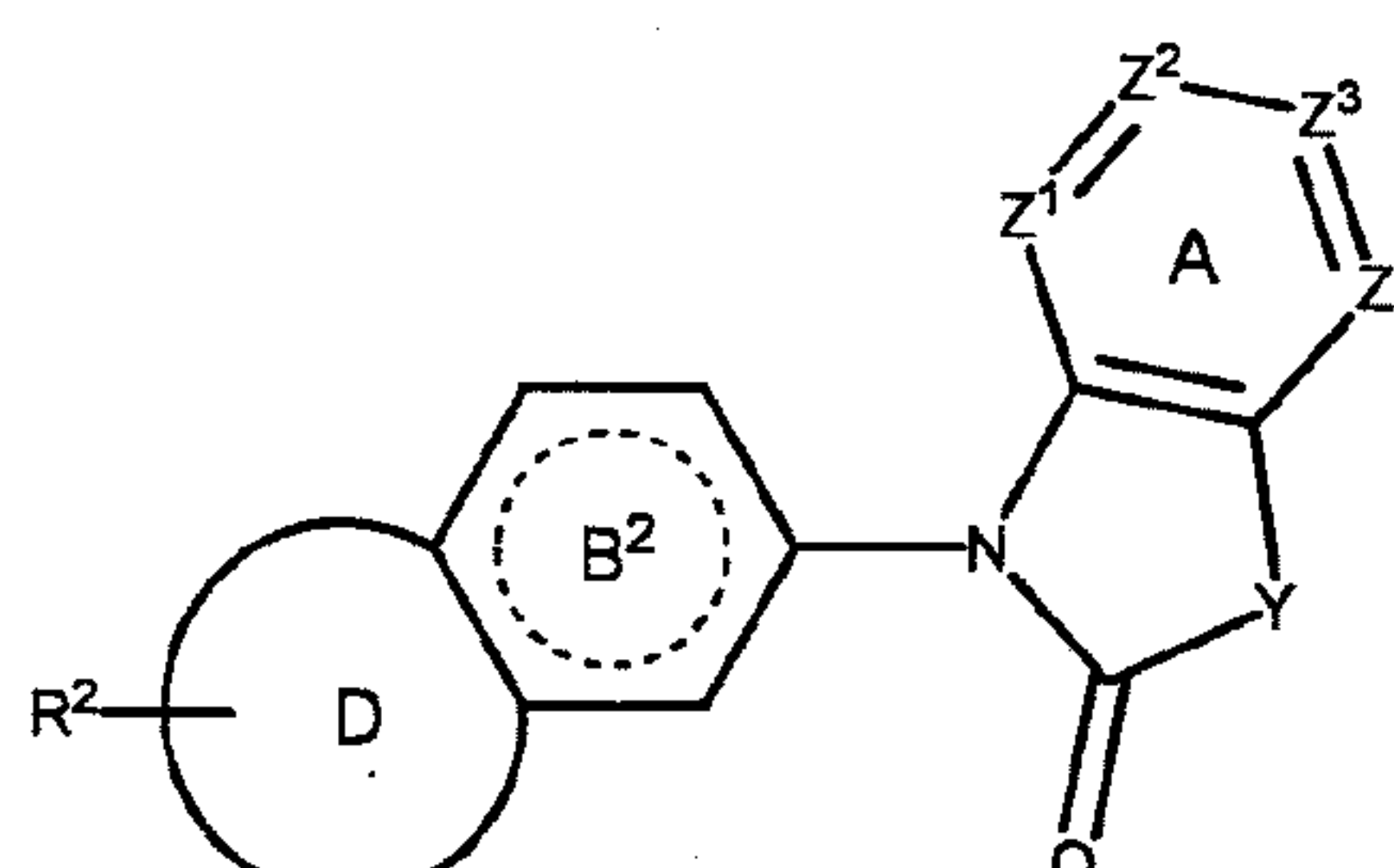


[0107]

That is, the compound represented by the formula (I) or a
 10 salt thereof encompasses a compound represented by the formula
 (I-1) or the formula (I-2):



(I-1)

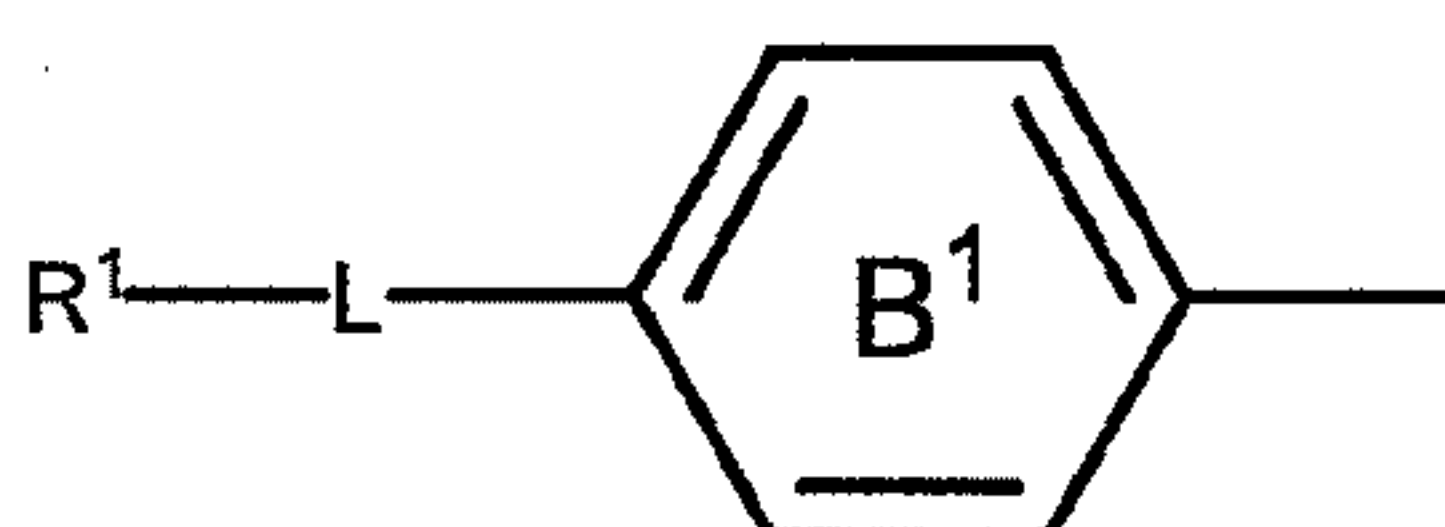


(I-2)

[0108]

Each symbol for R is explained in the following.

15 [0109]

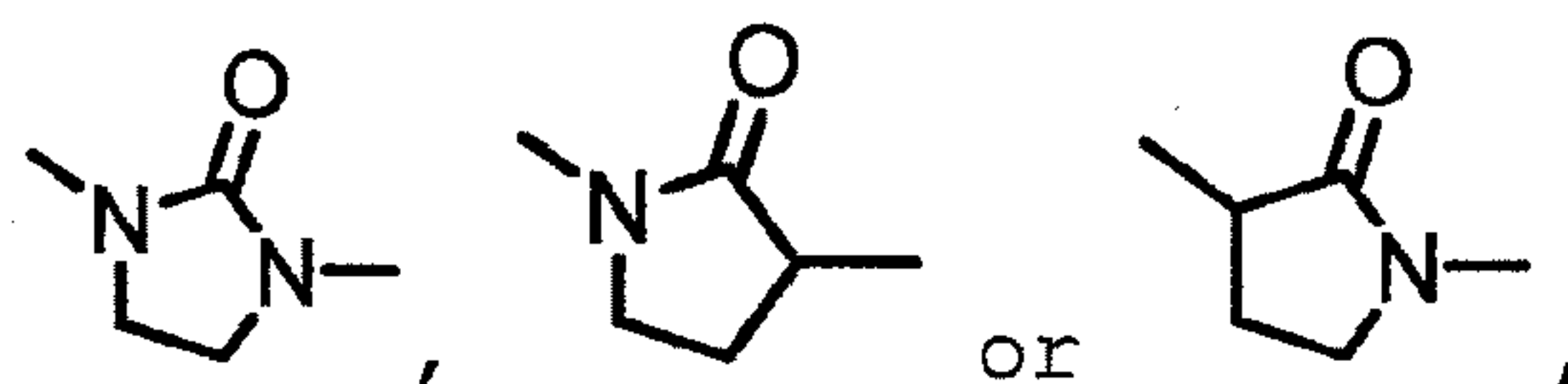


wherein

R¹ is a phenyl group or a 5- to 10-membered heterocyclic
 group, each of which is optionally substituted,

20 L is a sulfur atom (-S-), an oxygen atom (-O-), an
 optionally substituted methylene group, -CO-, -NR^a-, -CH₂O-,
 -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-, -NR^aCOCH₂-, -CH₂CONR^a-,

$-\text{NR}^a\text{CO}-$, $-\text{CONR}^a-$,



wherein

R^a and R^b are the same or different and each is a
 5 hydrogen atom or an optionally substituted C_{1-6} alkyl
 group, or

L and R^1 in combination optionally form an optionally
 substituted bi- or tri-cyclic fused heterocyclic group, and
 ring B^1 is a benzene ring, a pyridine ring, a pyrimidine
 10 ring, a pyrazine ring or a pyridazine ring, each of which
 is optionally substituted.

[0110]

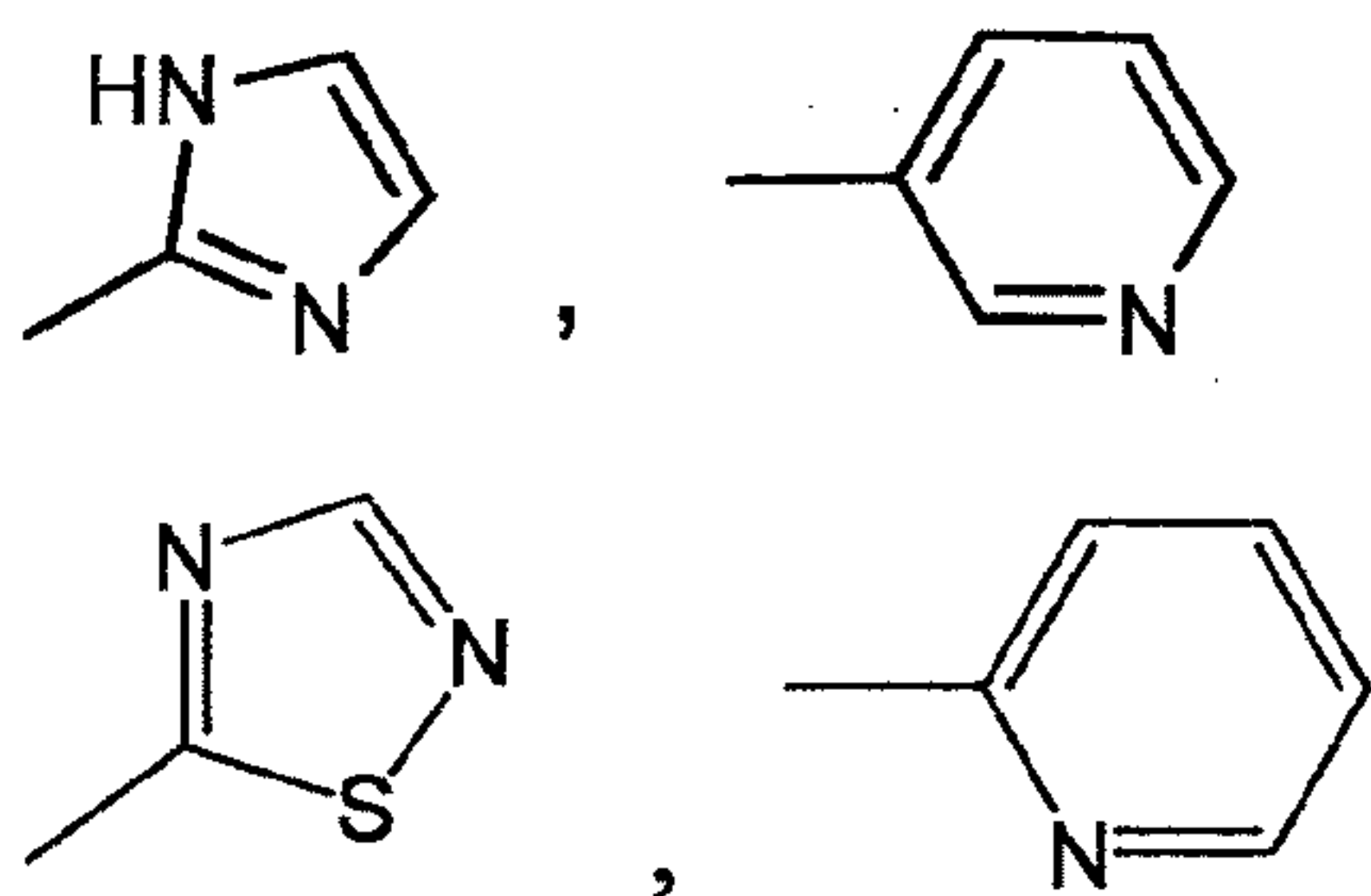
Examples of the "5- to 10-membered heterocyclic group" of
 the "optionally substituted 5- to 10-membered heterocyclic
 15 group" for R^1 include a 5- to 10-membered heterocyclic group
 from among the "3- to 14-membered heterocyclic groups"
 exemplified above.

Among them, a 5- or 6-membered monocyclic heterocyclic
 group, a bicyclic fused heterocyclic group (preferably a 9- to
 20 10-membered bicyclic fused heterocyclic group) and the like
 are preferable.

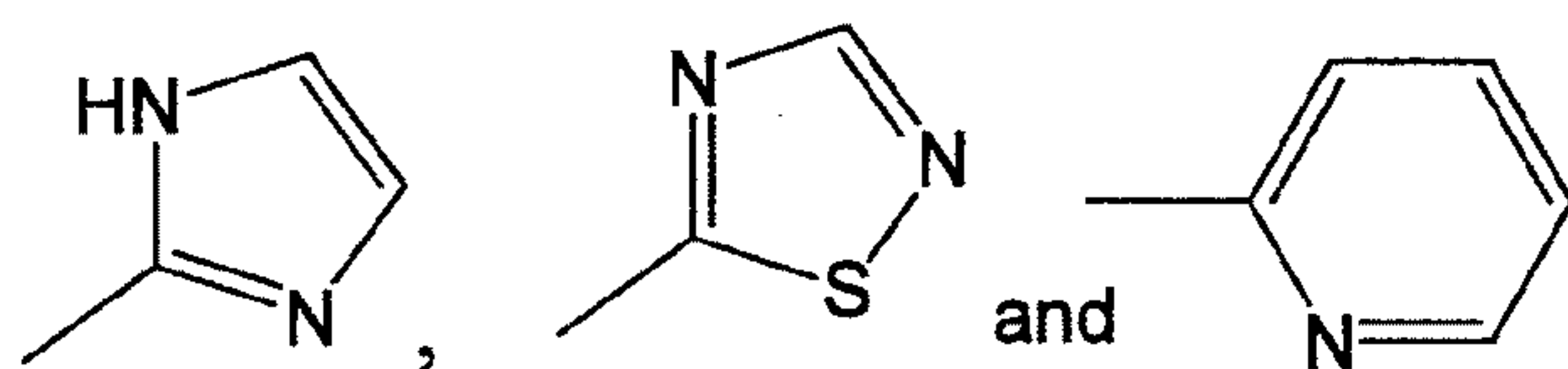
The nitrogen atom(s) contained in the "5- to 10-membered
 heterocyclic group" of the "optionally substituted 5- to 10-
 membered heterocyclic group" for R^1 may be oxidized.

25 [0111]

The "5- or 6-membered monocyclic heterocyclic group" is
 preferably, for example, a 5- or 6-membered monocyclic
 nitrogen-containing aromatic heterocyclic group such as
 imidazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl,
 30 thiadiazolyl and the like. Among them, imidazolyl, pyridyl and
 thiadiazolyl are preferable, and the following groups:



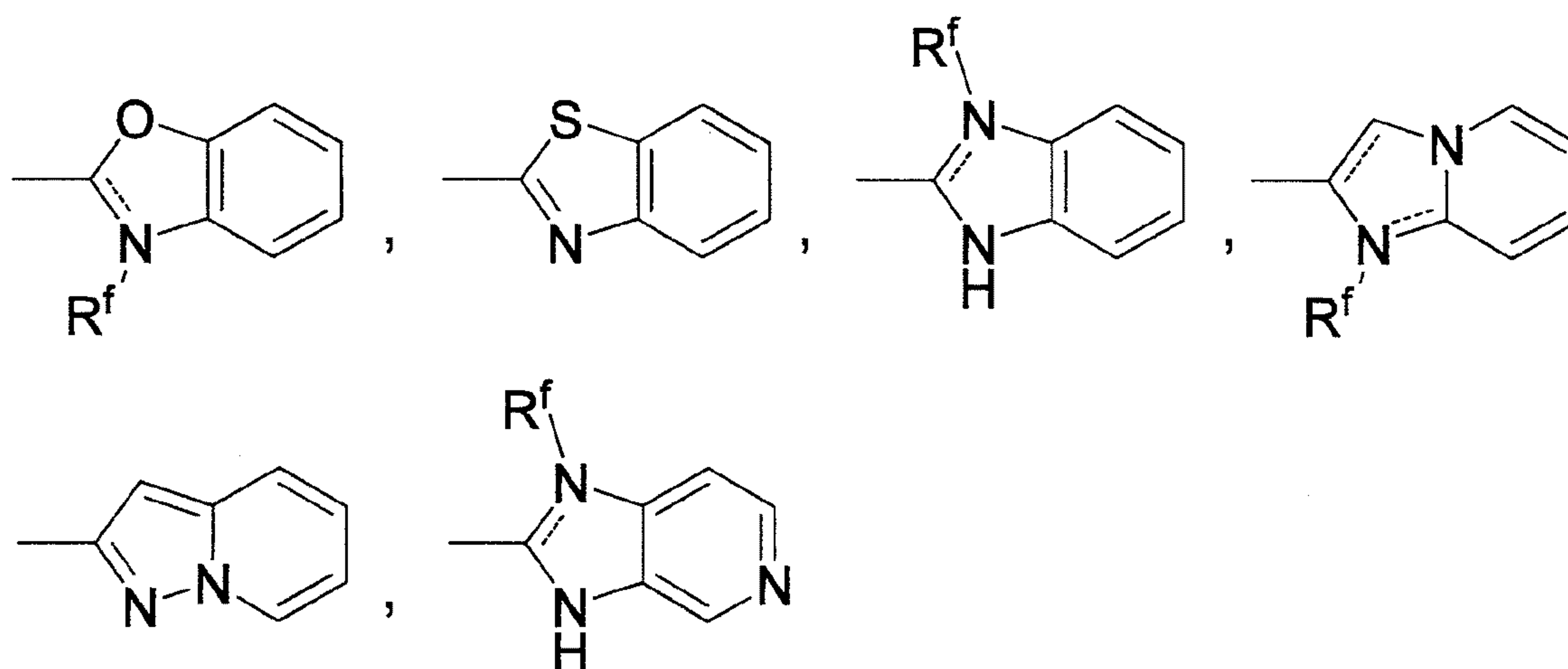
and the like are more preferable, and the following groups:

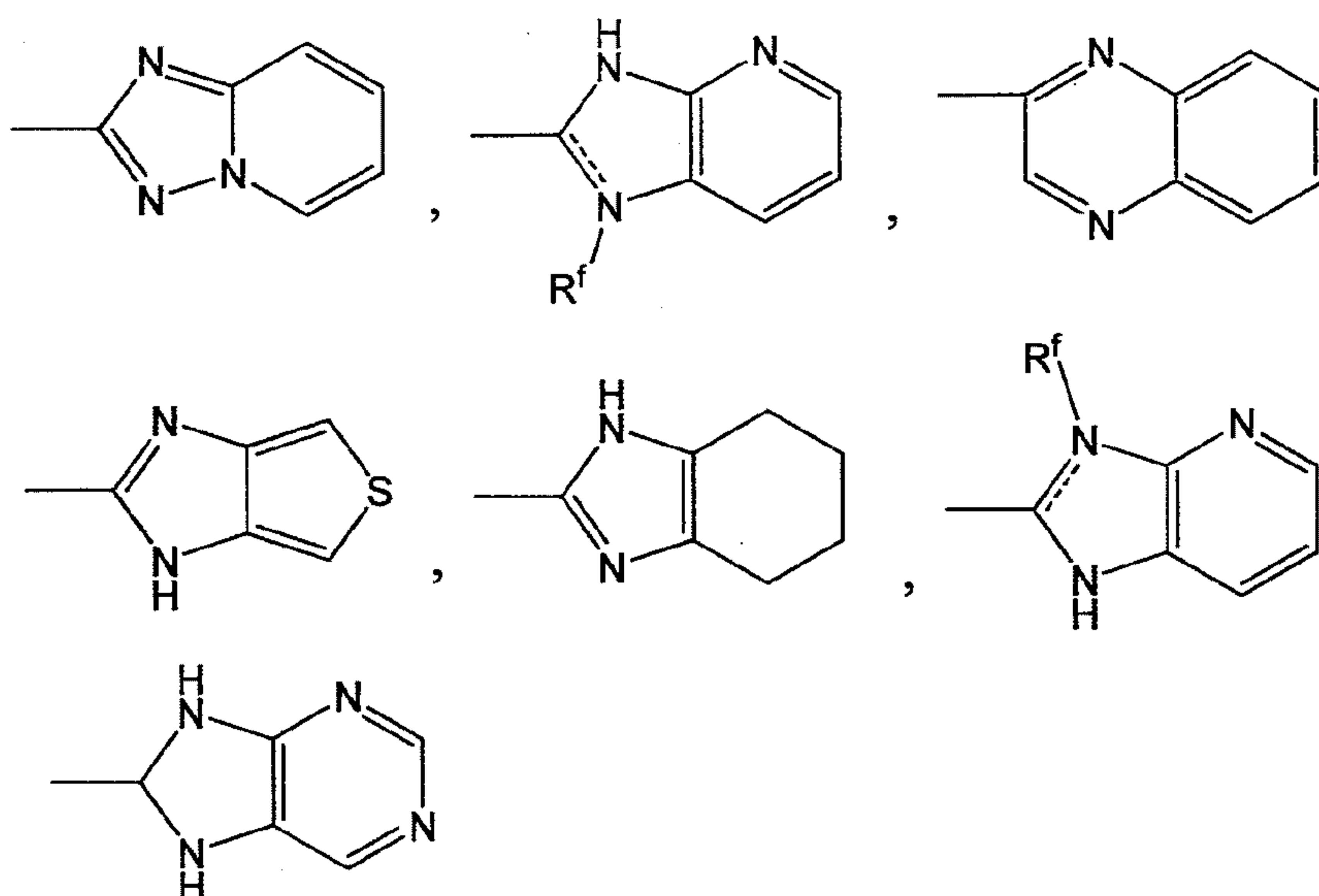


5 are particularly preferable.

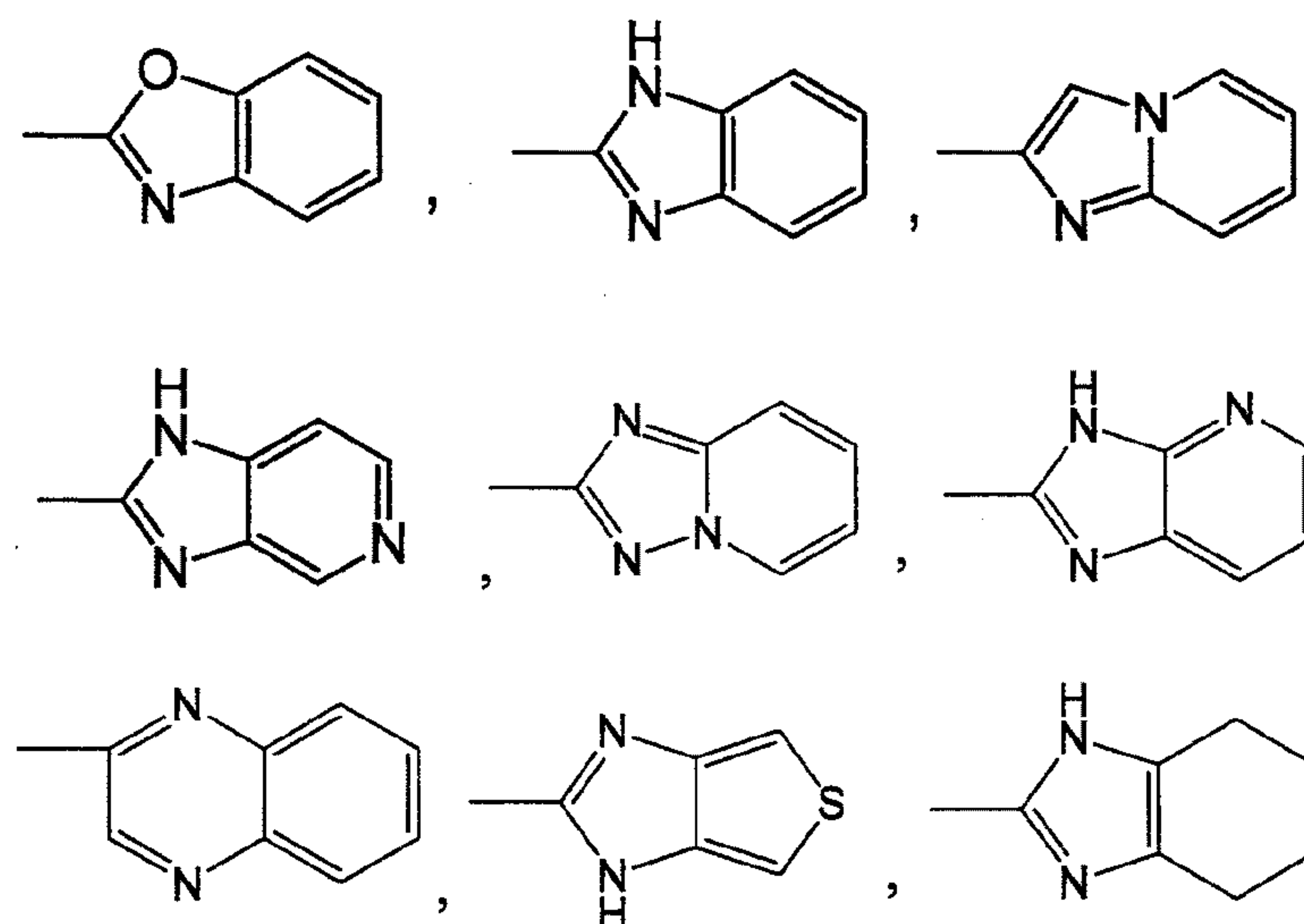
[0112]

Examples of the aforementioned "bicyclic fused heterocyclic group" include (1) a fused heterocyclic group formed by condensation of a phenyl group with a 5- or 6-
 10 membered heterocycle, (2) a fused heterocyclic group formed by condensation of a 5- or 6-membered heterocyclic group with a carbocycle having 5 or 6 carbon atoms, and (3) a fused heterocyclic group formed by condensation of a 5- or 6-membered heterocyclic group with a 5- or 6-membered
 15 heterocycle. Among them, the following groups:





wherein R^f is absent or a hydrogen atom (when R^f is absent, $-N(R^f)-$ is $=N-$; R^f is preferably absent), and the like are preferable, and the following groups:



5

and the like are more preferable.

[0113]

Examples of the substituent of the "phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted" for R^1 include substituents selected from the above-mentioned Substituent Group A.

Among them,

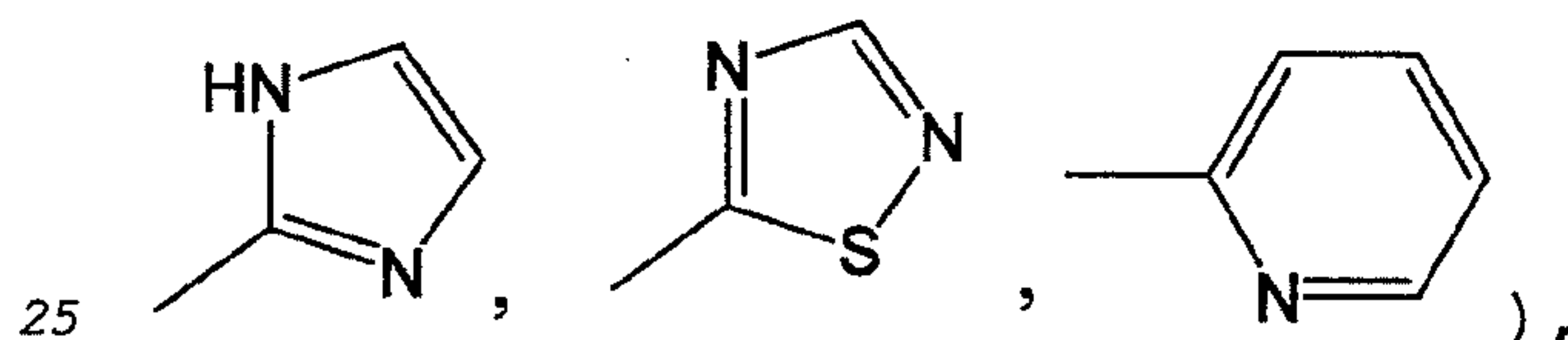
- (a) a halogen atom,
- (b) an optionally esterified carboxy group,
- 15 (c) an optionally substituted alkyl group,

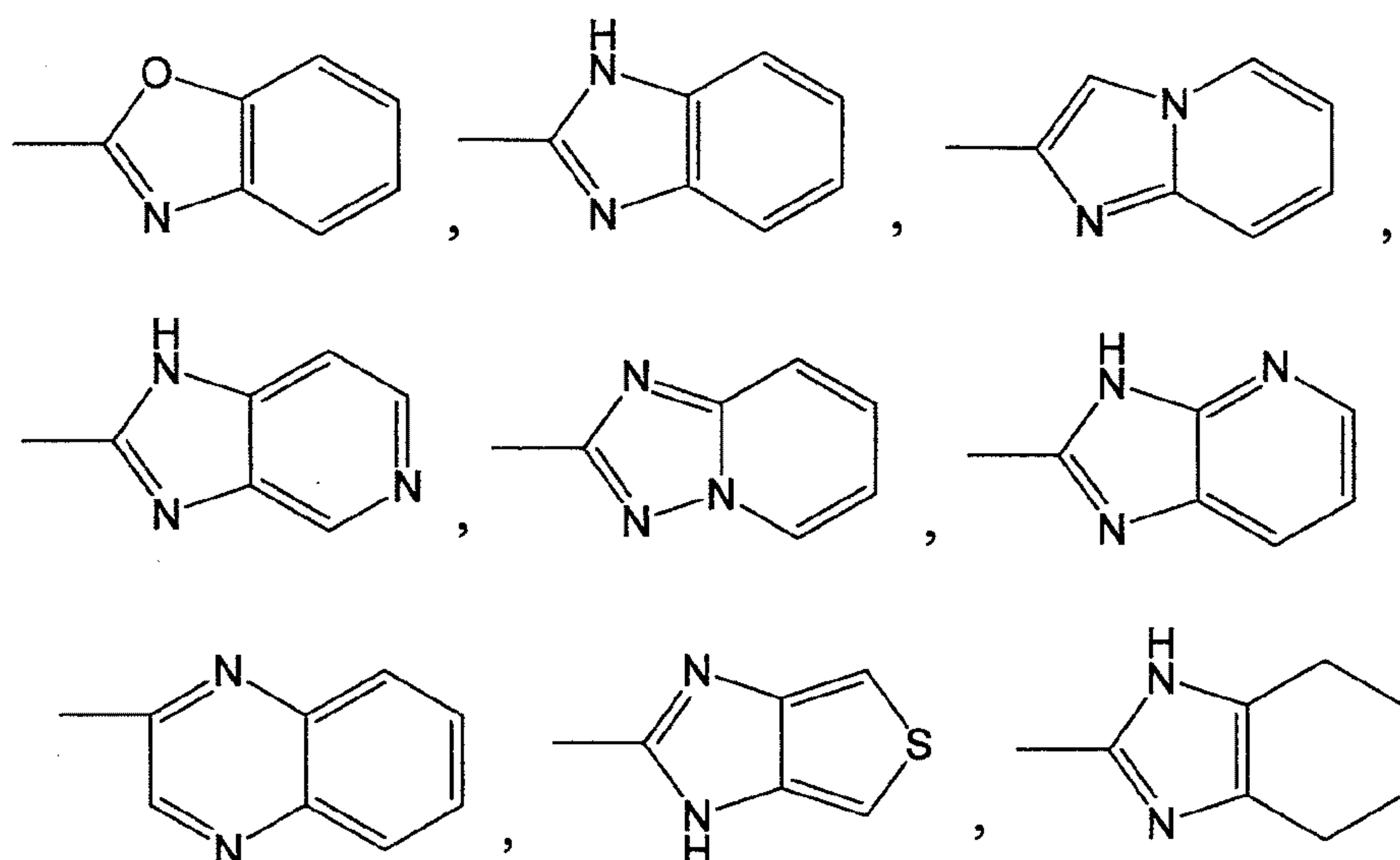
- (d) an optionally substituted C₆₋₁₄ aryl group,
 (e) an optionally substituted alkyl-carbonyl group,
 and the like are preferable,
 (a) a halogen atom (preferably fluorine, bromine, chlorine),
 5 (b) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
 (c) a C₁₋₆ alkyl group (preferably methyl, ethyl, butyl,
 isobutyl) optionally substituted by one or more (preferably 1
 to 3) substituents selected from the group consisting of
 (i) a halogen atom (preferably a fluorine atom),
 10 (ii) a hydroxy group, and
 (iii) an optionally substituted C₁₋₆ alkoxy group (e.g., a
 C₁₋₆ alkoxy group (preferably ethoxy) optionally substituted
 by trimethylsilyl),
 (d) a C₆₋₁₄ aryl group (preferably phenyl),
 15 (e) a C₁₋₆ alkyl-carbonyl group (preferably acetyl),
 and the like are more preferable.

The number of the substituents of the "phenyl group or 5-
 to 10-membered heterocyclic group, each of which is optionally
 substituted" for R¹ is preferably 0 (i.e., unsubstituted), or 1
 20 to 3. When the number of the substituents is not less than 2,
 the respective substituents may be the same or different.

[0114]

R¹ is preferably a phenyl group, imidazolyl, pyridyl,
 thiadiazolyl (preferably the following group:



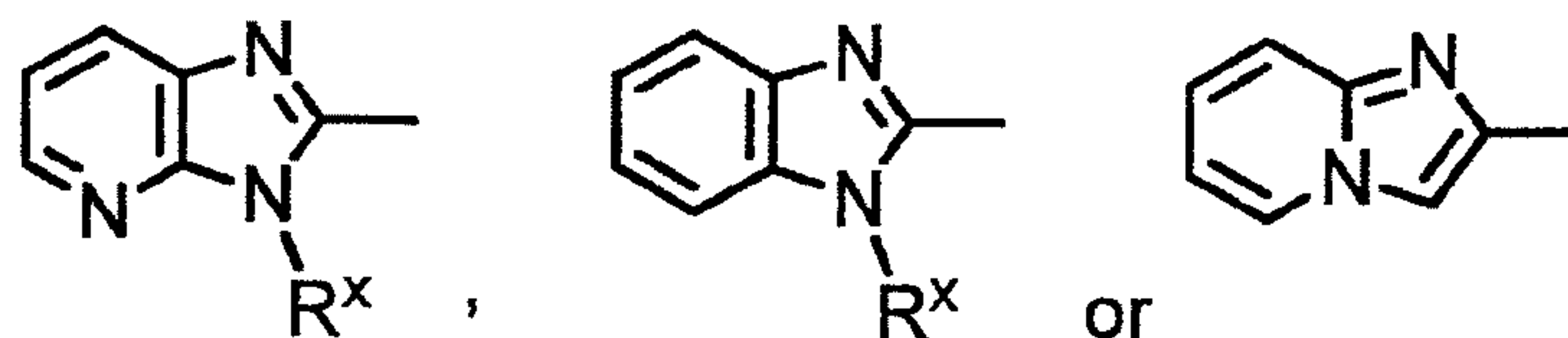


or the like, each of which is optionally substituted by 1 to 3 substituents selected from the group consisting of

- (a) a halogen atom,
 - 5 (b) an optionally esterified carboxy group,
 - (c) an optionally substituted alkyl group,
 - (d) an optionally substituted C₆₋₁₄ aryl group, and
 - (e) an optionally substituted alkyl-carbonyl group
- [preferably
- 10 (a) a halogen atom (preferably fluorine, bromine, chlorine),
 - (b) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
 - (c) a C₁₋₆ alkyl group (preferably methyl, ethyl, butyl, isobutyl) optionally substituted by one or more (preferably
 - 15 1 to 3) substituents selected from the group consisting of
 - (i) a halogen atom (preferably fluorine),
 - (ii) a hydroxy group, and
 - (iii) an optionally substituted C₁₋₆ alkoxy group (e.g., a C₁₋₆ alkoxy group (preferably ethoxy) optionally substituted by trimethylsilyl),
 - 20 (d) a C₆₋₁₄ aryl group (preferably phenyl), and
 - (e) a C₁₋₆ alkyl-carbonyl group (preferably acetyl)].

[0115]

In another embodiment, R¹ is preferably



wherein

R^x is a hydrogen atom or an optionally substituted C_{1-6} alkyl group (preferably a C_{1-6} alkyl group),

5 or the like.

[0116]

Examples of the substituent of the "optionally substituted methylene group" for L include substituents selected from the above-mentioned Substituent Group A.

10 The "optionally substituted methylene group" for L is preferably (unsubstituted) methylene.

[0117]

Preferable examples of the substituent of the "optionally substituted C_{1-6} alkyl group" for R^a include substituents
15 selected from the above-mentioned Substituent Group A.

R^a is preferably a hydrogen atom, a C_{1-6} alkyl group or the like, more preferably a hydrogen atom, methyl or the like.

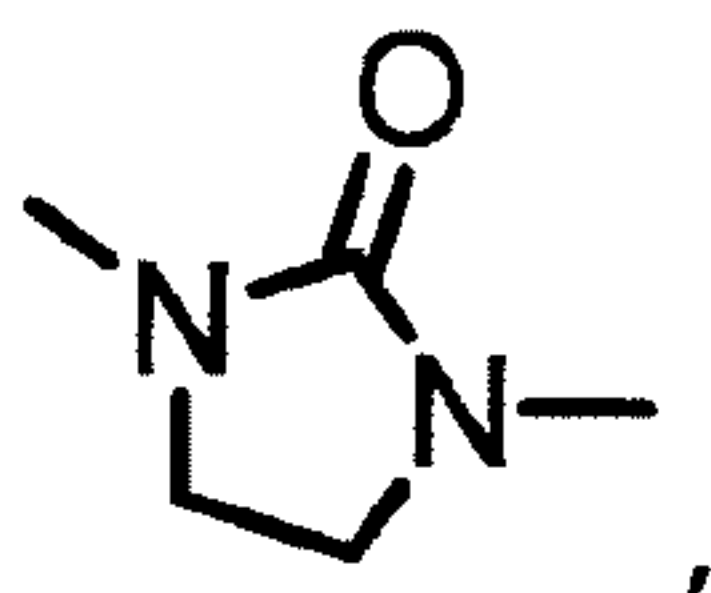
[0118]

Preferable examples of the substituent of the "optionally substituted C_{1-6} alkyl group" for R^b include substituents
20 selected from the above-mentioned Substituent Group A.

R^b is preferably a hydrogen atom, a C_{1-6} alkyl group or the like, more preferably a hydrogen atom, methyl or the like.

[0119]

25 L is preferably an oxygen atom ($-O-$), $-CO-$, $-NR^a-$, $-NR^aCOO-$ wherein R^a is preferably a hydrogen atom or a C_{1-6} alkyl group (preferably methyl), or

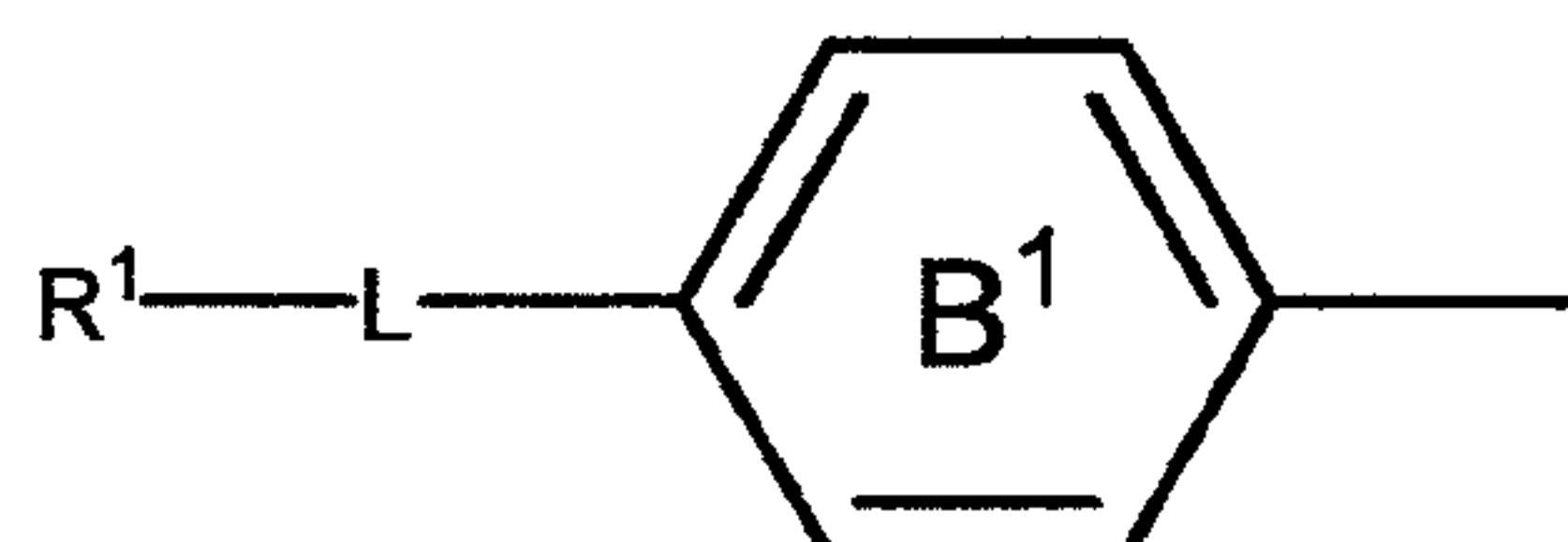


more preferably an oxygen atom or $-NR^a-$ wherein R^a is a
30 hydrogen atom or a C_{1-6} alkyl group (preferably methyl), or the

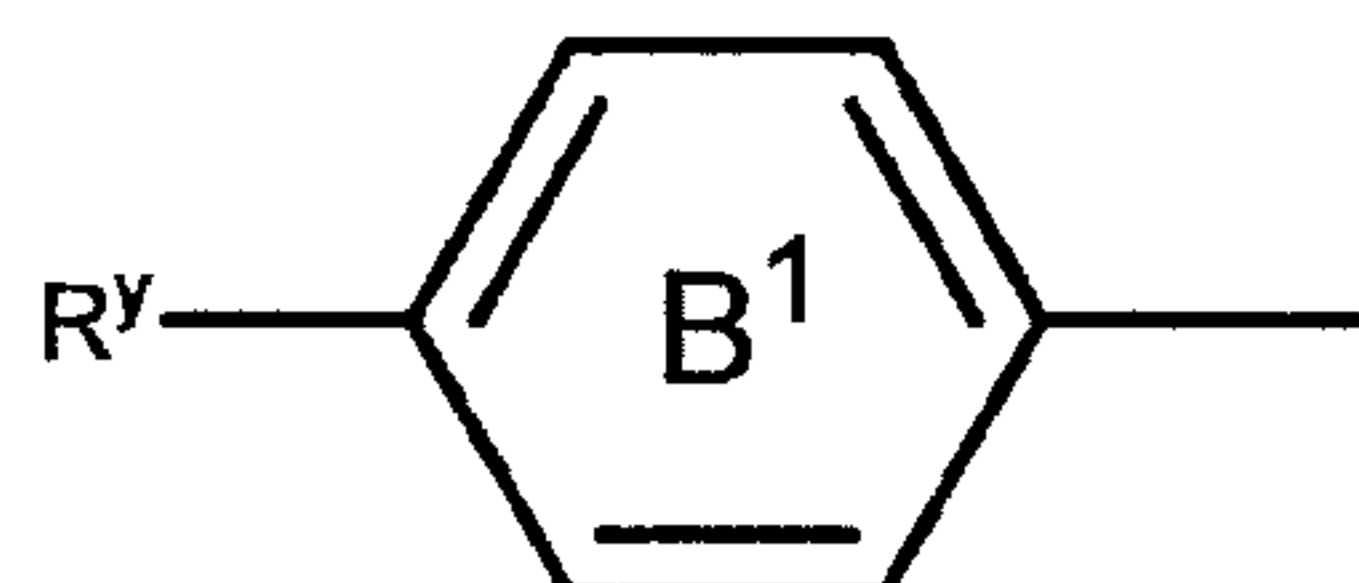
like,
further more preferably an oxygen atom or the like.

[0120]

The "optionally substituted bi- or tri-cyclic fused
5 heterocyclic group formed by L and R¹ in combination" means
that the moiety represented by the formula:



is a moiety represented by the formula:

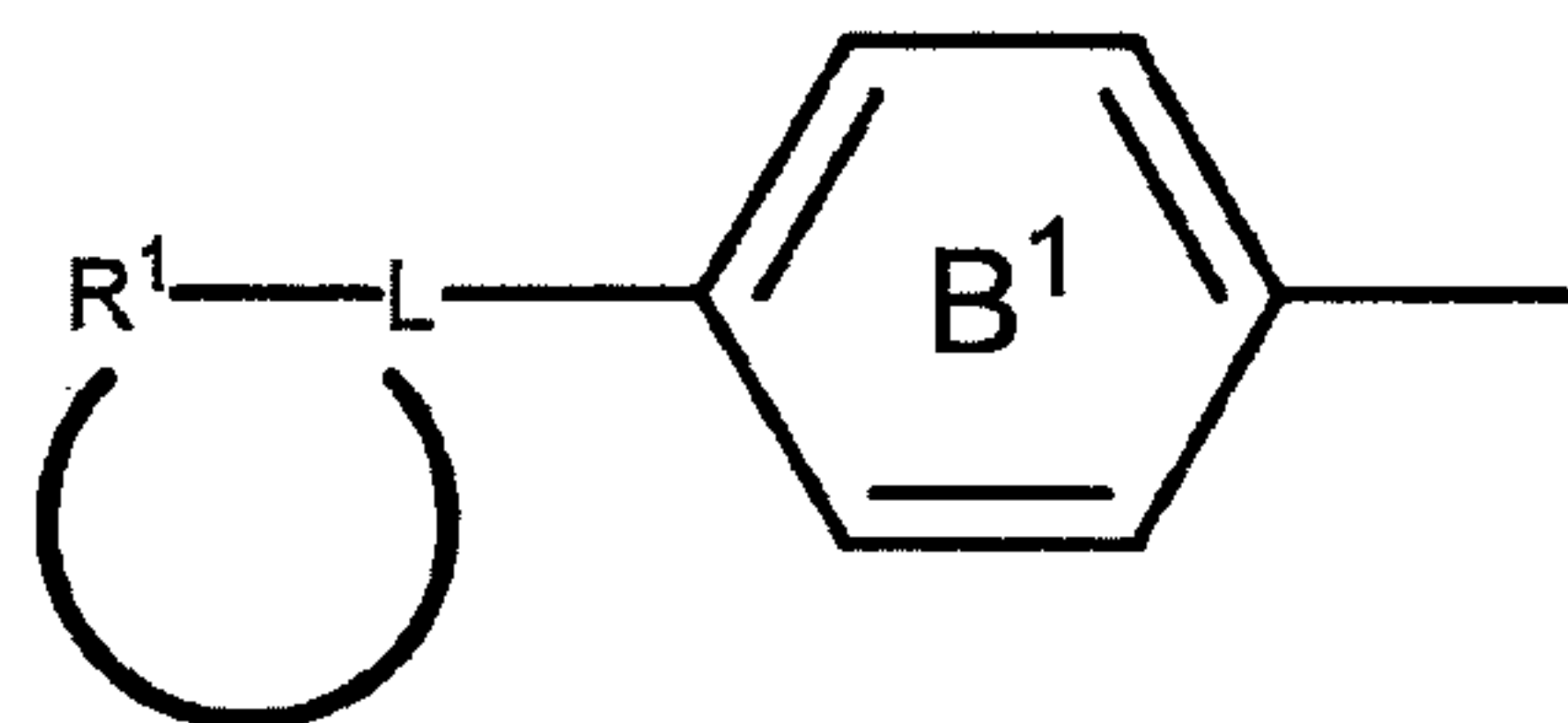


10 wherein

R^ʸ is an optionally substituted bi- or tri-cyclic fused
heterocyclic group, and

B¹ is as defined above.

That is, the substituent on the ring-constituting atom of
15 the "phenyl group" or the "5- to 10-membered heterocyclic
group" for R¹ and the substituent on the main chain-
constituting atom of L form a ring together with the ring-
constituting atom and the main chain-constituting atom. In the
present specification, this structure is sometimes represented
20 by the following formula:

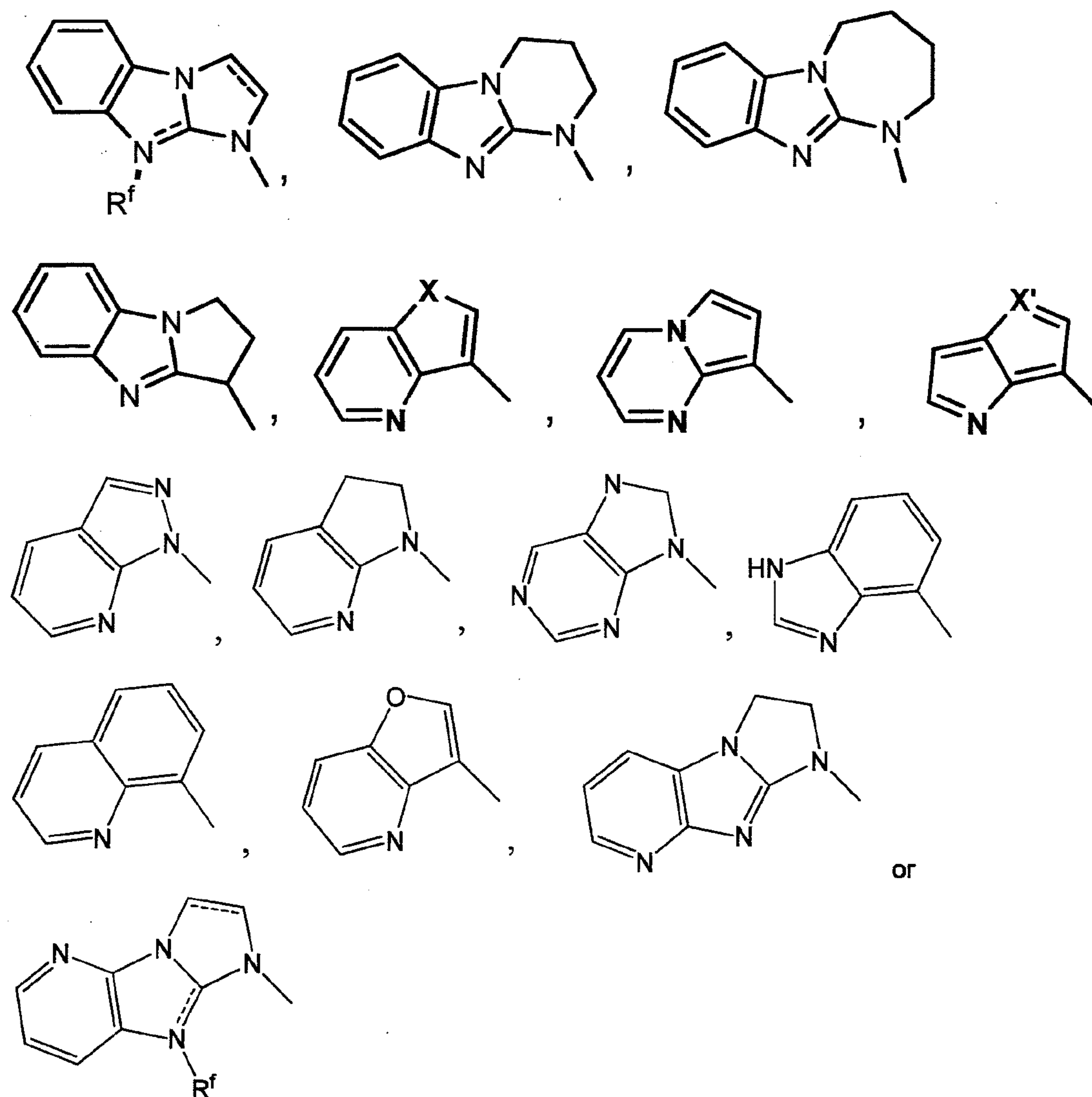


[0121]

Examples of the "bi- or tri-cyclic fused heterocyclic
group" of the "optionally substituted bi- or tri-cyclic fused
25 heterocyclic group" formed by L and R¹ in combination include a
bi- or tri-cyclic group, from among the aforementioned "3- to
14-membered heterocyclic groups containing 1 to 5 hetero atoms
selected from a nitrogen atom, a sulfur atom and an oxygen

atom".

The "bi- or tri-cyclic fused heterocyclic group" is preferably the following group:



5

wherein

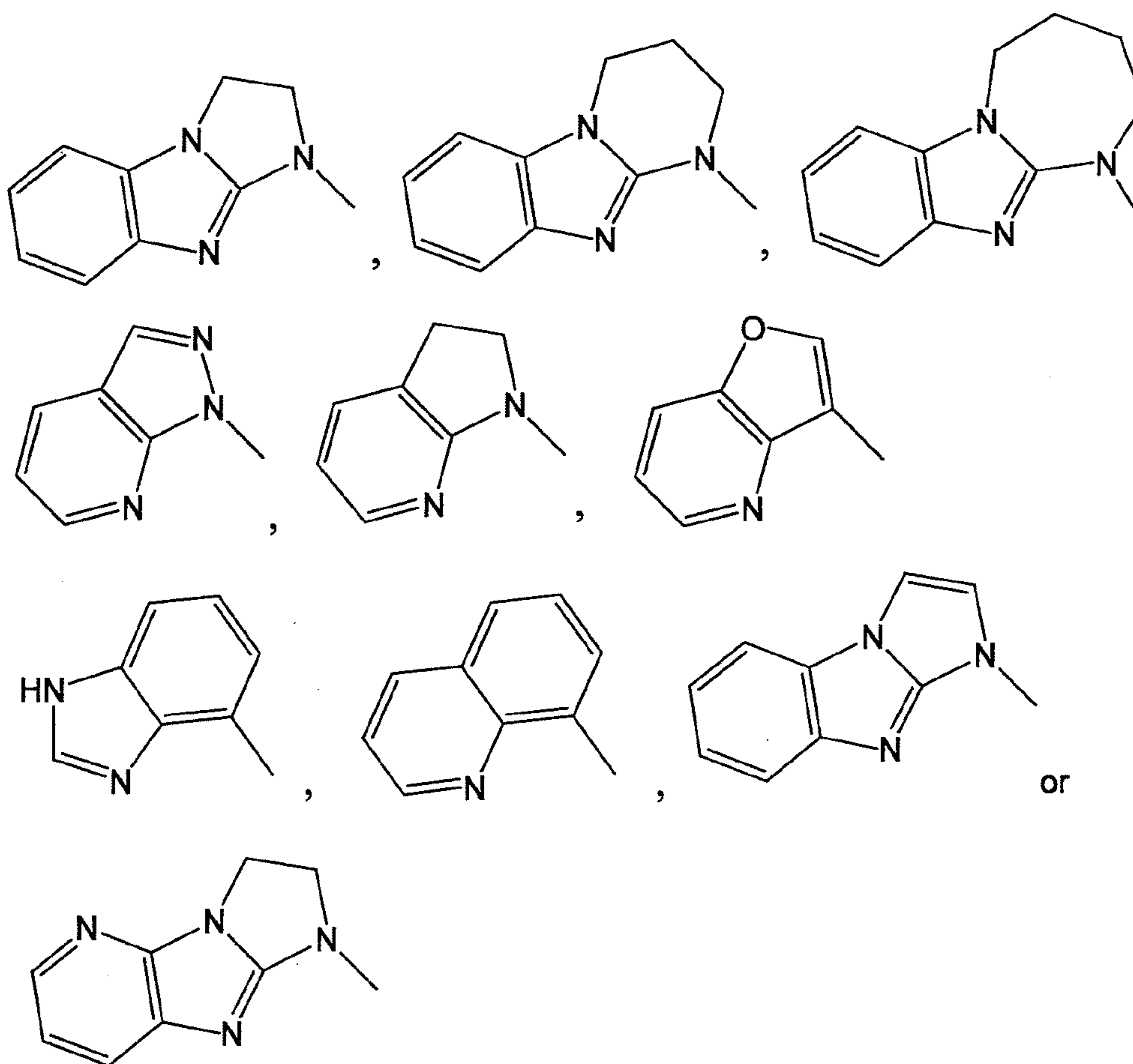
X is $-\text{CH}_2-$, $-\text{NH}-$, an oxygen atom or a sulfur atom,

X' is $=\text{CH}-$ or $=\text{N}-$, and

R^f is absent or a hydrogen atom (when R^f is absent, $-\text{N}(R^f)-$ is $=\text{N}-$; R^f is preferably absent),

10

or the like, more preferably the following group:



[0122]

Examples of the substituent of the "optionally substituted bi- or tri-cyclic fused heterocyclic group" optionally formed by L and R¹ in combination include substituents selected from the aforementioned Substituent Group A and an oxo group.

Among them,

- (a) a halogen atom,
 - 10 (b) an optionally esterified carboxy group,
 - (c) an optionally substituted alkyl group,
 - (d) an oxo group
- and the like are preferable, and
- (a) a halogen atom,
 - 15 (b) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
 - (c) a C₁₋₆ alkyl group (preferably methyl) optionally substituted by C₆₋₁₄ aryl group(s) (preferably phenyl),

(d) an oxo group
and the like are more preferable, and
(a) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
(b) a C₁₋₆ alkyl group (preferably methyl) optionally
5 substituted by C₆₋₁₄ aryl group(s) (preferably phenyl), and
(c) an oxo group
are further more preferable.

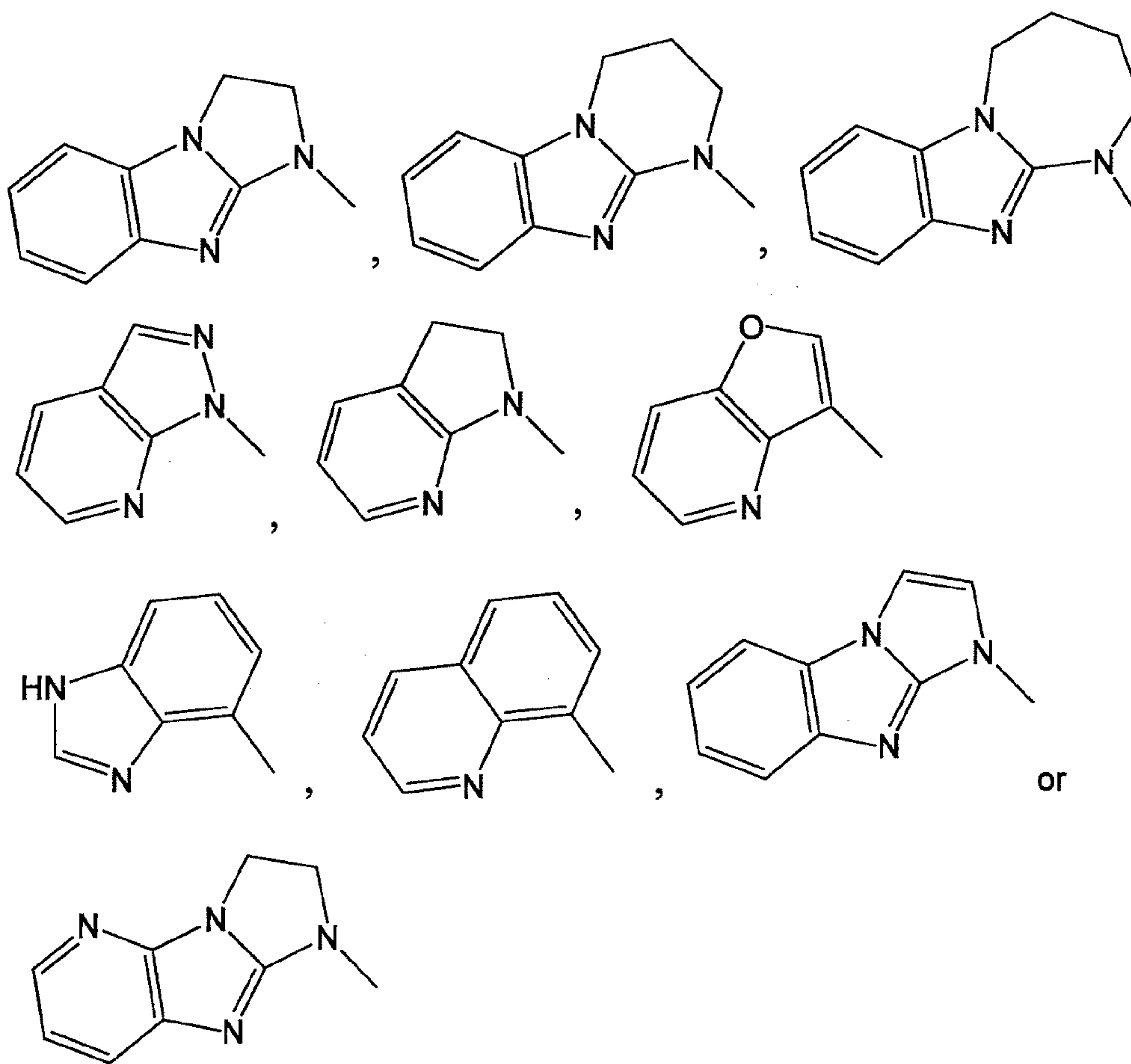
In another embodiment, as the substituents of the
"optionally substituted bi- or tri-cyclic fused heterocyclic
10 group" optionally formed by L and R¹ in combination,

(a) a halogen atom,
(b) an optionally esterified carboxy group,
(c) an optionally substituted alkyl group,
and the like are preferable, and
15 (a) a halogen atom,
(b) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
(c) a C₁₋₆ alkyl group (preferably methyl) optionally
substituted by C₆₋₁₄ aryl group(s) (preferably phenyl),
and the like are more preferable, and
20 (a) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
and
(b) a C₁₋₆ alkyl group (preferably methyl) optionally
substituted by C₆₋₁₄ aryl group(s) (preferably phenyl)
are further more preferable.

25 The number of the substituents of the "optionally
substituted bi- or tri-cyclic fused heterocyclic group"
optionally formed by L and R¹ in combination is preferably 0
(i.e., unsubstituted), or 1 to 3. When the number of the
substituents is not less than 2, the respective substituents
30 may be the same or different.

[0123]

The "optionally substituted bi- or tri-cyclic fused
heterocyclic group" optionally formed by L and R¹ in
combination is preferably



each of which is optionally substituted by 1 to 3 substituents selected from the group consisting of

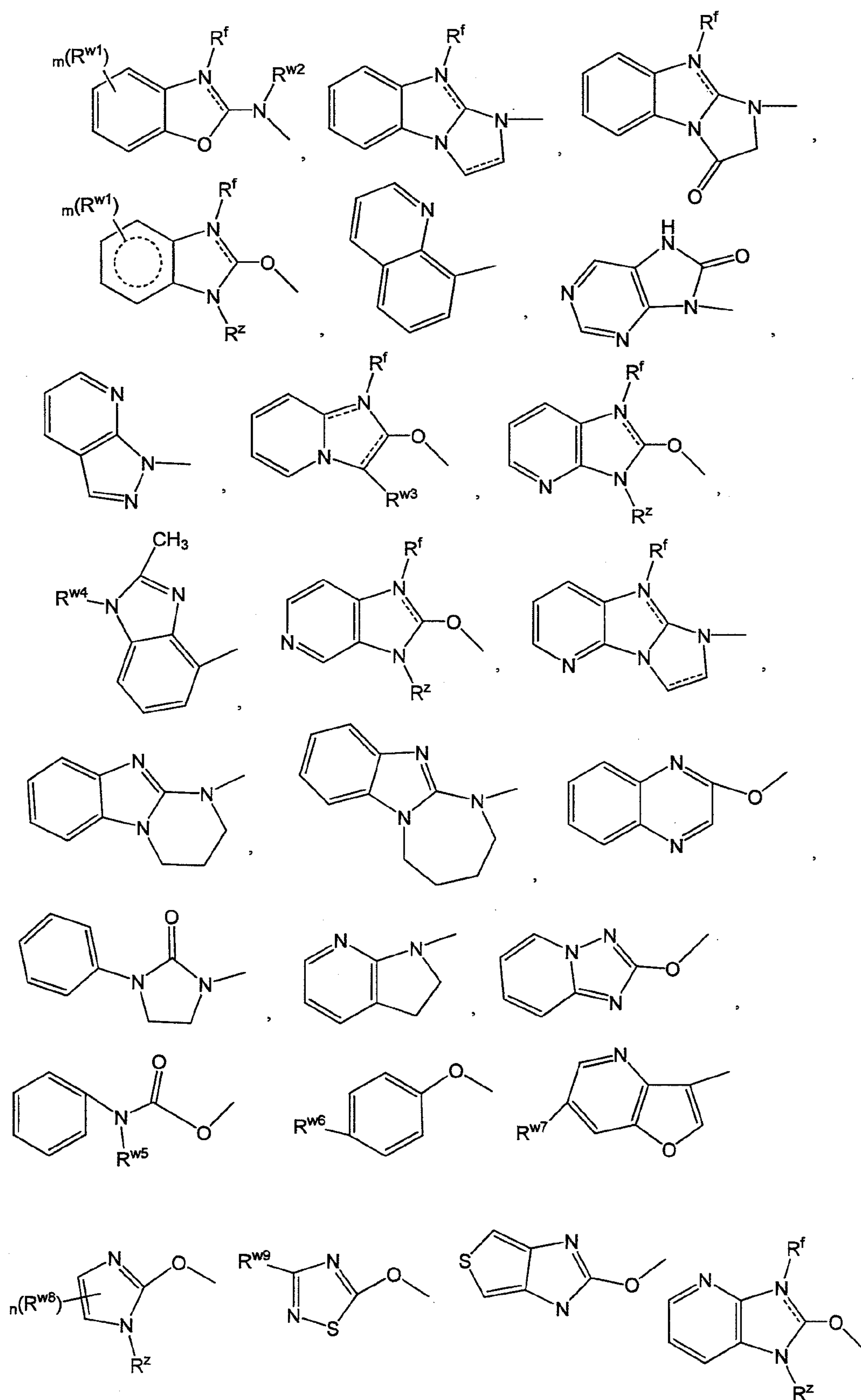
- (a) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
- 5 (b) C₁₋₆ alkyl group (preferably methyl) optionally substituted by C₆₋₁₄ aryl group(s) (preferably phenyl), and
- (c) an oxo group.

[0124]

The partial structure of the formula (I-1):



is preferably a group represented by the following formula:



wherein

R^f is absent or a hydrogen atom (when R^f is absent, -

$N(R^f)-$ is $=N-$; R^f is preferably absent);

R^z is (i) a hydrogen atom, (ii) a C_{1-4} alkyl group optionally substituted by one substituent selected from (1) a hydroxy group (preferably, methyl, ethyl, hydroxyethyl, buthyl, hydroxyisobutyl) and (2) a C_{1-4} alkoxy group optionally substituted by trimethylsilyl (preferably, trimethylsilylmethoxy), or (iii) a C_{1-6} alkyl-carbonyl group (preferably, acetyl);

R^{w1} is a halogen atom (preferably, fluorine);

10 m is 0 to 2;

R^{w2} is a hydrogen atom or a methyl group;

R^{w3} is a hydrogen atom or a C_{1-2} alkoxy-carbonyl group (preferably, ethoxycarbonyl);

R^{w4} is a hydrogen atom or benzyl;

15 R^{w5} is a hydrogen atom or methyl;

R^{w6} is a hydrogen atom, a halogen atom (preferably, fluorine, chlorine), or a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms (preferably, trifluoromethyl);

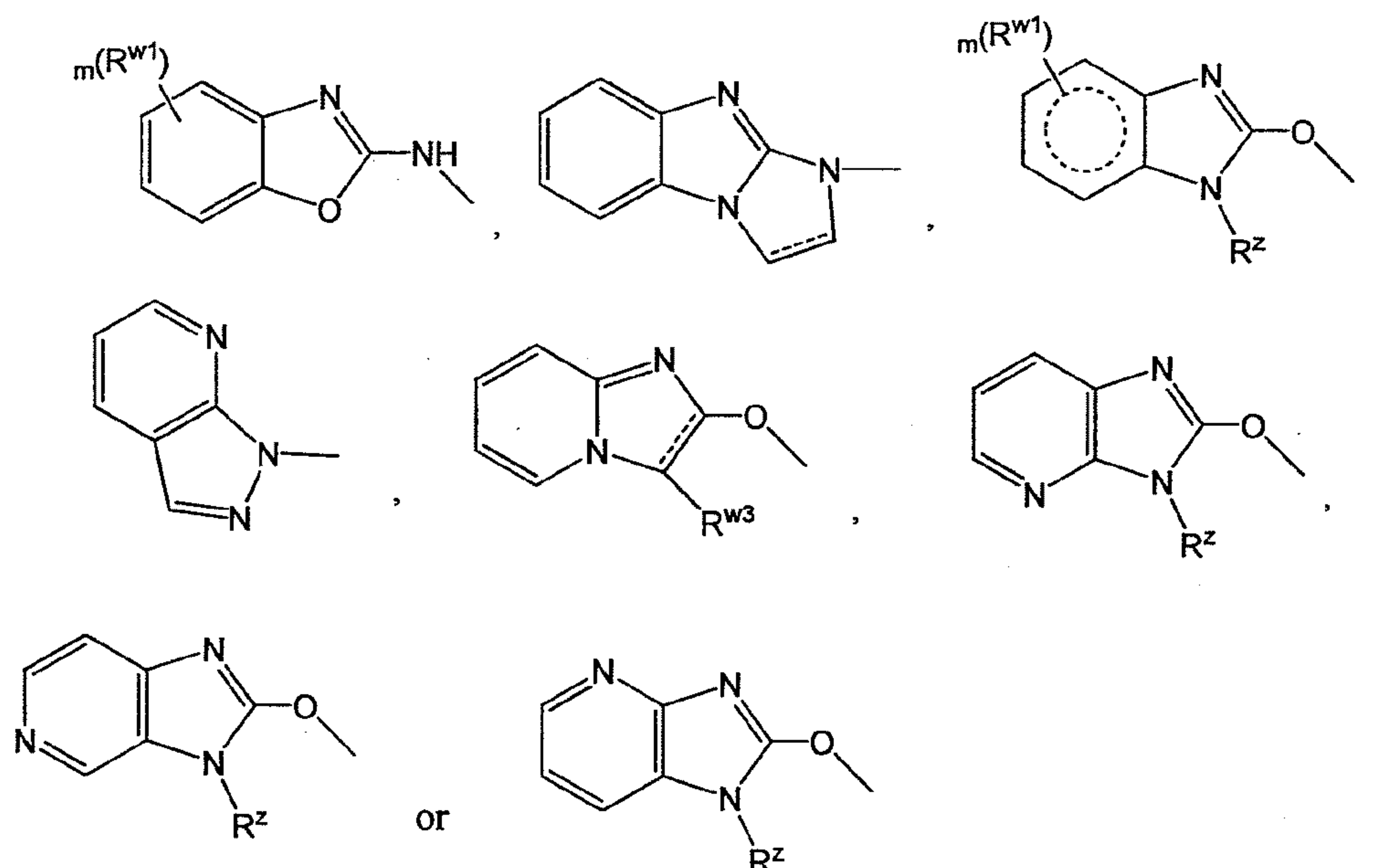
20 R^{w7} is a C_{1-6} alkoxyl-carbonyl group (preferably, ethoxycarbonyl);

R^{w8} is a halogen atom (preferably, chlorine, bromine), or a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms (preferably, trifluoromethyl);

25 n is 0 to 2;

R^{w9} is a hydrogen atom or a halogen atom (preferably, bromine);

more preferably a group represented by the following formula:



wherein

R^{w1} is a halogen atom (preferably, fluorine);

m is 0 to 1;

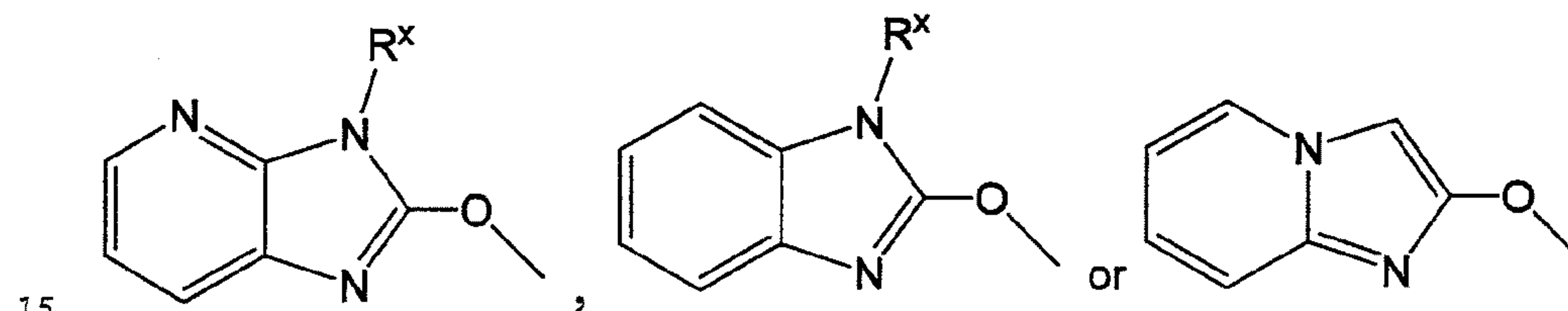
- 5 R^z is (i) a hydrogen atom, (ii) a C_{1-4} alkyl group optionally substituted by one hydroxy group (preferably, methyl, hydroxyethyl, hydroxyisobutyl) and R^{w3} is a hydrogen atom or a C_{1-2} alkoxy-carbonyl group (preferably, ethoxycarbonyl).

10 [0125]

In another embodiment, the partial structure of the formula (I-1):



is preferably a group represented by the following formula:



15 wherein

R^x is an optionally substituted C_{1-6} alkyl group, each of which is further optionally substituted.

The "optionally substituted C_{1-6} alkyl group" for R^x is

preferably a C₁₋₆ alkyl group (preferably methyl, ethyl, butyl, isobutyl) optionally substituted by one or more (preferably 1 to 3) substituents selected from the group consisting of

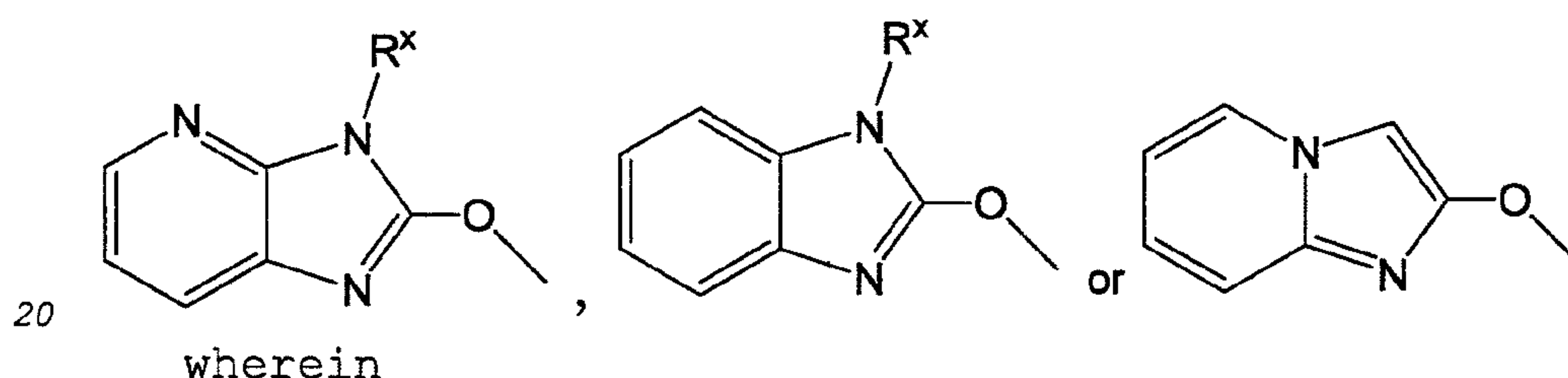
- (i) a halogen atom (preferably a fluorine atom),
- 5 (ii) a hydroxy group, and
- (iii) an optionally substituted C₁₋₆ alkoxy group (e.g., a C₁₋₆ alkoxy group (preferably ethoxy) optionally substituted by trimethylsilyl),

more preferably a C₁₋₆ alkyl group (preferably methyl, ethyl, butyl, isobutyl) optionally substituted by one or more (preferably 1 to 3) substituents selected from the group consisting of

- (i) a hydroxy group, and
- (ii) an optionally substituted C₁₋₆ alkoxy group (e.g., a C₁₋₆ alkoxy group (preferably ethoxy) optionally substituted by trimethylsilyl).

[0126]

As the substituent that the group represented by the formula:



R^x is an optionally substituted C₁₋₆ alkyl group, optionally further has,

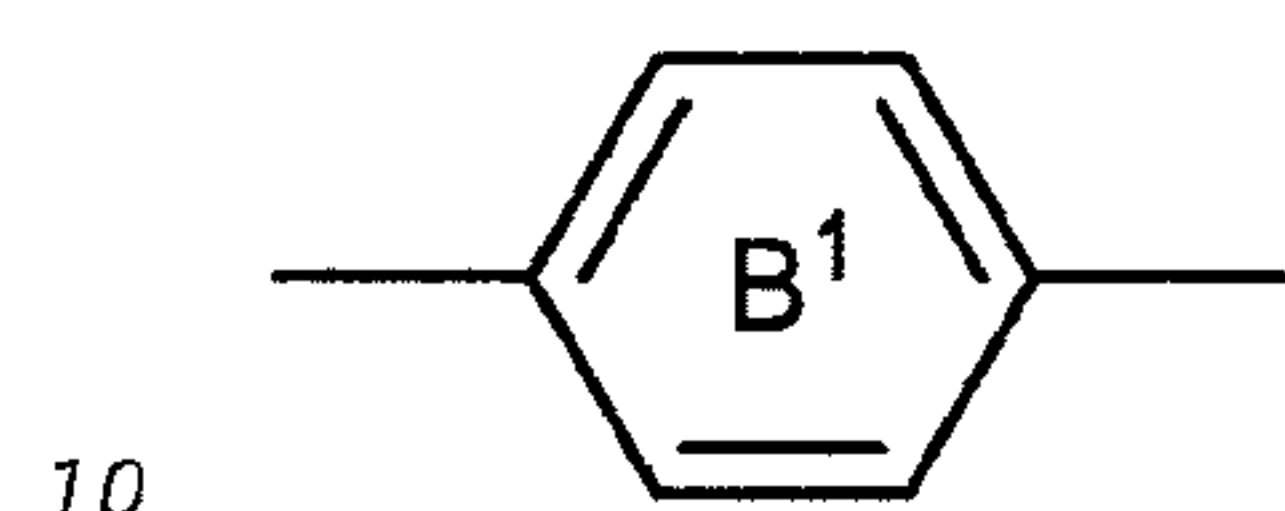
- (a) a halogen atom,
- 25 (b) an optionally esterified carboxy group,
- (c) an optionally substituted alkyl group,
- (d) an optionally substituted C₆₋₁₄ aryl group,
- (e) an optionally substituted alkyl-carbonyl group,
- and the like are preferable, and
- 30 (a) a halogen atom (preferably fluorine),
- (b) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
- (c) a C₁₋₆ alkyl group (preferably methyl)

and the like are more preferable.

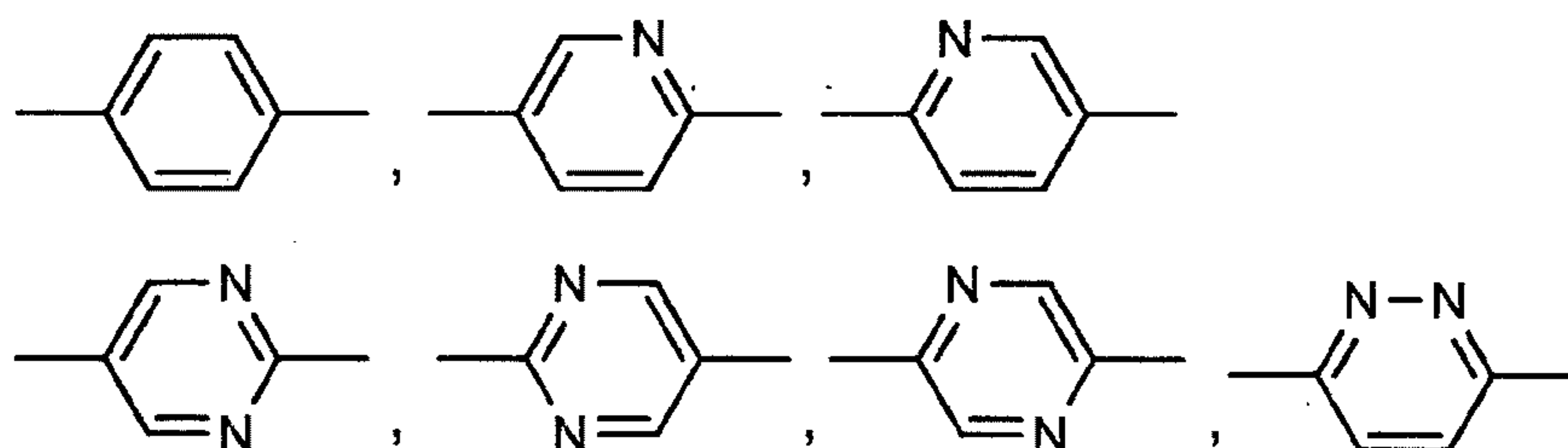
The number of the substituents is preferably 0 (i.e., unsubstituted), or 1 to 3, more preferably 0 (i.e., unsubstituted), or 1. When the number of the substituents is
5 not less than 2, the respective substituents may be the same or different.

[0127]

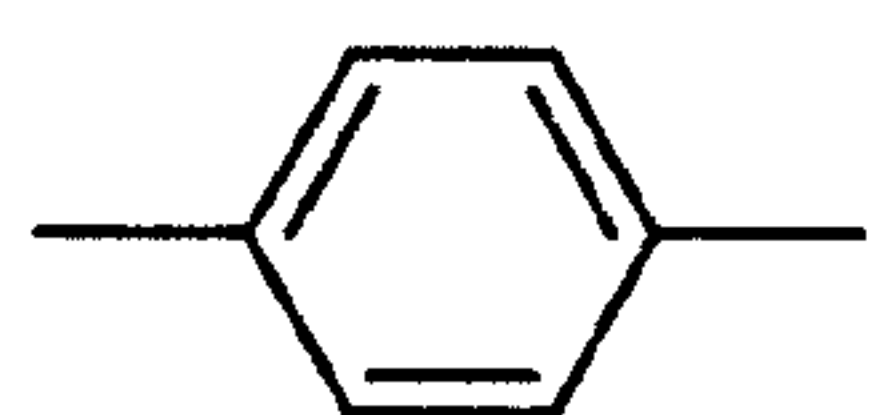
The cyclic moiety of the group represented by the formula:



(i.e., the moiety other than the substituent) is preferably



or the like, more preferably



15 [0128]

Examples of the substituent of the "benzene ring, pyridine ring, pyrimidine ring, pyrazine ring or pyridazine ring, each of which is optionally substituted" for ring B¹ include substituents selected from the above-mentioned
20 Substituent Group A.

Among them, a halogen atom, an optionally substituted alkyl group and the like are preferable,
a halogen atom, an optionally substituted C₁₋₆ alkyl group and the like are more preferably, and
25 a halogen atom (preferably a fluorine atom),
a C₁₋₆ alkyl group (preferably methyl) and the like are further more preferable.

[0129]

The number of the substituents of the "benzene ring, pyridine ring, pyrimidine ring, pyrazine ring or pyridazine ring, each of which is optionally substituted" for ring B¹ is preferably 0 (i.e., unsubstituted), or 1 to 3, more preferably 0 or 1. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

Ring B¹ is preferably an optionally substituted benzene ring, more preferably a benzene ring optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and an optionally substituted alkyl group [more preferably a halogen atom and an optionally substituted C₁₋₆ alkyl group, further more preferably a halogen atom (preferably a fluorine atom) and a C₁₋₆ alkyl group (preferably methyl), particularly preferably a halogen atom (preferably a fluorine atom)].

[0130]

The compound represented by the formula (I-1) or a salt thereof is preferably a compound wherein Z¹ is -N= and the others (i.e., Z², Z³, and Z⁴) are -CH=; or Z¹ and Z³ are -N= and the others (i.e., Z² and Z⁴) are -CH= [preferably Z¹ is -N= and the others (i.e., Z², Z³, and Z⁴) are -CH=];

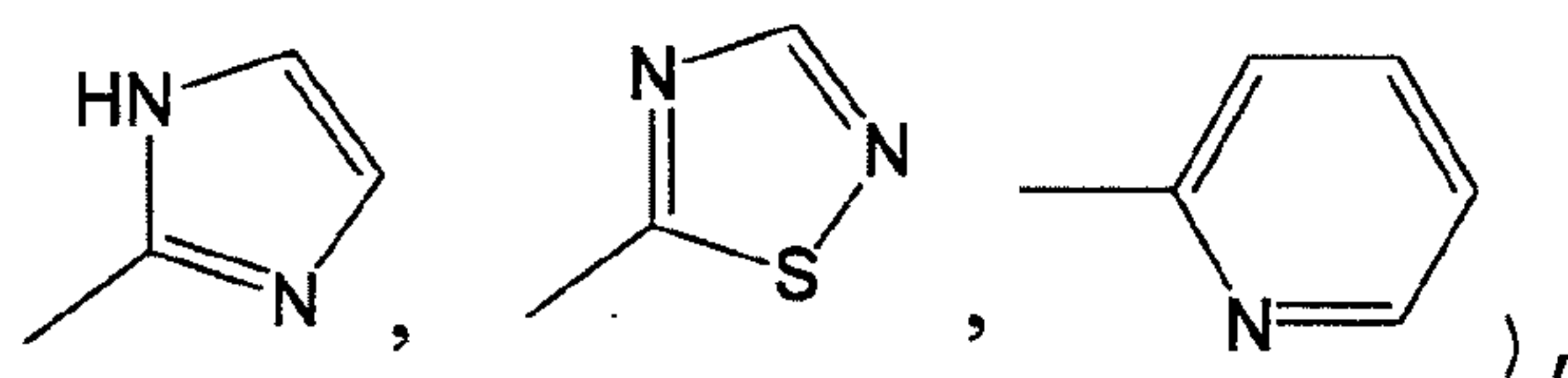
ring A is a pyridine ring or a pyrimidine ring, each of which is optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, cyano, an optionally substituted alkyl group and an optionally substituted alkoxy group [preferably a halogen atom, cyano, an optionally substituted C₁₋₆ alkyl group and an optionally substituted C₁₋₆ alkoxy group, further more preferably a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, a C₁₋₆ alkyl group (preferably methyl) optionally substituted by 1 to 3 substituents selected from the group consisting of (1) a halogen atom (preferably a fluorine atom), (2) hydroxyl, and (3) C₁₋₆ alkyl-carbonyl group (preferably acetoxy), and a C₁₋₆

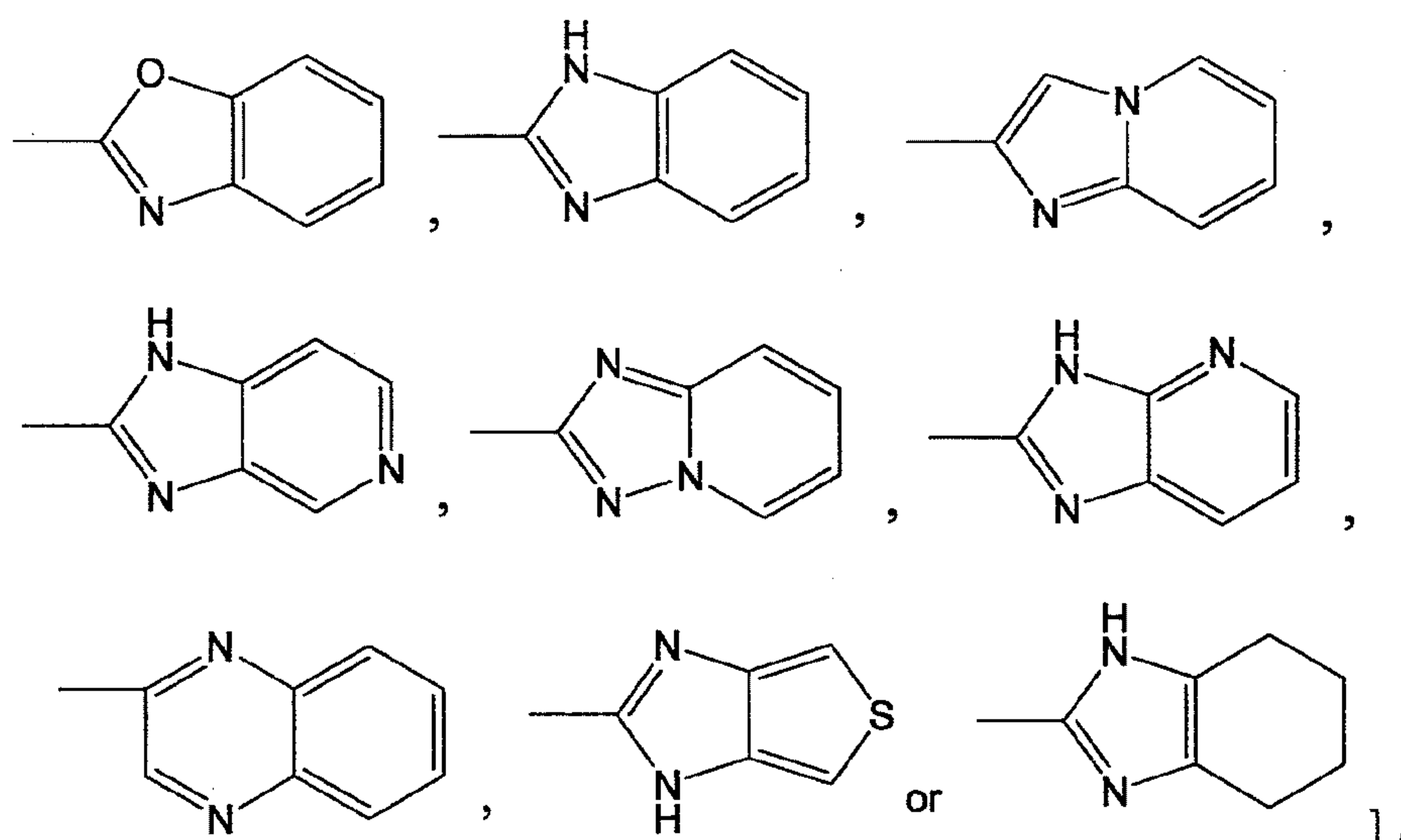
alkoxy group (preferably methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom)];

Y is an oxygen atom, an optionally substituted methylene group,
 5 or $-NR^c-$ wherein R^c is preferably a hydrogen atom, an optionally substituted alkyl group or an optionally substituted C_{3-7} cycloalkyl group {preferably an oxygen atom,

10 a methylene group optionally substituted by 1 or 2 C_{1-6} alkyl groups (preferably methyl) (the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C_{3-6} cycloalkane (preferably cyclobutane)), or $-NR^c-$ wherein R^c is preferably (i) a hydrogen atom, (ii) a C_{1-6}
 15 alkyl group (e.g., methyl, ethyl, propyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom (preferably a fluorine atom), a hydroxy group, a C_{3-7} cycloalkyl group (preferably cyclopropyl), an optionally substituted C_{1-6} alkoxy group (e.g.,
 20 methoxy, ethoxy, a trimethylsilyl- C_{1-6} alkoxy group (preferably trimethylsilyl-ethoxy)), and an C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl), or (iii) a C_{3-7} cycloalkyl group (preferably cyclopropyl));

R^1 is a phenyl group or a 5- to 10-membered heterocyclic group
 25 [preferably imidazolyl, pyridyl, thiadiazolyl (preferably the following group:

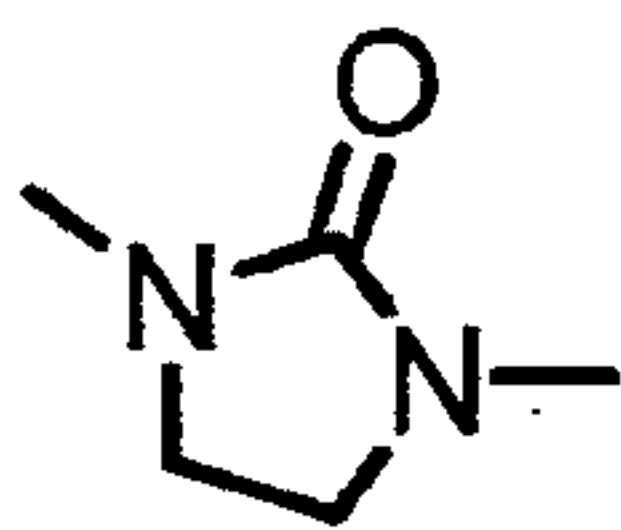




each of which is optionally substituted by 1 to 3 substituents selected from the group consisting of

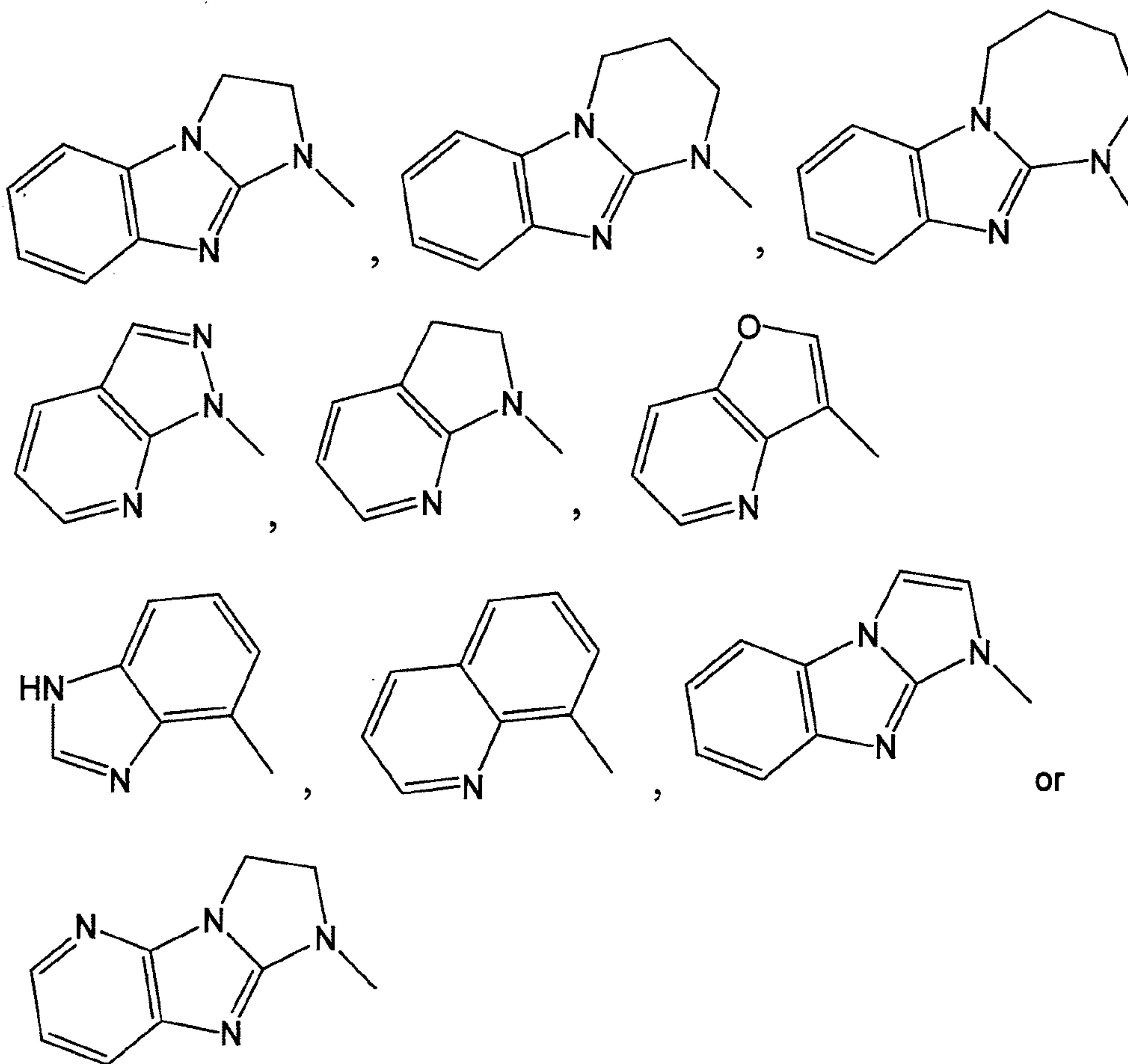
- (a) a halogen atom,
- 5 (b) an optionally esterified carboxy group,
- (c) an optionally substituted alkyl group,
- (d) an optionally substituted C₆₋₁₄ aryl group, and
- (e) an optionally substituted alkyl-carbonyl group [preferably
- 10 (a) a halogen atom (preferably fluorine, bromine, chlorine),
- (b) a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl),
- (c) a C₁₋₆ alkyl group (preferably methyl, ethyl, butyl, isobutyl) optionally substituted by one or more (preferably 1 to 3) substituents selected from the group consisting of
- 15 (i) a halogen atom (preferably fluorine),
- (ii) a hydroxy group, and
- (iii) an optionally substituted C₁₋₆ alkoxy group (e.g., a C₁₋₆ alkoxy group (preferably ethoxy) optionally substituted by trimethylsilyl),
- 20 (d) a C₆₋₁₄ aryl group (preferably phenyl), and
- (e) a C₁₋₆ alkyl-carbonyl group (preferably acetyl)];

L is an oxygen atom (-O-), -CO-, -NR^a-, -NR^aCOO- wherein R^a is preferably a hydrogen atom or a C₁₋₆ alkyl group (preferably methyl), or



[preferably an oxygen atom, or $-NR^a-$ wherein R^a is a hydrogen atom or a C_{1-6} alkyl group (preferably methyl)]; or
 L and R^1 in combination optionally form a bi- or tri-cyclic
 5 fused heterocyclic group optionally substituted by 1 to 3
 substituents selected from the group consisting of

- (a) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl),
- (b) a C_{1-6} alkyl group (preferably methyl) optionally
 substituted by C_{6-14} aryl group(s) (preferably phenyl), and
- 10 (c) an oxo group
 (preferably



); and

ring B^1 is preferably an optionally substituted benzene ring,
 15 more preferably a benzene ring optionally substituted by 1 to
 3 substituents selected from the group consisting of a halogen

atom and an optionally substituted alkyl group [preferably a halogen atom and an optionally substituted C₁₋₆ alkyl group, more preferably a halogen atom (preferably a fluorine atom) and a C₁₋₆ alkyl group (preferably methyl)],
5 or a salt thereof.

[0131]

In another embodiment, the compound represented by the formula (I-1) or a salt thereof is preferably a compound wherein

10 Z¹ is -N=,
Z², Z³ and Z⁴ are -CH=,
Y is -NR^c- or a di-C₁₋₆ alkylmethylene group,
R^c is a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen
15 atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a trimethylsilyl-C₁₋₆ alkoxy group and a C₁₋₆ alkoxy-carbonyl group,
R¹ is a 5- to 10-membered heterocyclic group optionally substituted by 1 to 3 substituents selected from

- (a) a halogen atom,
- 20 (b) a C₁₋₆ alkoxy-carbonyl group,
- (c) a C₁₋₆ alkyl group optionally substituted by one or more (preferably 1 to 3) substituents selected from the group consisting of
 - (i) a hydroxy group, and
 - 25 (ii) an optionally substituted C₁₋₆ alkoxy group (e.g., a C₁₋₆ alkoxy group optionally substituted by trimethylsilyl), and
- (d) a C₁₋₆ alkyl-carbonyl group;

L is an oxygen atom, or -NR^a- wherein R^a is a hydrogen atom or
30 a C₁₋₆ alkyl group, or

L and R¹ in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by 1 to 3 substituents selected from the group consisting of

- (a) a halogen atom,
- 35 (b) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl

group(s), and

(c) an oxo group, and

ring B¹ is a benzene ring,
or a salt thereof.

5 [0132]

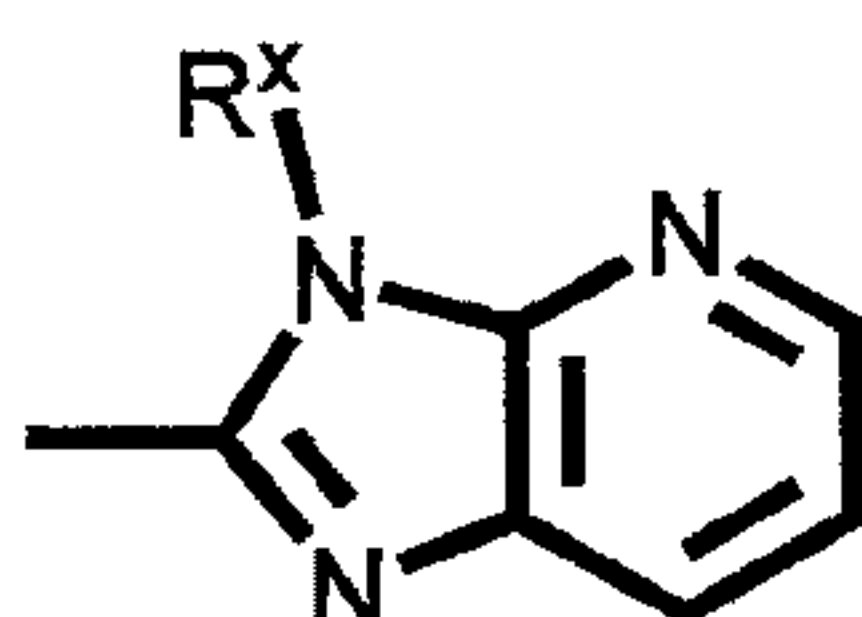
The compound represented by the formula (I-1) or a salt thereof is more preferably a compound wherein

Z¹ is -N=,

Z², Z³ and Z⁴ are -CH=,

10 Y is -NR^c- wherein R^c is a C₁₋₆ alkyl group, or a di-C₁₋₆ alkylmethylene group,

R¹ is

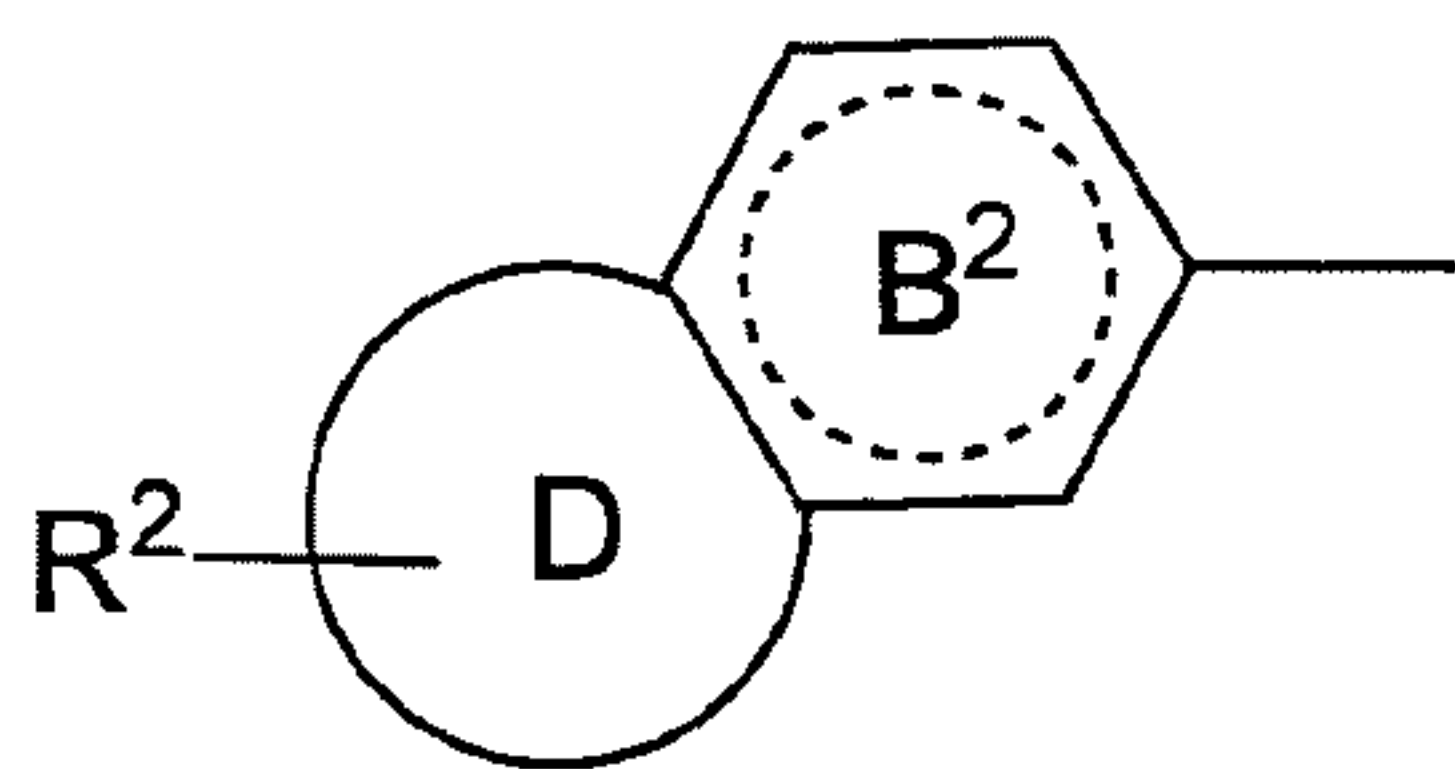


wherein R^x is a hydrogen atom or a C₁₋₆ alkyl group,

15 L is an oxygen atom, and
ring B¹ is a benzene ring,
or a salt thereof.

[0133]

In the partial structure of the formula (I-2):



20

R² is a phenyl group or a 5- to 10-membered heterocyclic group,
each of which is optionally substituted,

ring B² is a benzene ring, a pyridine ring, a pyrimidine ring,
a pyrazine ring or a pyridazine ring, each of which is

25 optionally substituted, and

ring D is an optionally further substituted 5- or 6-membered
ring.

[0134]

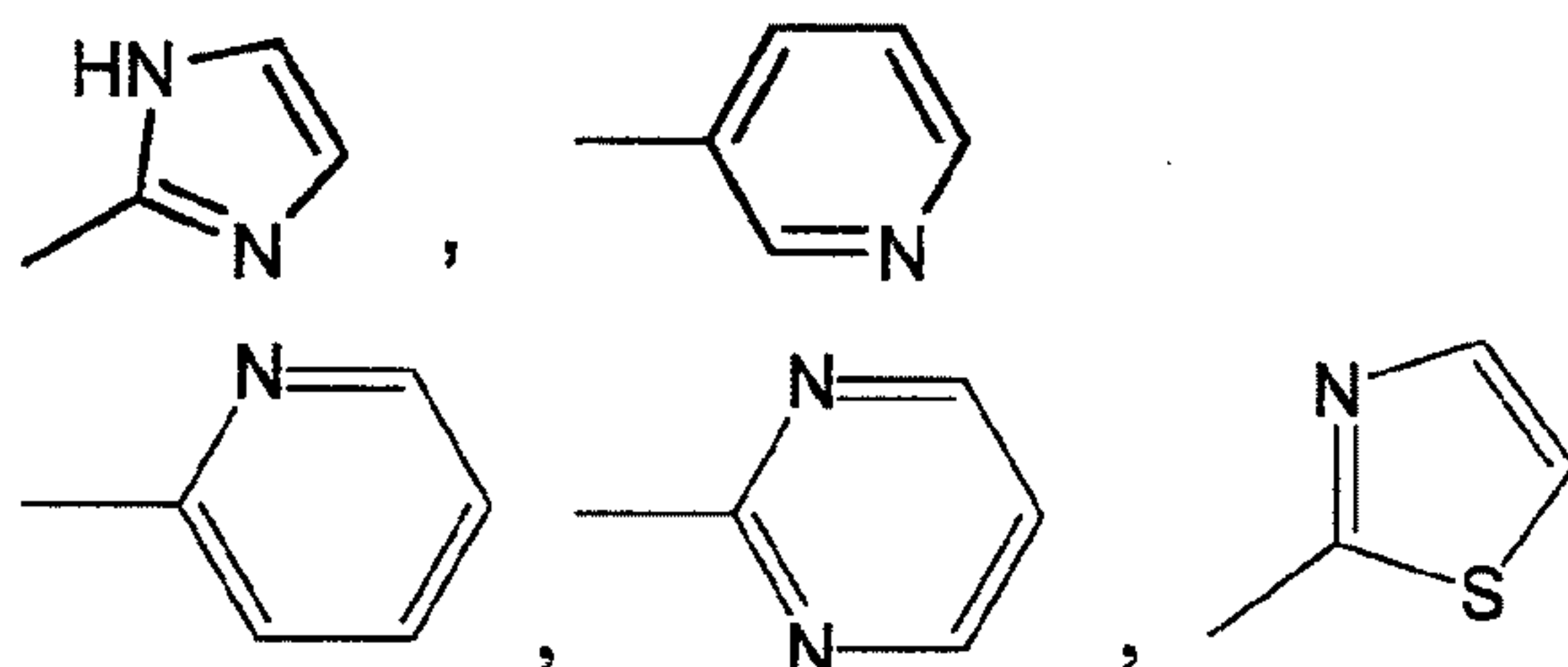
Examples of the "5- to 10-membered heterocyclic group" of

the "phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted" for R² include those similar to the "5- to 10-membered heterocyclic group" of the "optionally substituted 5- to 10-membered heterocyclic group" for R¹.

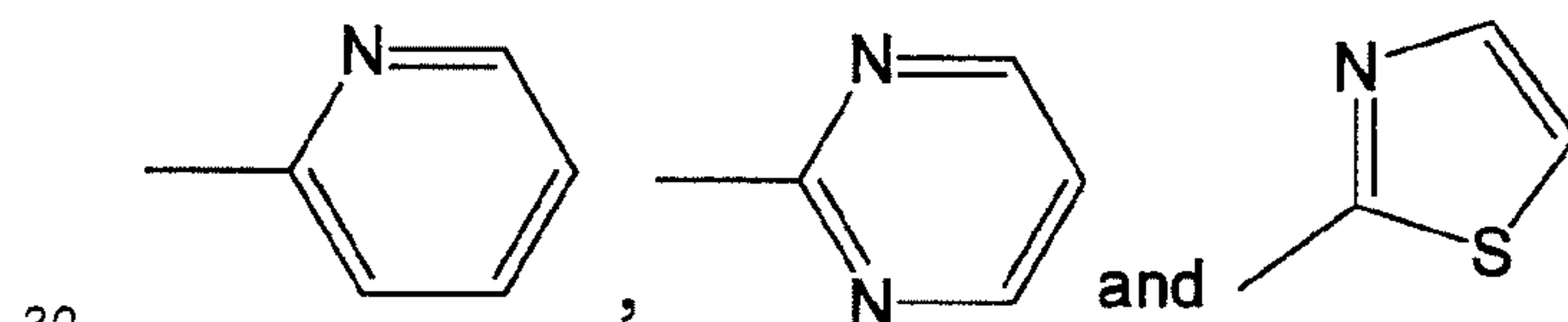
Among them, a 5- or 6-membered monocyclic heterocyclic group, a bicyclic fused heterocyclic group (preferably a 9- or 10-membered bicyclic fused heterocyclic group) and the like are preferable.

10 [0135]

The "5- or 6-membered monocyclic heterocyclic group" is preferably, for example, a 5- or 6-membered monocyclic nitrogen-containing aromatic heterocyclic group such as imidazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, 15 thiazolyl and the like, (preferably pyridyl, pyrimidinyl, thiazolyl etc.). Among them, the following group:



and the like are preferable, and the following group:

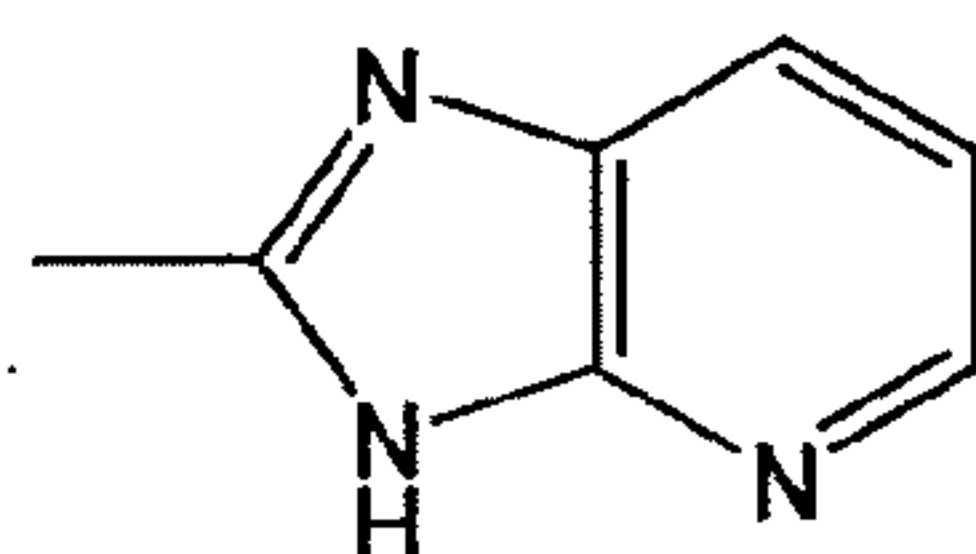
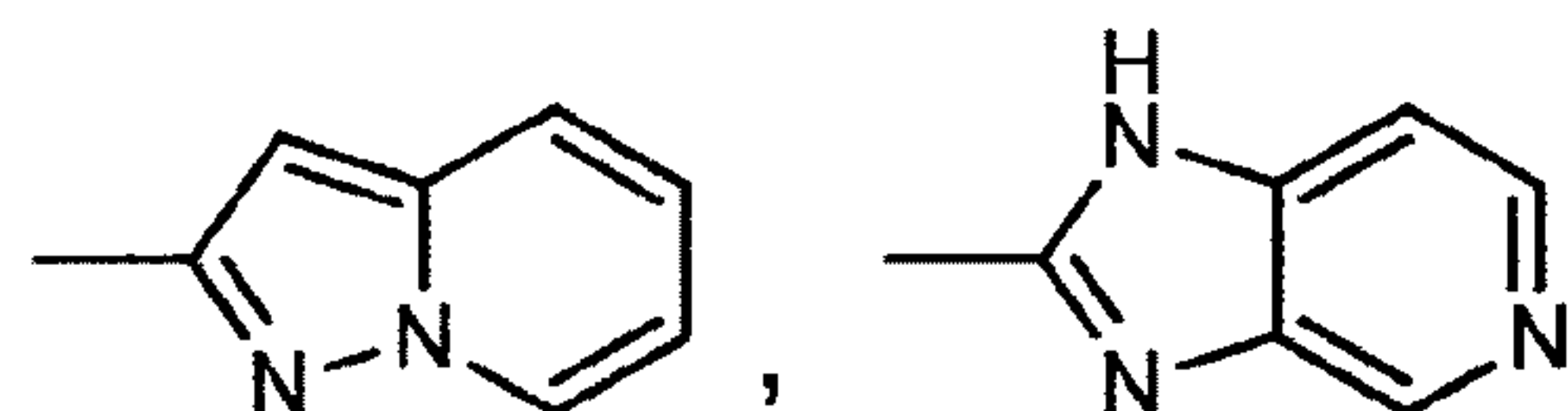
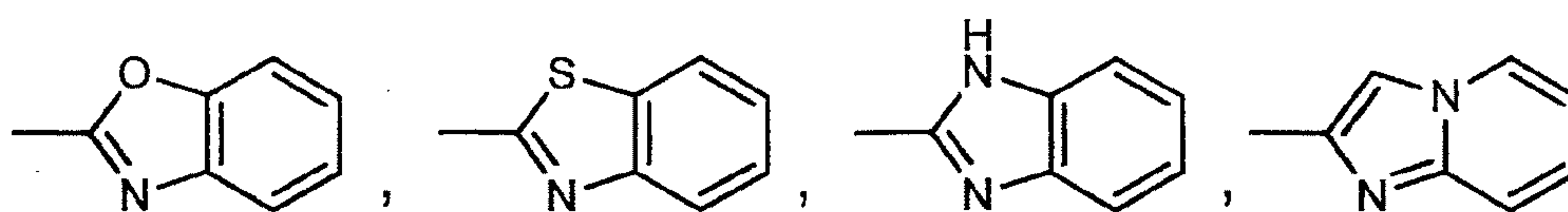


20

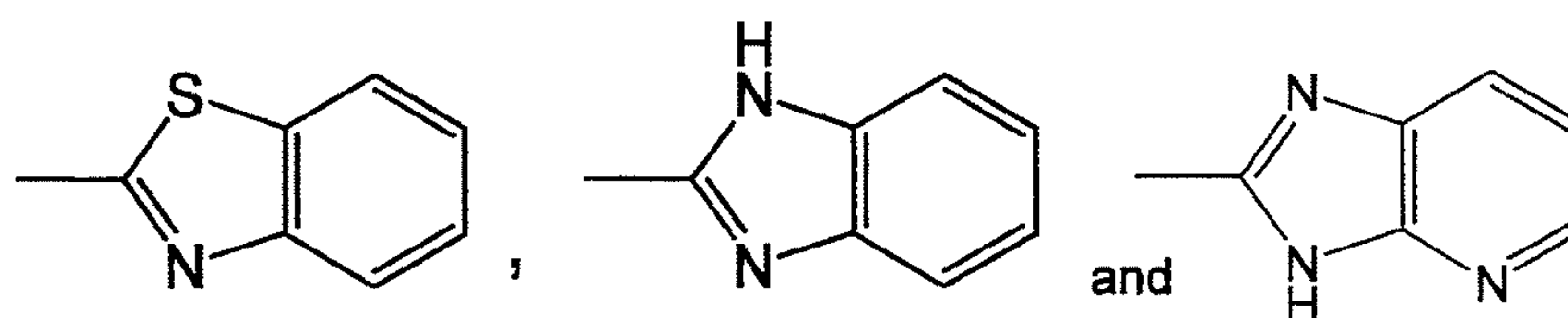
are more preferable.

[0136]

Examples of the aforementioned "bicyclic fused heterocyclic group" include (1) a fused heterocyclic group formed by condensation of a phenyl group with a 5- or 6-membered heterocycle, (2) a fused heterocyclic group formed by condensation of a 5- or 6-membered heterocyclic group with a benzene ring, and (3) a fused heterocyclic group formed by condensation of a 5- or 6-membered heterocyclic group with a 30 5- or 6-membered heterocycle. Among them, the following group:



and the like are preferable, and the following group:



5 are more preferable.

[0137]

Examples of the substituent of the "phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted" for R^2 include substituents selected from the
10 above-mentioned Substituent Group A.

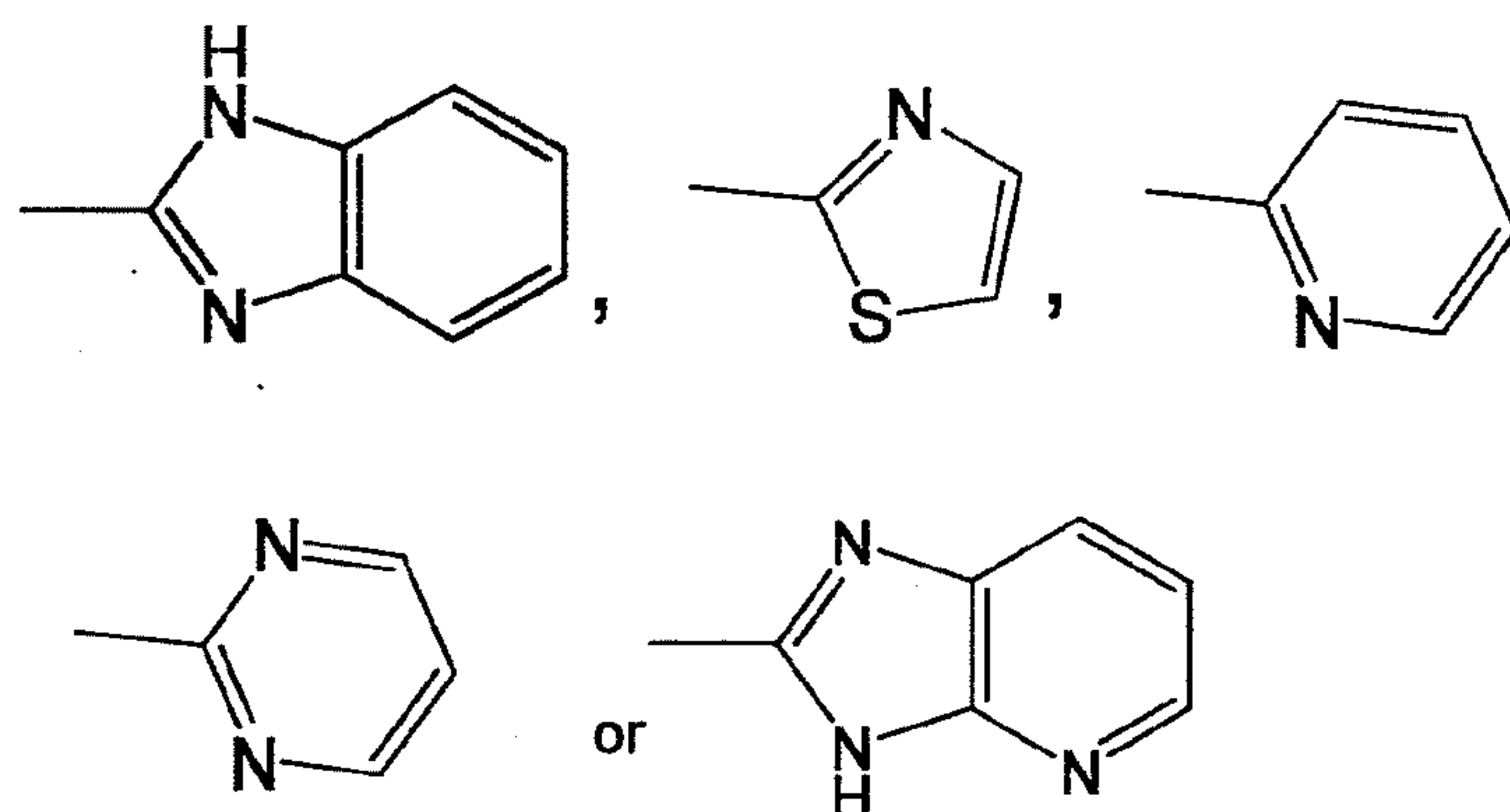
Among them, an optionally substituted alkyl group and the like are preferable, a C_{1-6} alkyl group and the like are more preferable, and methyl is further more preferable.

[0138]

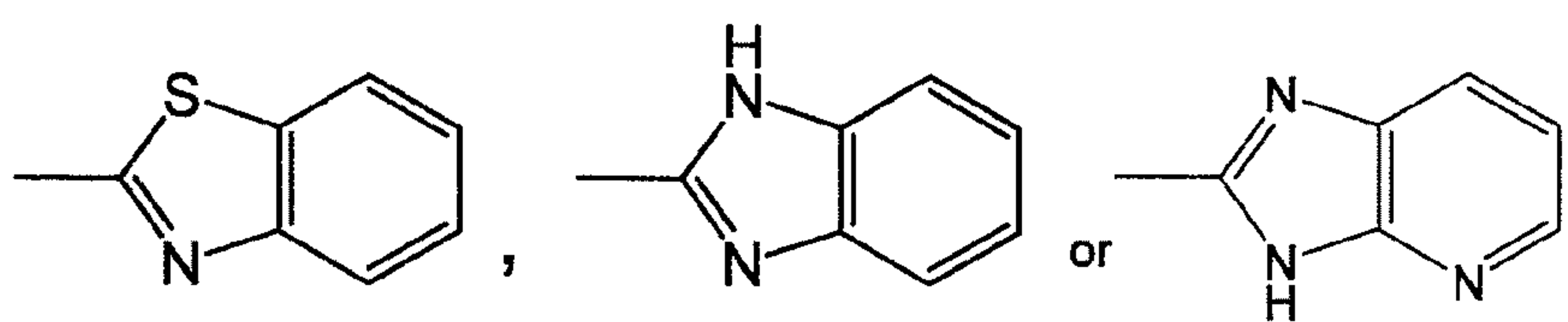
15 The number of the substituents of the "phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted" for R^2 is preferably 0 (i.e., unsubstituted), or 1 to 3, more preferably 0 or 1. When the number of the substituents is not less than 2, the respective substituents
20 may be the same or different.

[0139]

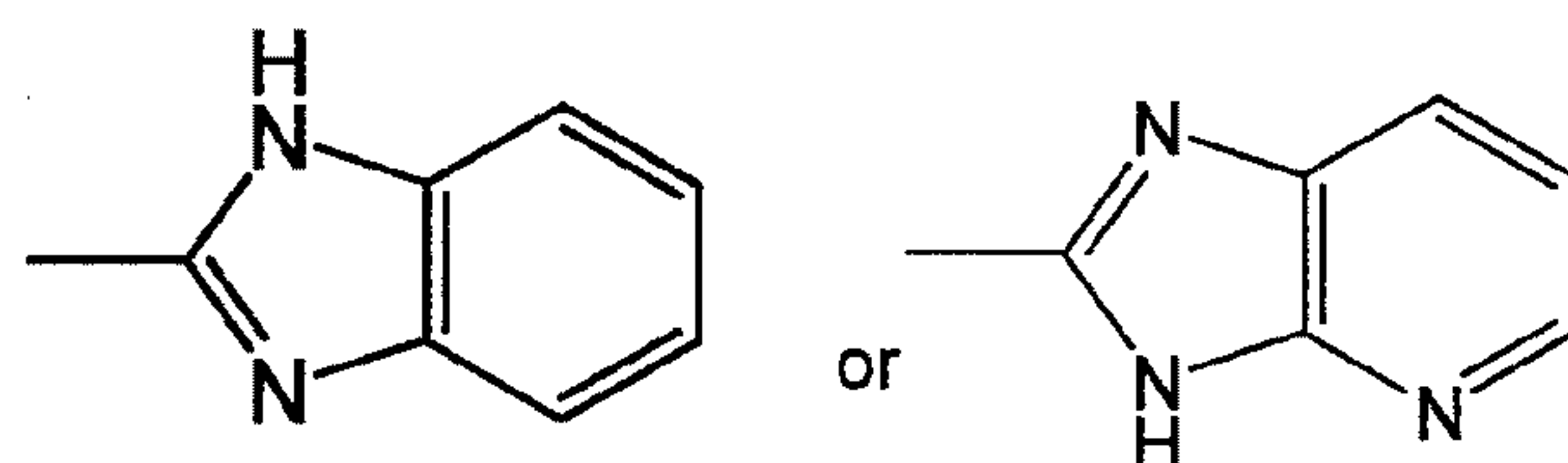
R^2 is preferably a 5- to 10-membered heterocyclic group (preferably the following group:



more preferably the following group:



further more preferably the following group:



5

),

optionally substituted by 1 to 3 (preferably 1) substituents selected from an optionally substituted alkyl group (preferably a C₁₋₆ alkyl group, more preferably methyl).

[0140]

10 Examples of the substituent of the "benzene ring, pyridine ring, pyrimidine ring, pyrazine ring or pyridazine ring, each of which is optionally substituted" for ring B² include substituents selected from the above-mentioned Substituent Group A.

15 The number of the substituents is preferably 0 (i.e., unsubstituted), or 1 to 3, more preferably 0. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

Ring B² is preferably an optionally substituted benzene
20 ring, more preferably a benzene ring.

[0141]

The "5- or 6-membered ring" of the "optionally further substituted 5- or 6-membered ring" for ring D is a carbocycle having 5 or 6 carbon atoms (e.g., benzene) or a 5- or 6-membered heterocycle (e.g., pyrrolidine, dihydropyrrole, dihydropyrazole).

Among them, a pyrrolidine ring, a dihydropyrrole ring and a dihydropyrazole ring are preferable, and a pyrrolidine ring is more preferable.

10 [0142]

Examples of the substituent of the "optionally further substituted 5- or 6-membered ring" for ring D include substituents selected from the above-mentioned Substituent Group A.

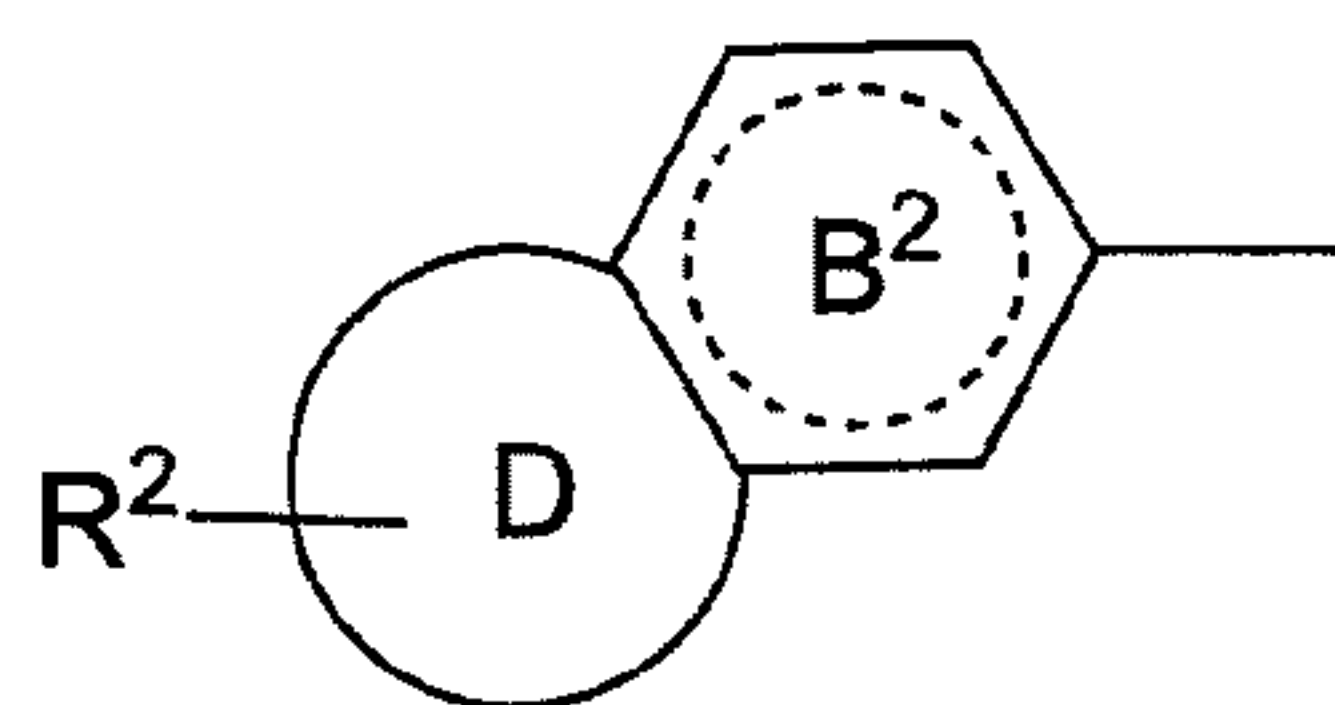
15 Among them, an optionally substituted alkyl group and the like are preferable, a C₁₋₆ alkyl group and the like are more preferable, and methyl is further more preferable.

The number of the substituents of the "optionally further substituted 5- or 6-membered ring" for ring D is preferably 0 (i.e., unsubstituted), or 1 to 3, more preferably 0 or 1, more preferably 0. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

Ring D is preferably a pyrrolidine ring, a dihydropyrrole ring or a dihydropyrazole ring, each of which is optionally substituted, more preferably a pyrrolidine ring, a dihydropyrrole ring or a dihydropyrazole ring.

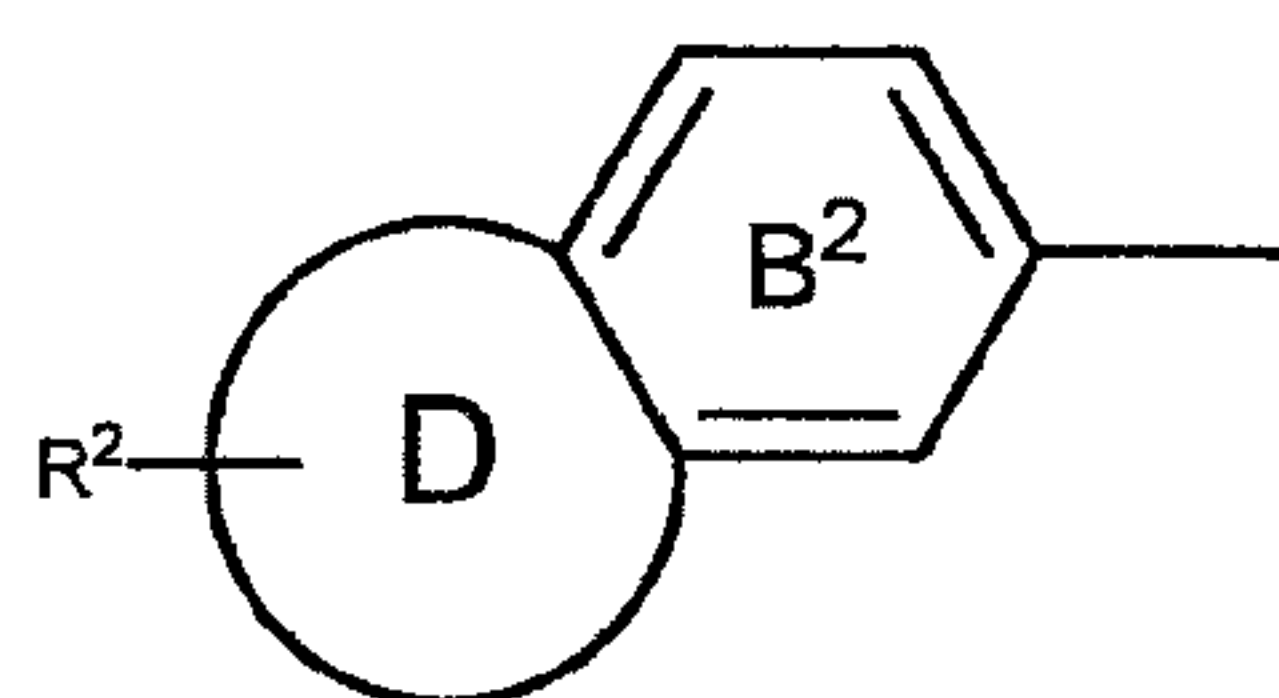
[0143]

The partial structure of the formula (I-2):



30

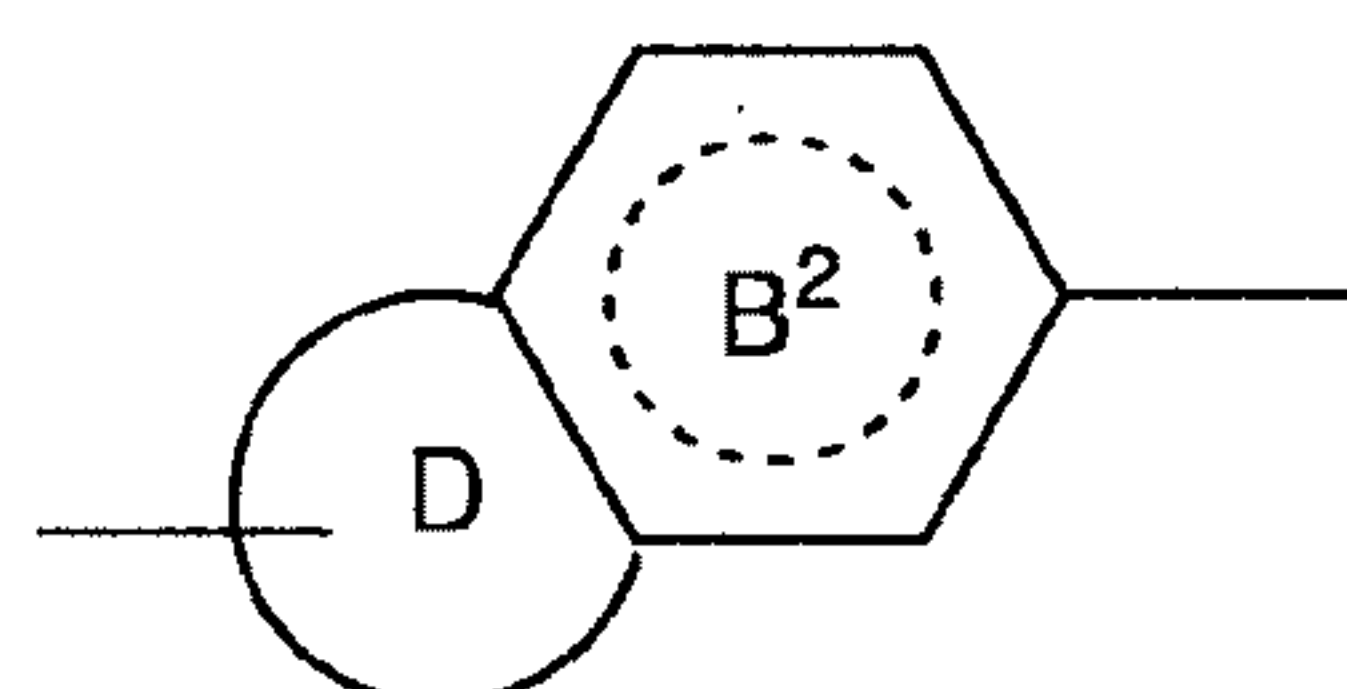
is preferably a structure represented by the formula:



wherein each symbol is as defined above.

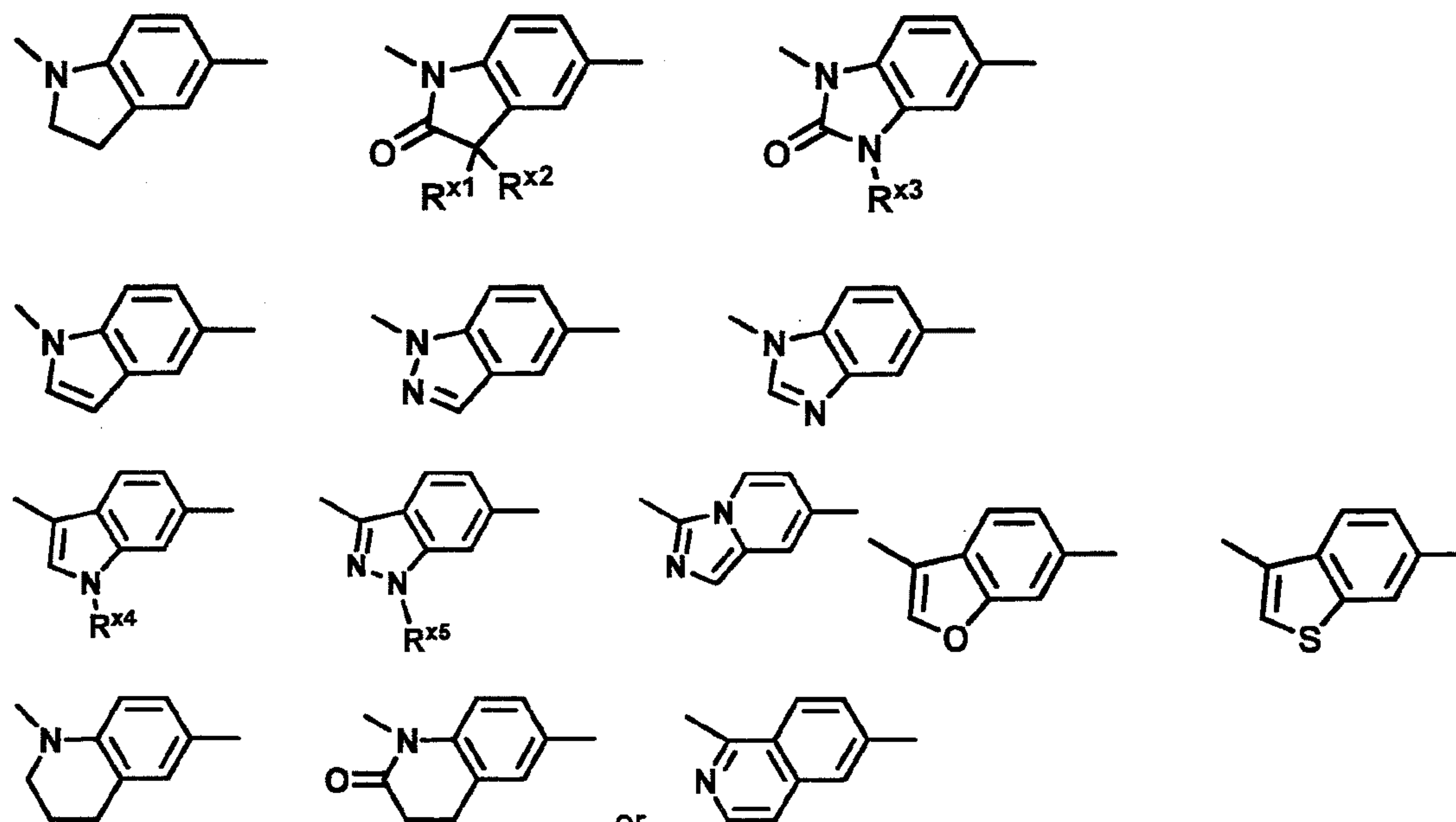
[0144]

The partial structure of the formula (I-2):



5

is preferably



10

wherein

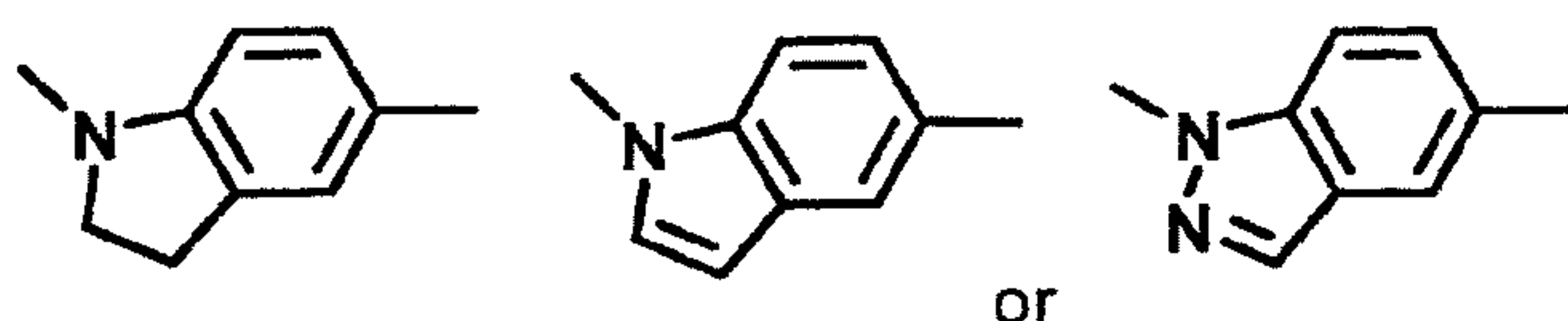
R^{x1} and R^{x2} are the same or different and each is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,

R^{x3} - R^{x5} are each a hydrogen atom or an optionally substituted C_{1-6} alkyl group, and

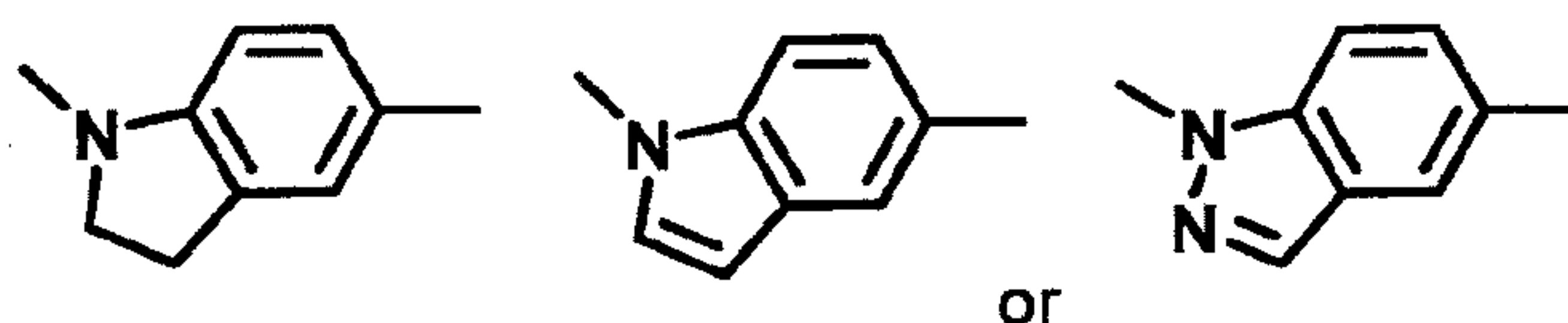
15

the ring-constituting atom(s) optionally further have substituent(s),

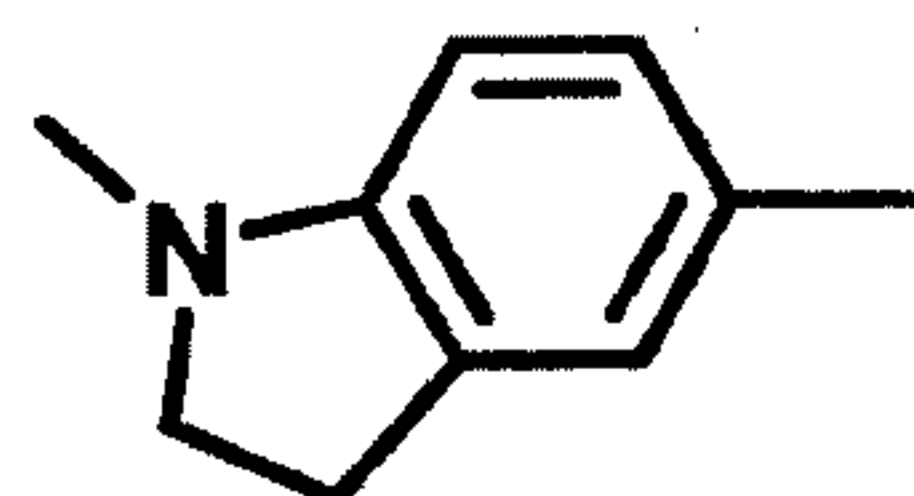
and the like, more preferably



wherein the ring-constituting atom(s) optionally further have substituent(s), further more preferably



5 particularly preferably



Examples of the "optionally substituted C₁₋₆ alkyl group" for R^{x1} or R^{x2} include those similar to the "optionally substituted C₁₋₆ alkyl group" exemplified as the substituent for ring D.

Examples of the "optionally substituted C₁₋₆ alkyl group" for R^{x3} - R^{x5} include those similar to the "optionally substituted C₁₋₆ alkyl group" exemplified as the substituent for ring D.

Examples of the substituent that the aforementioned ring-constituting atom(s) optionally further have include those similar to exemplified as the substituent for ring B² or ring D. [0145]

20 The compound represented by the formula (I-2) or a salt thereof is preferably a compound wherein Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=; or Z¹ and Z³ are -N= and the others (i.e., Z² and Z⁴) are -CH= [preferably Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=];

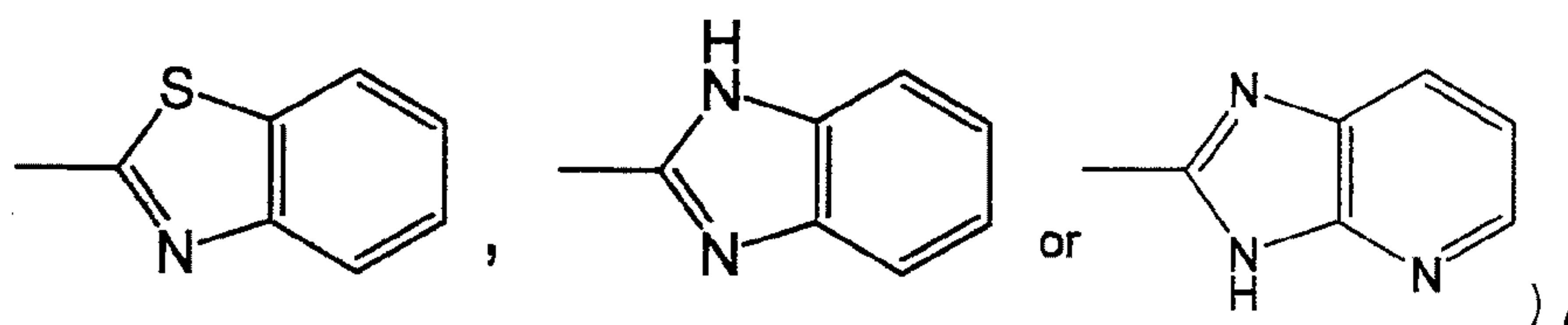
ring A is a pyridine ring or a pyrimidine ring, each of which is optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, cyano, an optionally substituted alkyl group and an optionally substituted alkoxy

group [preferably a halogen atom, cyano, optionally substituted C₁₋₆ alkyl and optionally substituted C₁₋₆ alkoxy, more preferably a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, C₁₋₆ alkyl (preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom), and C₁₋₆ alkoxy (preferably methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom)];

Y is an oxygen atom, an optionally substituted methylene group, or -NR^c- wherein R^c is preferably a hydrogen atom, an optionally substituted alkyl group or an optionally substituted C₃₋₇ cycloalkyl group

{preferably an oxygen atom, a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl group(s) (preferably methyl) (the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane (preferably cyclobutane)), or -NR^c- wherein R^c is preferably (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group (preferably methyl, ethyl, propyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom (preferably a fluorine atom), a hydroxy group, a C₃₋₇ cycloalkyl group (preferably cyclopropyl), an optionally substituted C₁₋₆ alkoxy group (e.g., a trimethylsilyl-C₁₋₆ alkoxy group (preferably trimethylsilyl-ethoxy)), and a C₁₋₆ alkoxy-carbonyl group (preferably ethoxycarbonyl), or (iii) a C₃₋₇ cycloalkyl group (preferably cyclopropyl)};

R² is a 5- to 10-membered heterocyclic group (preferably the following group:



optionally substituted by 1 to 3 (preferably 1) substituents selected from an optionally substituted alkyl group (preferably a C₁₋₆ alkyl group, more preferably methyl);

ring B² is an optionally substituted benzene ring (preferably a benzene ring); and

ring D is a pyrrolidine ring, a dihydropyrrole ring or a dihydropyrazole ring, each of which is optionally substituted
 5 (preferably a pyrrolidine ring, a dihydropyrrole ring or a dihydropyrazole ring),
 or a salt thereof.

[0146]

The compound represented by the formula (I) or a salt
 10 thereof is preferably a compound (W-1) wherein
 Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=; or Z¹
 and Z³ are -N= and the other (i.e., Z² and Z⁴) are -CH=;
 wherein the nitrogen atom of -N= for Z¹ may be oxidized;
 ring A is

15 (1) a pyridine ring which is optionally substituted by one
 substituent selected from (i) a C₁₋₆ alkyl group optionally
 substituted by 1 to 3 substituents selected from a halogen
 atom, hydroxy and a C₁₋₆ alkyl-carbonyloxy (preferably methyl,
 trifluoromethyl, acetoxymethyl, hydoroxyethyl), (ii) a
 20 halogen atom (preferably chlorine, fluorine), (iii) cyano, and
 (iv) a C₁₋₄ alkoxy optionally substituted by 1 to 3 halogen
 atoms (preferably methoxy, difluoromethoxy, difluoroethoxy,
 trifluoroethoxy), or
 (2) a pyrimidine ring,

25 Y is a oxygen atom, a methylene group which is optionally
 substituted by 1 to 2 C₁₋₆ alkyl group(s) (preferably
 methyl) (the two substituents for the methylene group
 optionally form, together with the adjacent carbon atom, a C₃₋₆
 cycloalkane (preferably cyclobutane)), or -NR^c- wherein R^c is
 30 (1) a hydrogen atom, (2) a C₁₋₆ alkyl group which is optionally
 substituted by 1 to 3 (preferably 1 or 2) substituents
 selected from the group consisting of (i) a C₁₋₆ alkoxy group
 optionally substituted by trimethylsilyl, and (ii) a halogen
 atom (preferably methyl, ethyl, propyl, isopropyl,
 35 trimethylsilyl-ethoxy-methyl, difluoromethyl), or (3) a C₃₋₇

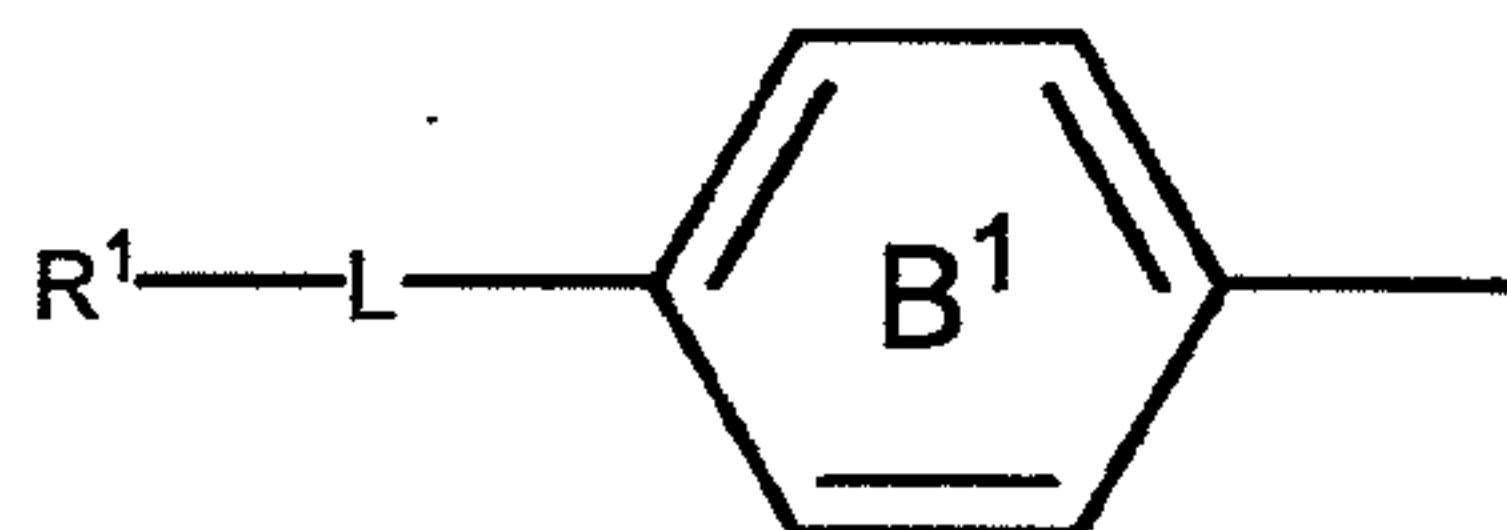
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cycloalkyl (preferably cyclopropyl),

R is

(1) a group represented by the formula:

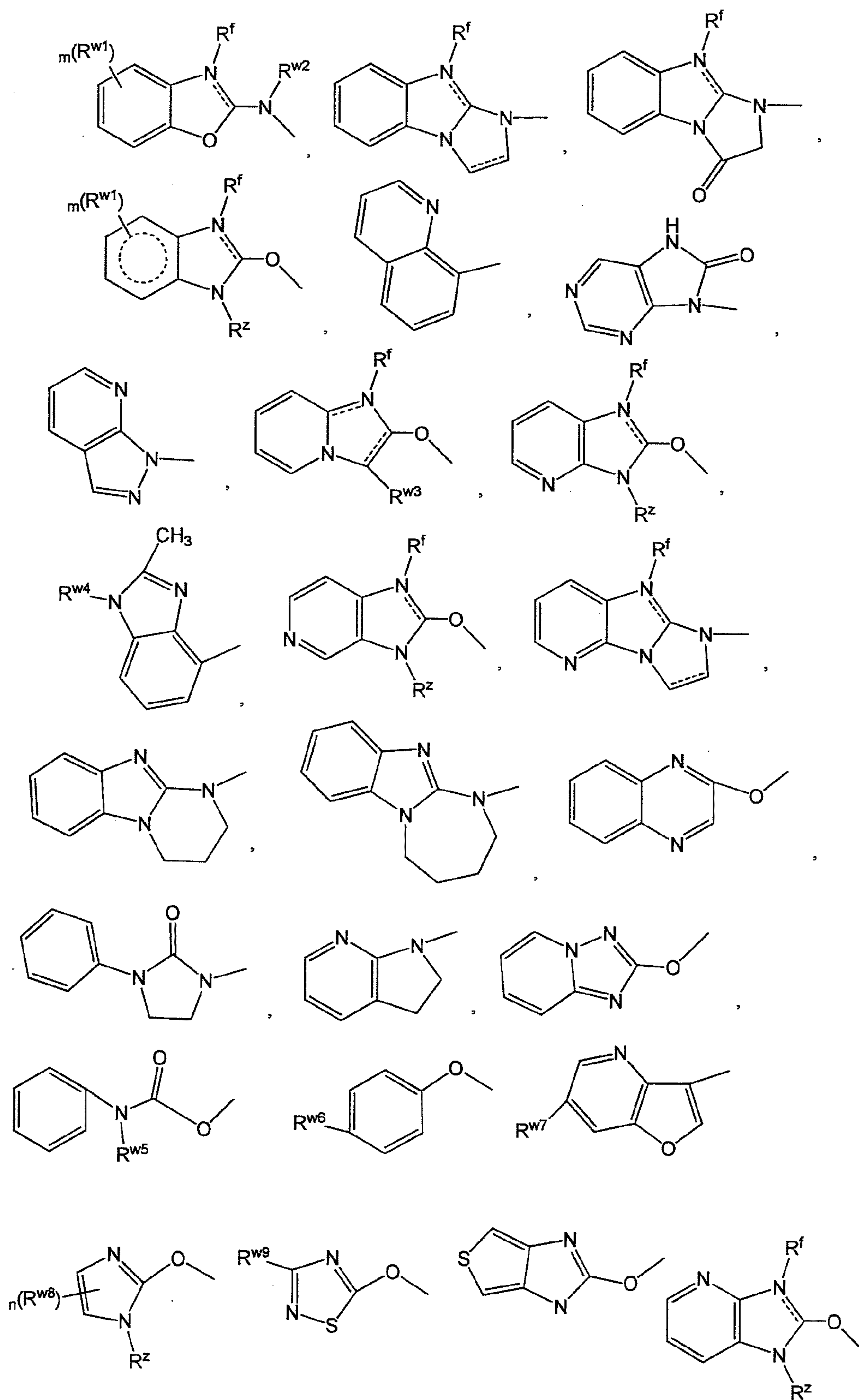


5 wherein

the partial structure:



is a group represented by the following formula:



wherein

R^f is absent or a hydrogen atom (when R^f is absent, $-N(R^f)-$

is =N-; R^f is preferably absent);

R^2 is (i) a hydrogen atom, (ii) a C_{1-4} alkyl group optionally substituted by one substituent selected from (1) a hydroxy group (preferably methyl, ethyl, hydroxyethyl, buthyl, hydroxyisobutyl) and (2) a C_{1-4} alkoxy group optionally substituted by trimethylsilyl (preferably trimethylsilylmethoxy), or (iii) a C_{1-6} alkyl-carbonyl group (preferably acetyl);

R^{w1} is a halogen atom (preferably fluorine);

10 m is 0 to 2;

R^{w2} is a hydrogen atom or a methyl group;

R^{w3} is a hydrogen atom or a C_{1-2} alkoxy-carbonyl group (preferably ethoxycarbonyl);

R^{w4} is a hydrogen atom or benzyl;

15 R^{w5} is a hydrogen atom or methyl;

R^{w6} is a hydrogen atom, a halogen atom (preferably fluorine, chlorine), or a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms (preferably trifluoromethyl);

20 R^{w7} is a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl);

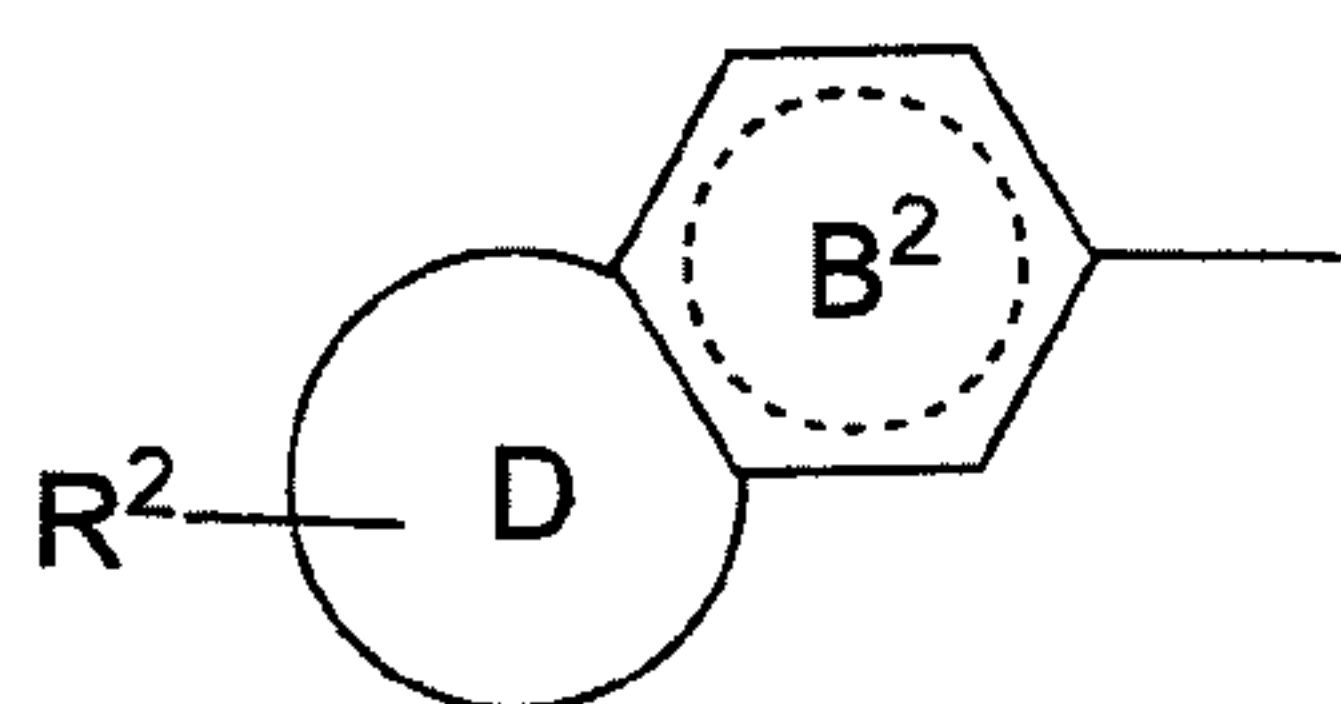
R^{w8} is a halogen atom (preferably chlorine, bromine), or a C_{1-6} alkyl optionally substituted by 1 to 3 halogen atoms (preferably trifluoromethyl);

n is 0 to 2; and

25 R^{w9} is a hydrogen atom or a halogen atom (preferably bromine); and

ring B^1 is a benzene ring optionally substituted by one halogen atom (preferably fluorine); or

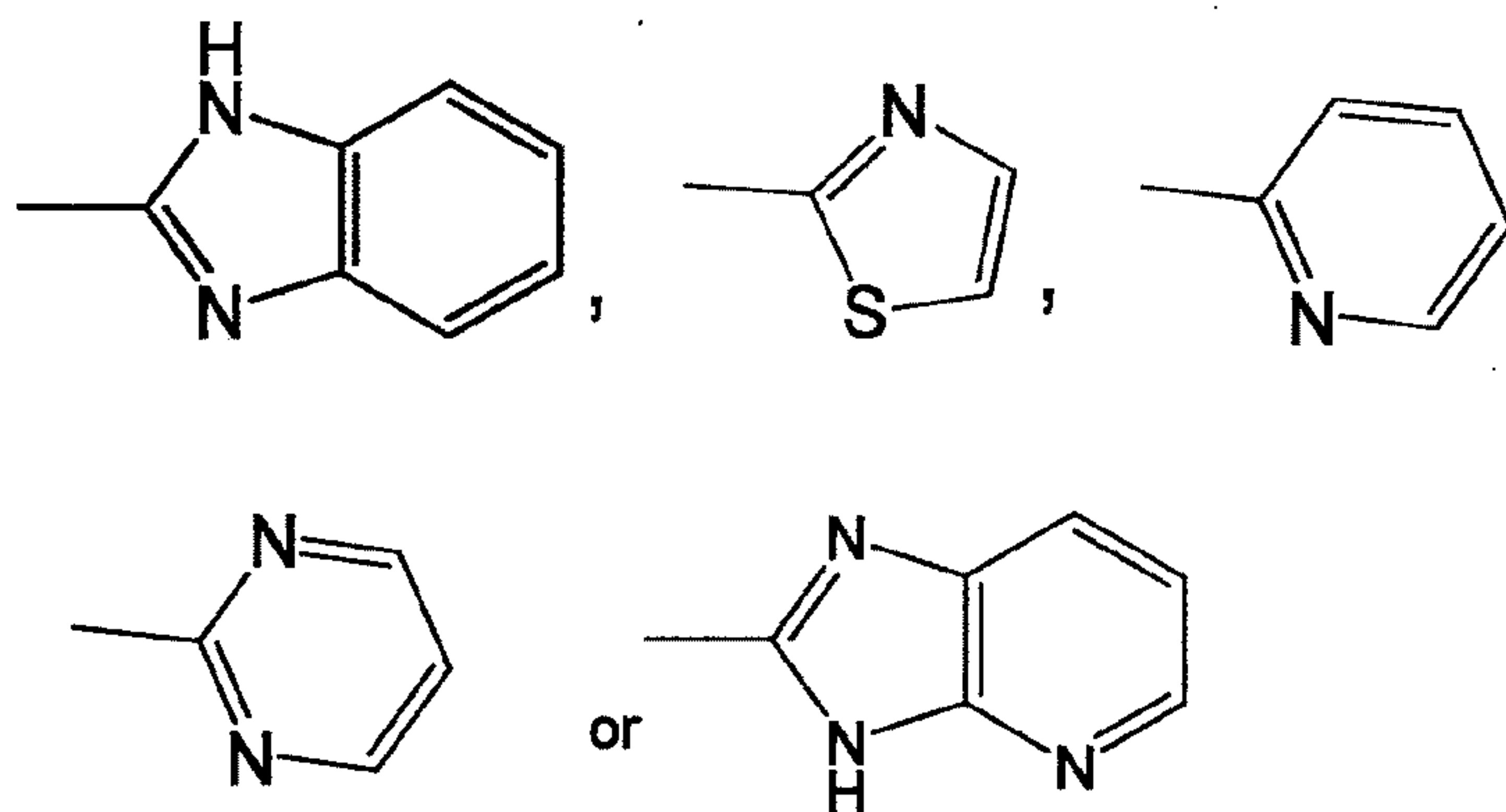
(2) a group represented by the formula:



wherein

R^2 is a 5- to 10-membered heterocyclic group (preferably the

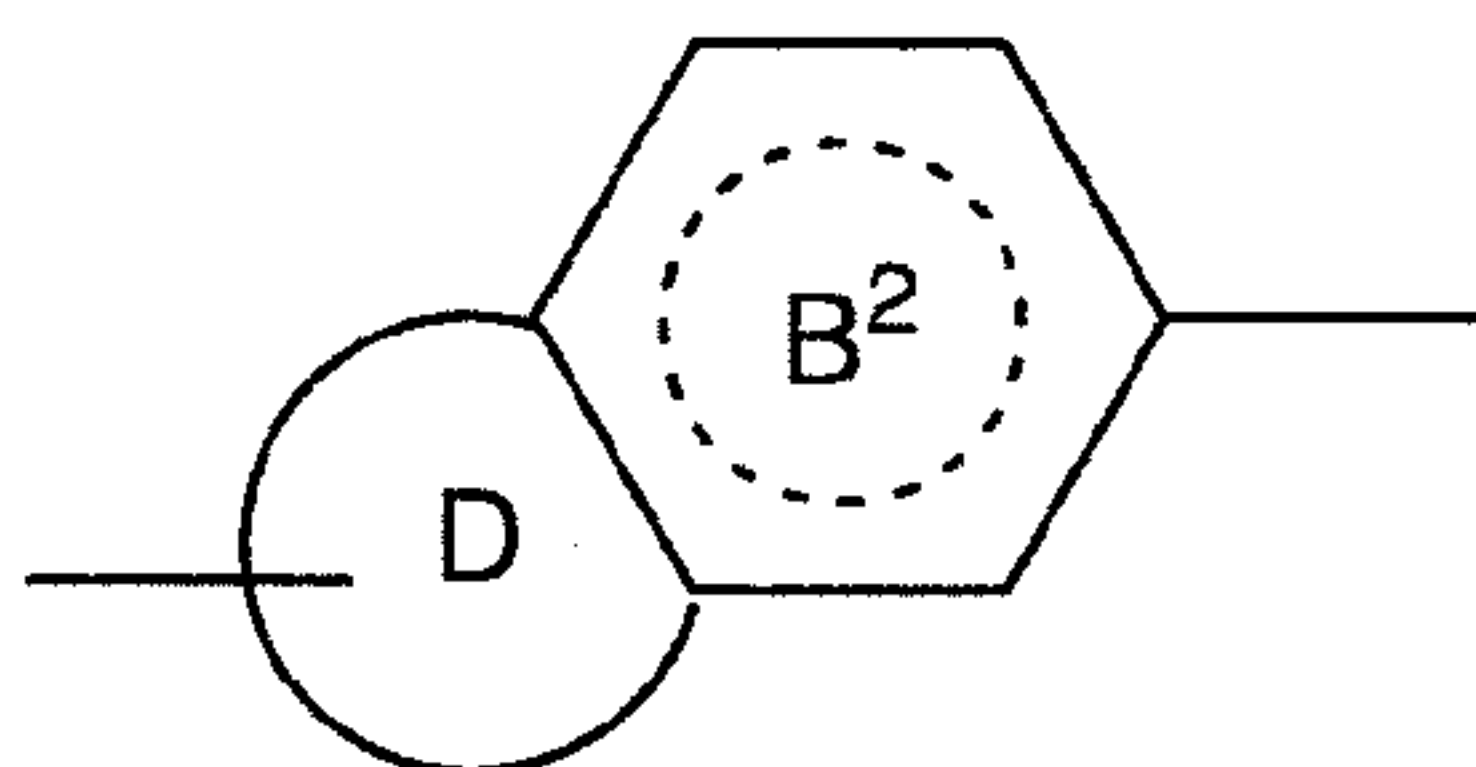
following group:



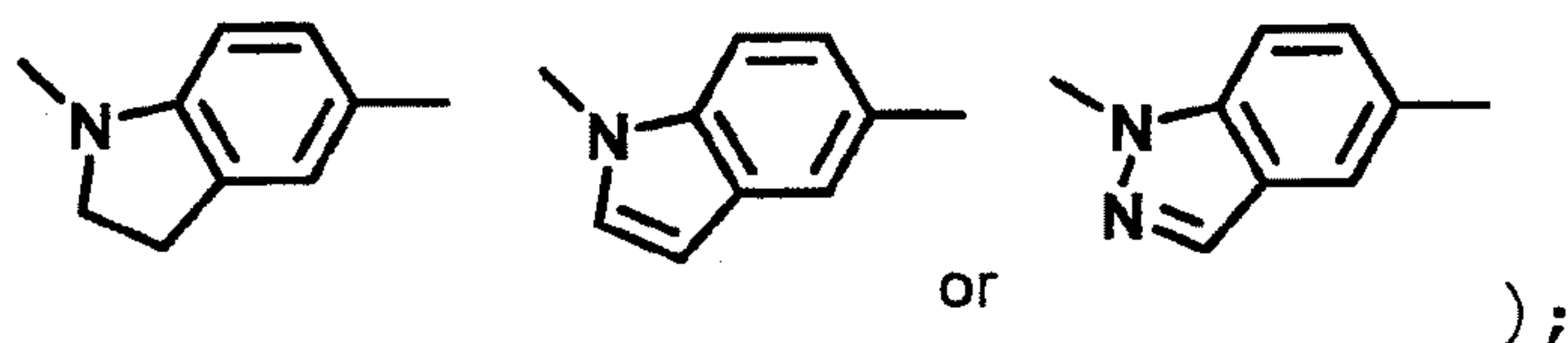
),

optionally substituted by one C₁₋₆ alkyl group (preferably methyl);

- 5 ring B² is a benzene ring; and
 ring D is a pyrrolidine ring, a dihydropyrrole ring, a dihydropirazole ring, (i.e., the partial structure of the formula:



10 is



or a salt thereof.

[0147]

In another embodiment, the compound represented by the
 15 formula (I) or a salt thereof is preferably a compound (W-2) wherein

Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=; or Z¹ and Z³ are -N= and the other (i.e., Z² and Z⁴) are -CH=;
 ring A is

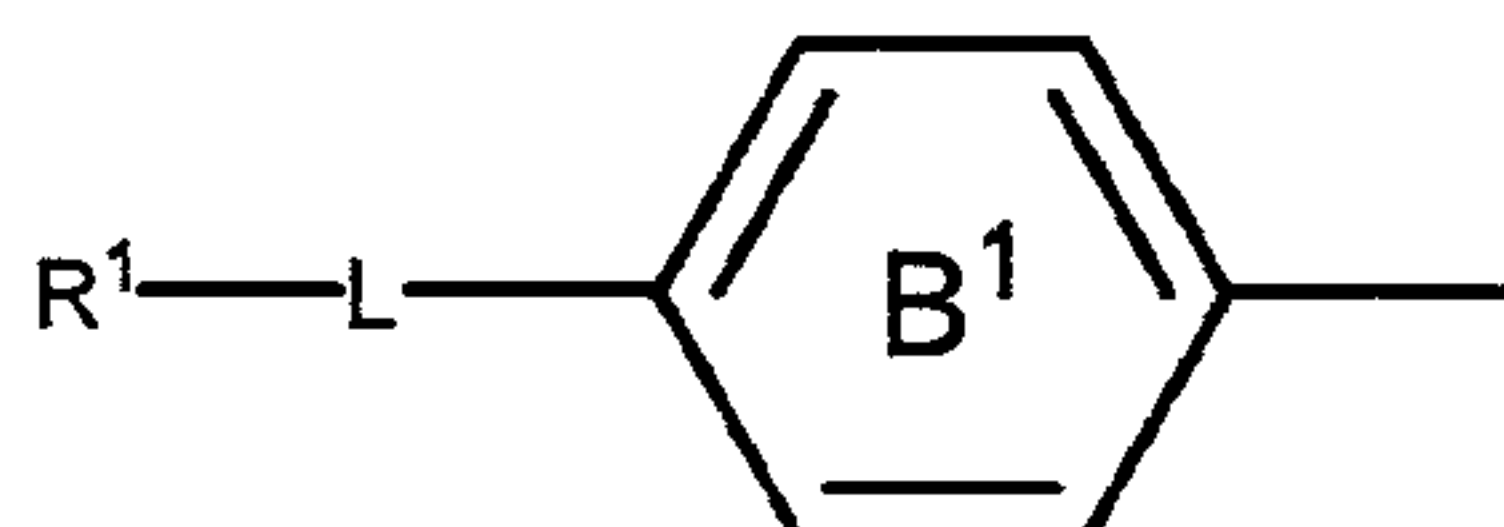
- 20 (1) a pyridine ring which is optionally substituted by one substituent selected from (i) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen

atom or hydroxy (preferably methyl, trifluoromethyl, hydroxymethyl), (ii) a halogen atom (preferably chlorine, fluorine), (iii) cyano, and (iv) a C₁₋₄ alkoxy optionally substituted by 1 to 3 halogen atoms (preferably methoxy, difluoromethoxy, difluoroethoxy, trifluoroethoxy), or
 5 (2) a pyrimidine ring,

Y is a methylene group which is optionally substituted by 1 to 2 C₁₋₆ alkyl group(s) (preferably methyl), or -NR^c- wherein R^c is (1) a hydrogen atom, (2) a C₁₋₆ alkyl which is optionally
 10 substituted by 1 to 3 substituents selected from the group consisting of hydroxy and a halogen atom (preferably methyl, ethyl, propyl, isopropyl, hydroxymethyl, difluoromethyl), or
 (3) a C₃₋₇ cycloalkyl (preferably cyclopropyl),

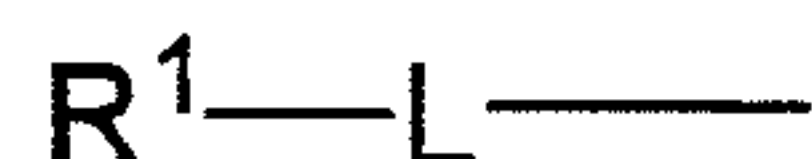
R is

15 (1) a group represented by the formula:

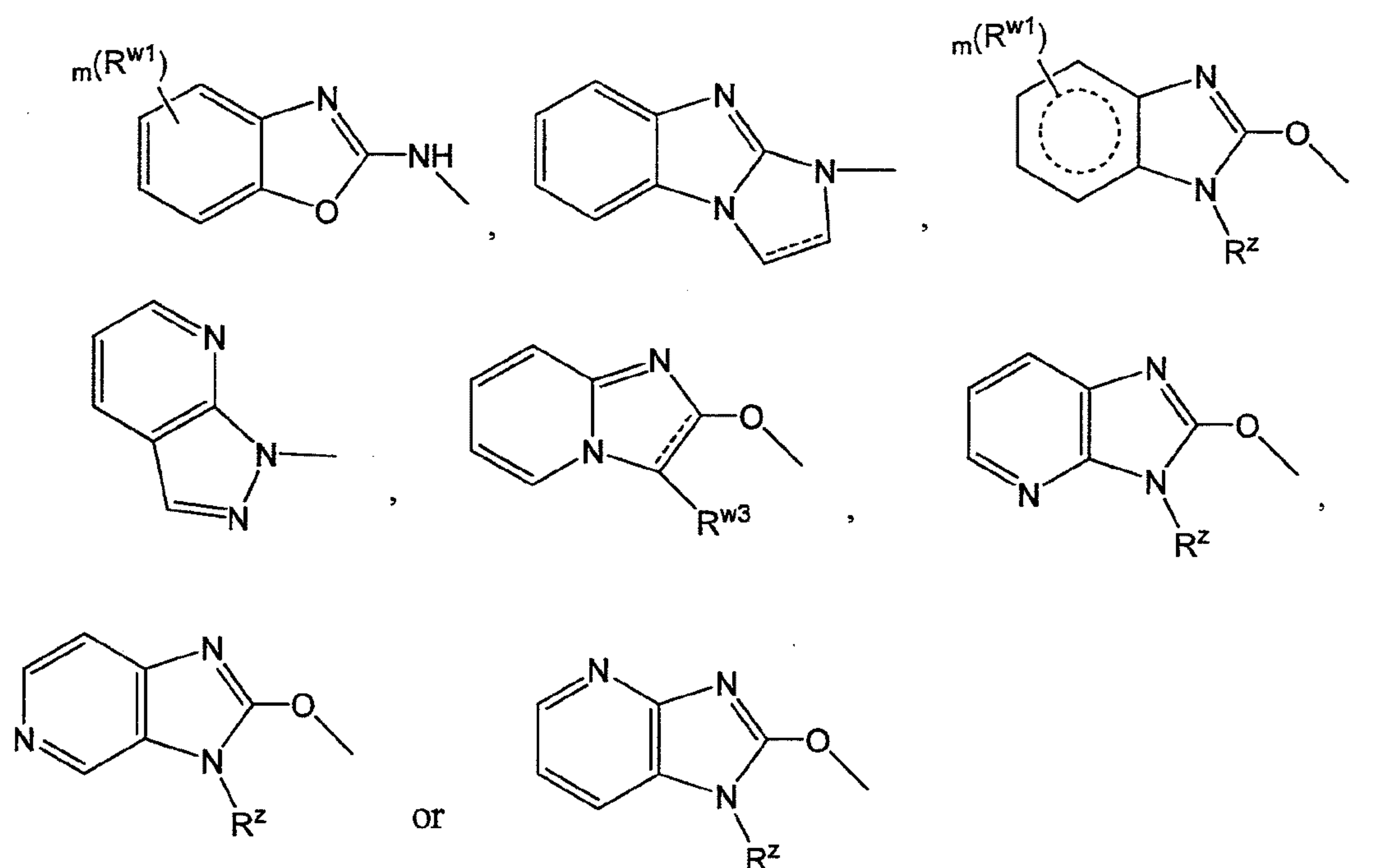


wherein

the partial structure:



20 is a group represented by the following formula:



wherein

R^{w1} is a halogen atom (preferably fluorine);

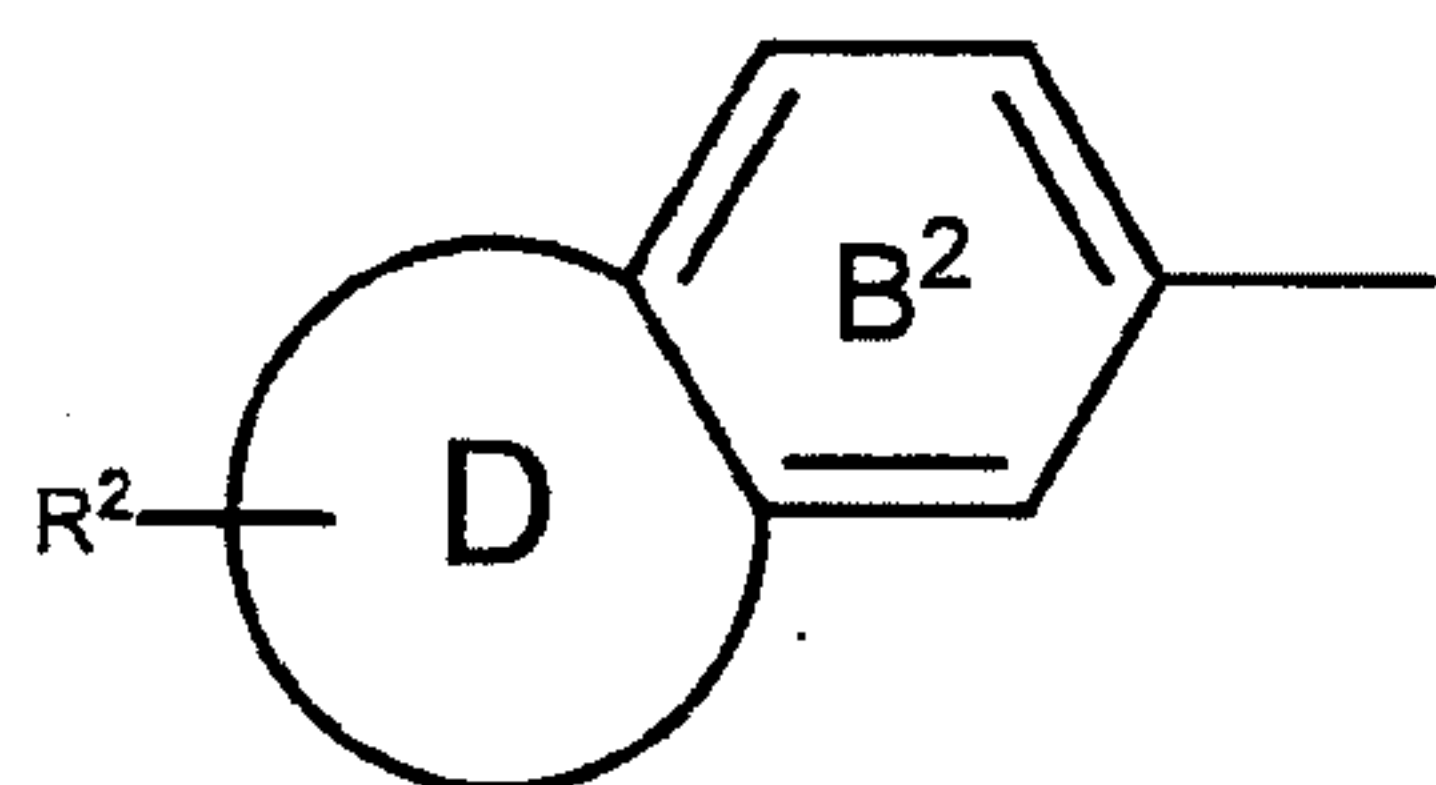
m is 0 to 1;

5 R^z is (i) a hydrogen atom, (ii) a C_{1-4} alkyl group optionally substituted by one hydroxy (preferably methyl, hydroxyethyl, hydroxyisobutyl); and

R^{w3} is a hydrogen atom or a C_{1-2} alkoxy-carbonyl group (preferably, ethoxycarbonyl), and

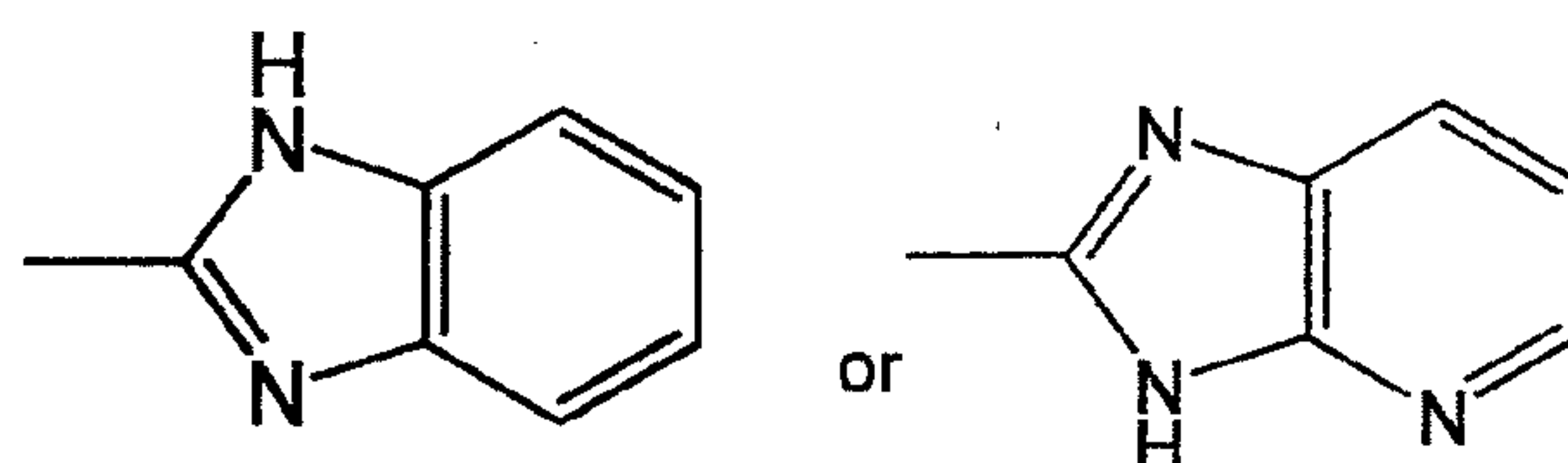
10 ring B^1 is a benzene ring; or

(2) a group represented by the formula:



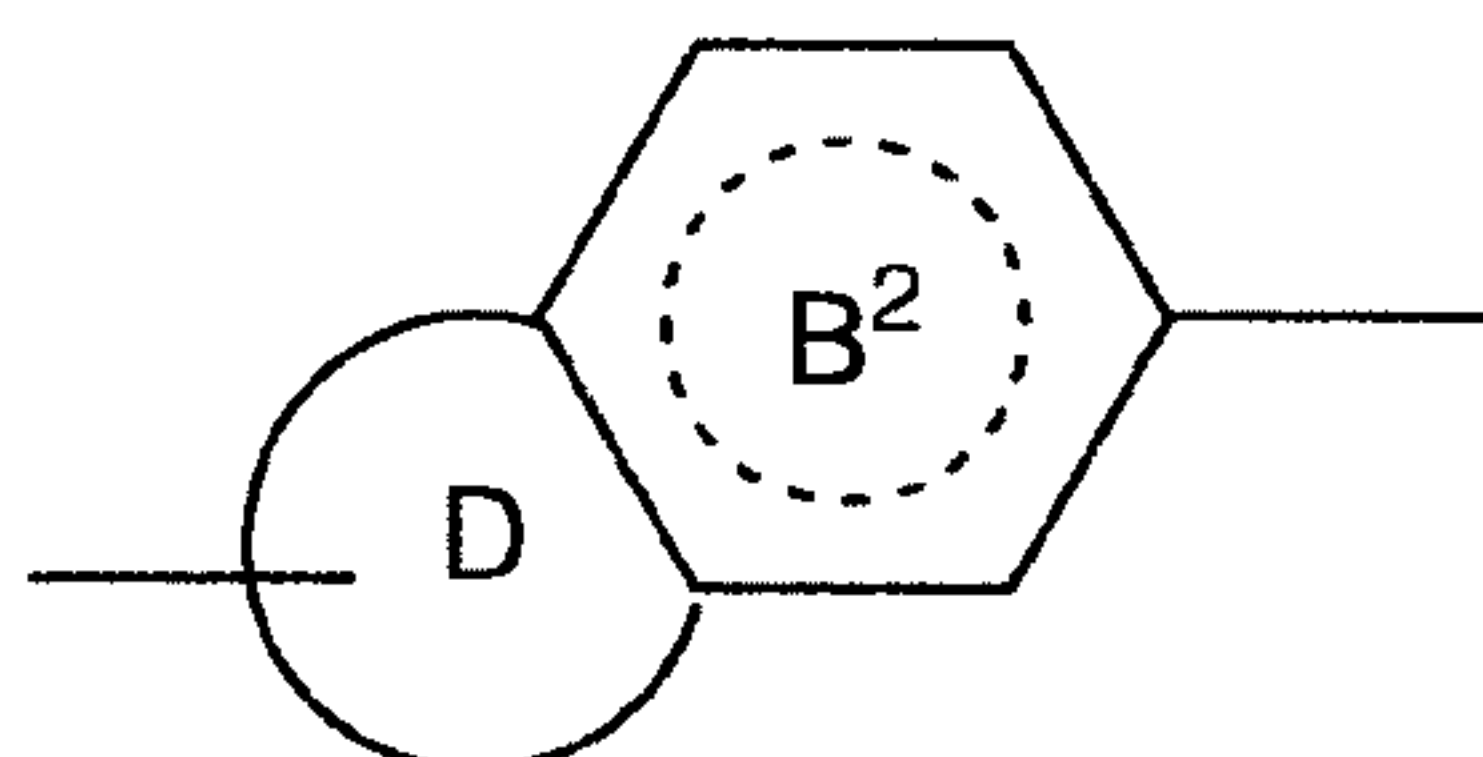
wherein

15 R^2 is a 5- to 10-membered heterocyclic group (preferably the following group:



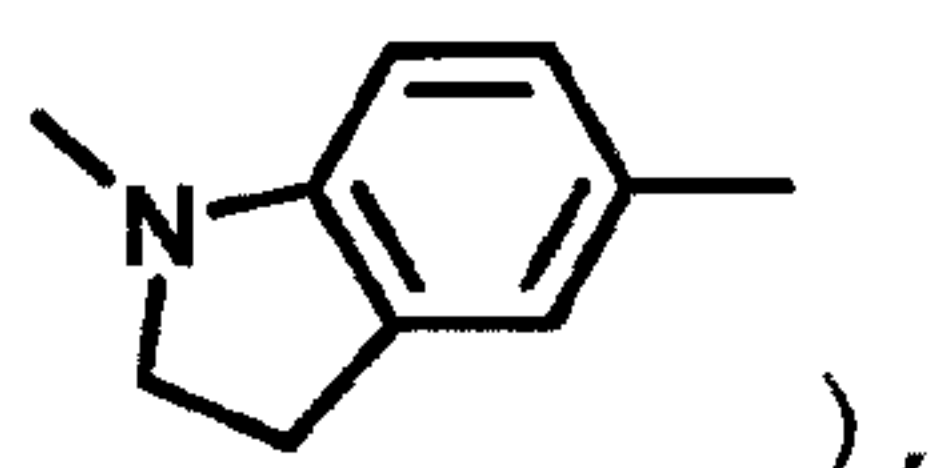
optionally substituted by one C₁₋₆ alkyl group (preferably methyl); and

the partial structure of the formula:



5

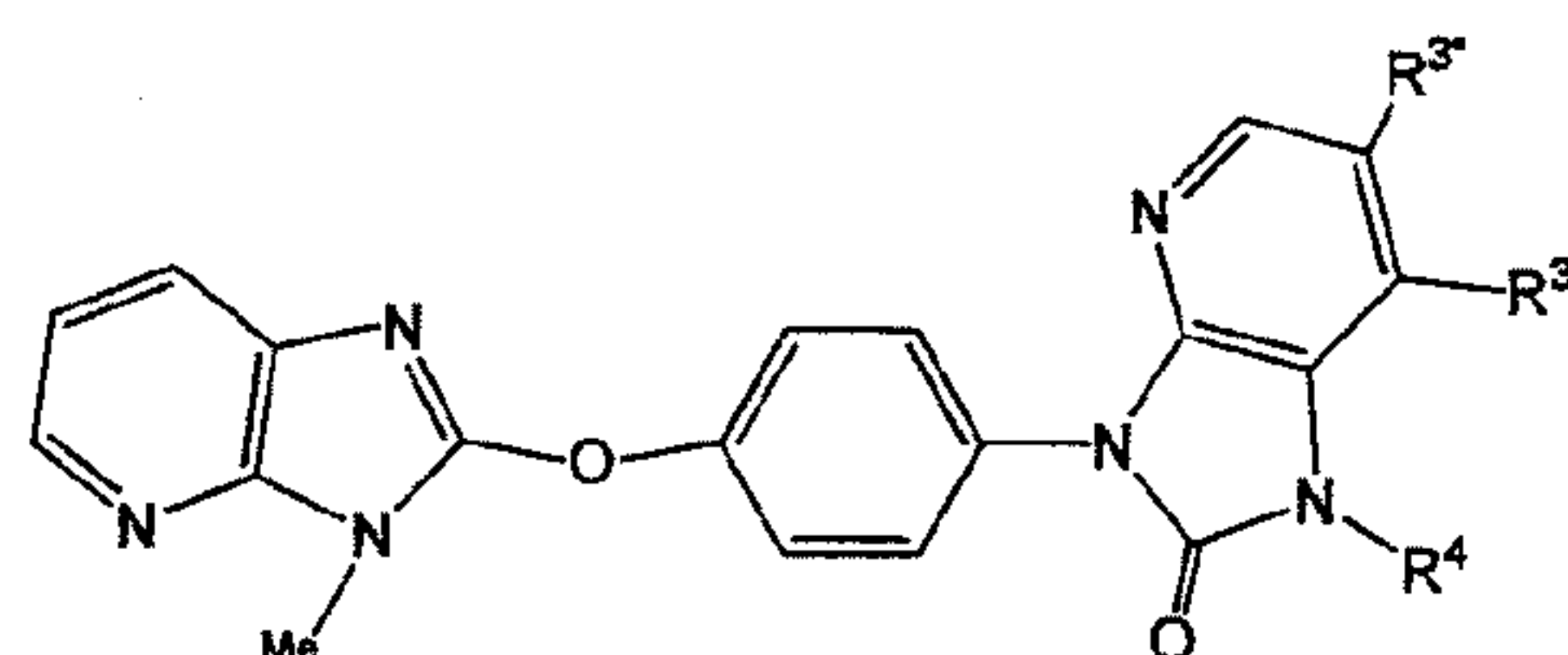
is



or a salt thereof.

[0148]

10 In another embodiment, the compound represented by the formula (I) or a salt thereof is preferably a compound represented by the formula:



(I-W-3)

wherein

15 R^{3'} is a hydrogen atom, or a C₁₋₆ alkyl which may optionally be substituted by one hydroxy (i.e., methyl, hydroxymethyl);

R^{3''} is a hydrogen atom, a halogen atom (preferably fluorine), a C₁₋₆ alkyl group (preferably methyl) or a C₁₋₆ alkoxy group (preferably methoxy);

20

R⁴ is a C₁₋₆ alkyl group (preferably methyl, ethyl, isopropyl);

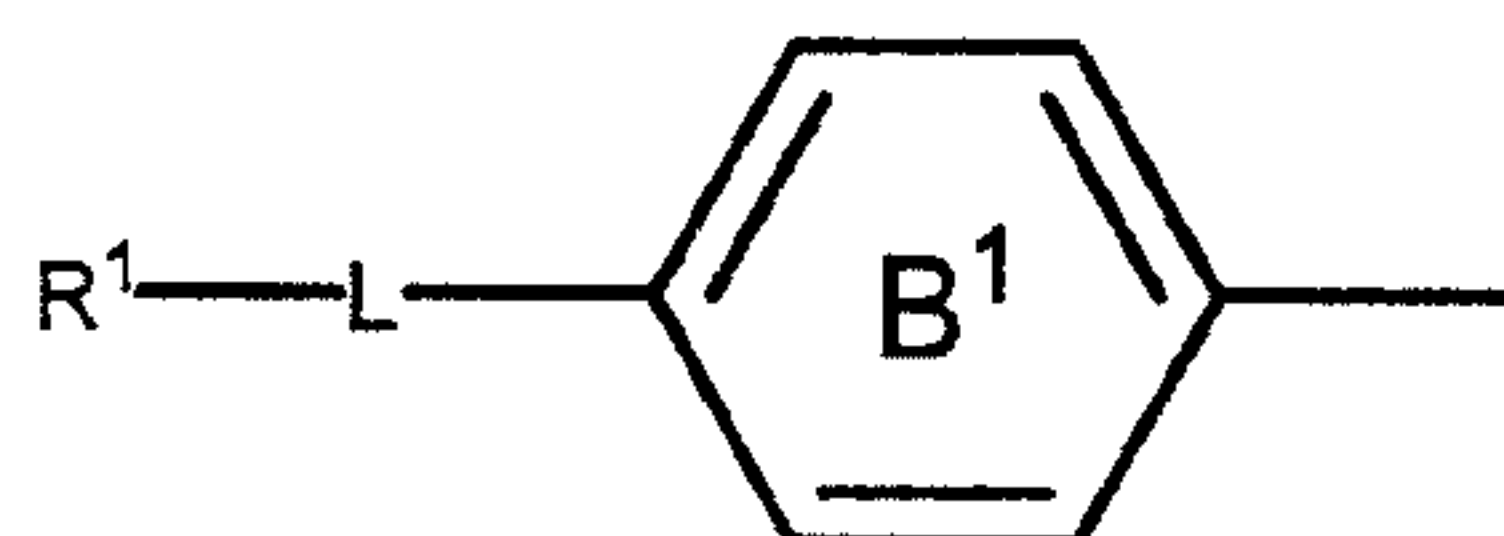
or a salt thereof.

[0149]

In another embodiment, the compound represented by the formula (I) or a salt thereof is preferably a compound wherein
 5 Z^1 is $-N=$ and the others (i.e., Z^2 , Z^3 and Z^4) are $-CH=$;
 ring A is a pyridine ring optionally substituted by a halogen atom, cyano, an optionally substituted alkyl group or an optionally substituted alkoxy group [preferably a halogen atom, cyano, optionally substituted C_{1-6} alkyl or optionally
 10 substituted C_{1-6} alkoxy, more preferably a halogen atom (preferably a chlorine atom, a fluorine atom), cyano, C_{1-6} alkyl (preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably a fluorine atom), or C_{1-6} alkoxy (preferably methoxy, ethoxy) optionally substituted by 1 to 3 halogen
 15 atoms (preferably a fluorine atom)];
 Y is $-NR^c-$ wherein R^c is preferably an optionally substituted alkyl group, more preferably a C_{1-6} alkyl group (preferably methyl, ethyl, propyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from the group
 20 consisting of a halogen atom (preferably a fluorine atom), a hydroxy group, a C_{3-7} cycloalkyl group (preferably cyclopropyl), an optionally substituted C_{1-6} alkoxy group (e.g., a trimethylsilyl- C_{1-6} alkoxy group (preferably trimethylsilyl-ethoxy)) and a C_{1-6} alkoxy-carbonyl group (preferably
 25 ethoxycarbonyl)]; and

R is

(1) a group represented by the formula:

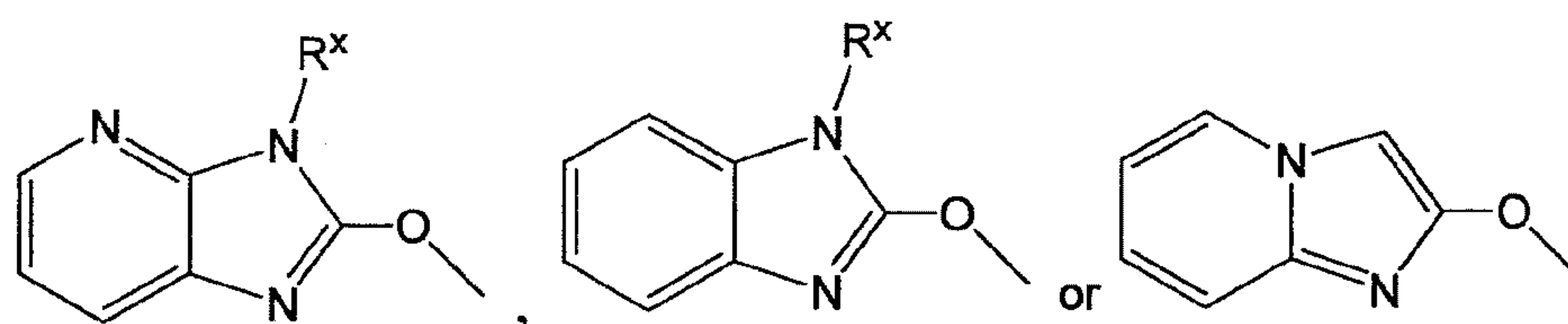


wherein

30 the partial structure:



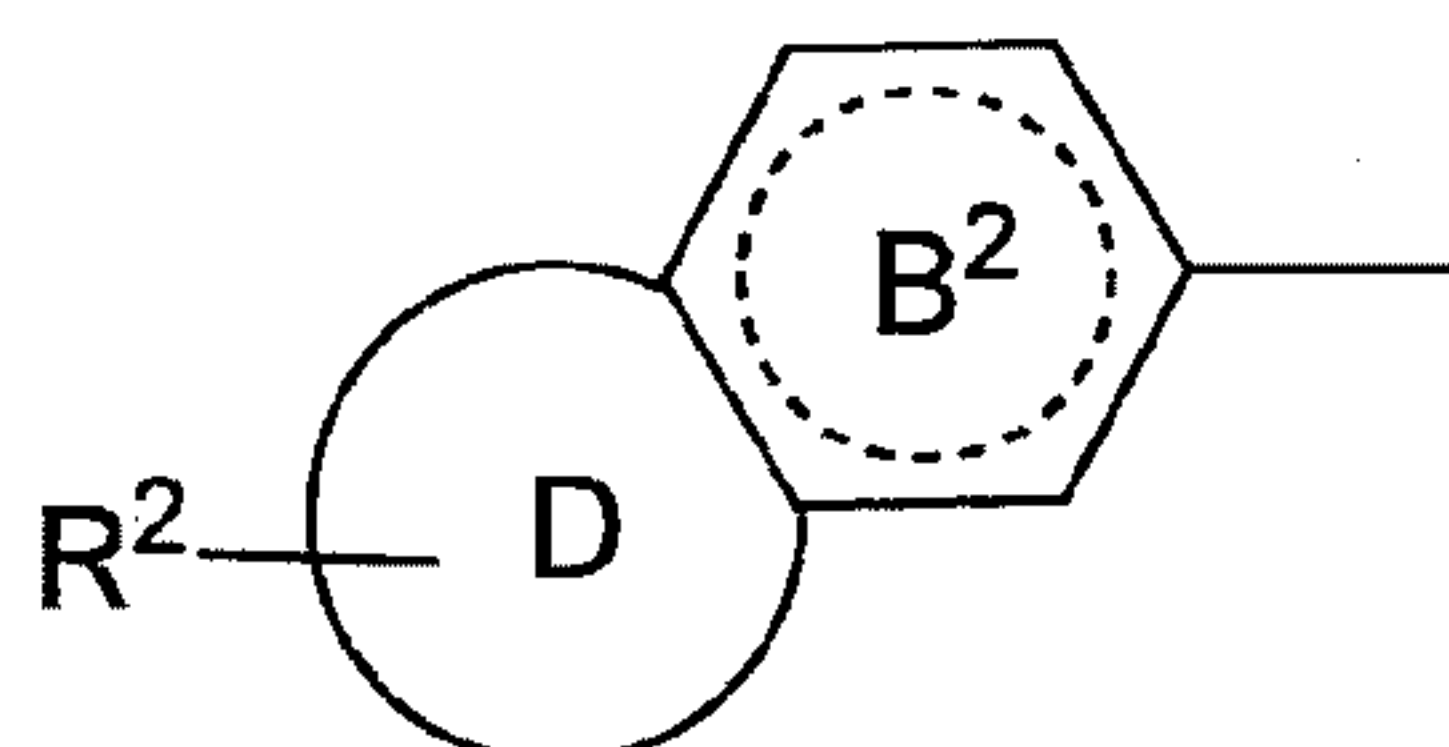
is a group represented by the following formula:



wherein

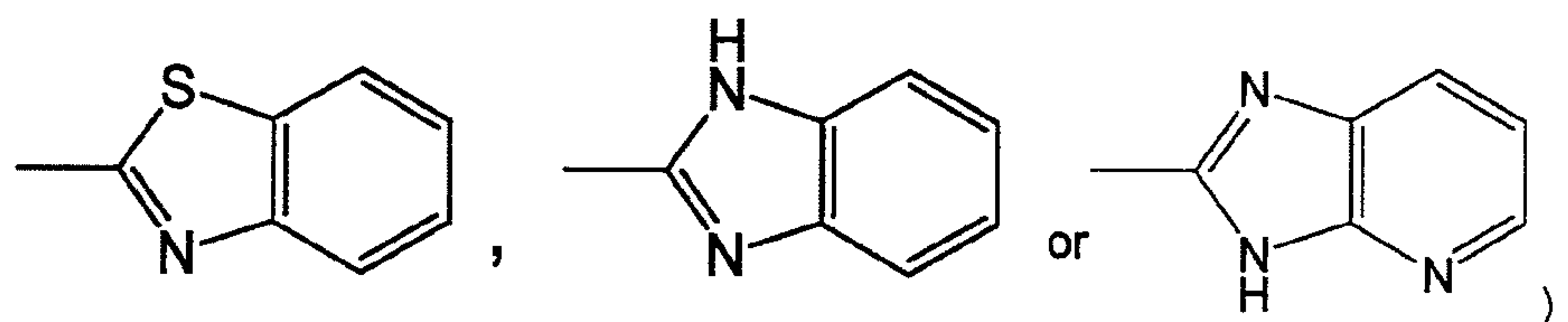
R^x is an optionally substituted C_{1-6} alkyl group
 [preferably a C_{1-6} alkyl group (preferably methyl, ethyl,
 butyl, isobutyl) optionally substituted by 1 to 3
 substituents selected from the group consisting of (i) a
 hydroxy group and (ii) an optionally substituted C_{1-6}
 alkoxy group (e.g., a C_{1-6} alkoxy group (preferably
 ethoxy) optionally substituted by trimethylsilyl)]; and
 ring B^1 is an optionally substituted benzene ring
 [preferably a benzene ring optionally substituted by 1 to 3
 substituents selected from the group consisting of a
 halogen atom and an optionally substituted alkyl group
 (preferably a halogen atom and an optionally substituted C_{1-6}
 alkyl group, more preferably a halogen atom (preferably a
 fluorine atom) and a C_{1-6} alkyl group (preferably methyl))],
 or

(2) a group represented by the formula:



wherein,

R^2 is a 5- to 10-membered heterocyclic group (preferably the
 following group:



optionally substituted by 1 to 3 (preferably 1)
 substituents selected from an optionally substituted alkyl
 group (preferably a C_{1-6} alkyl group, more preferably

methyl);

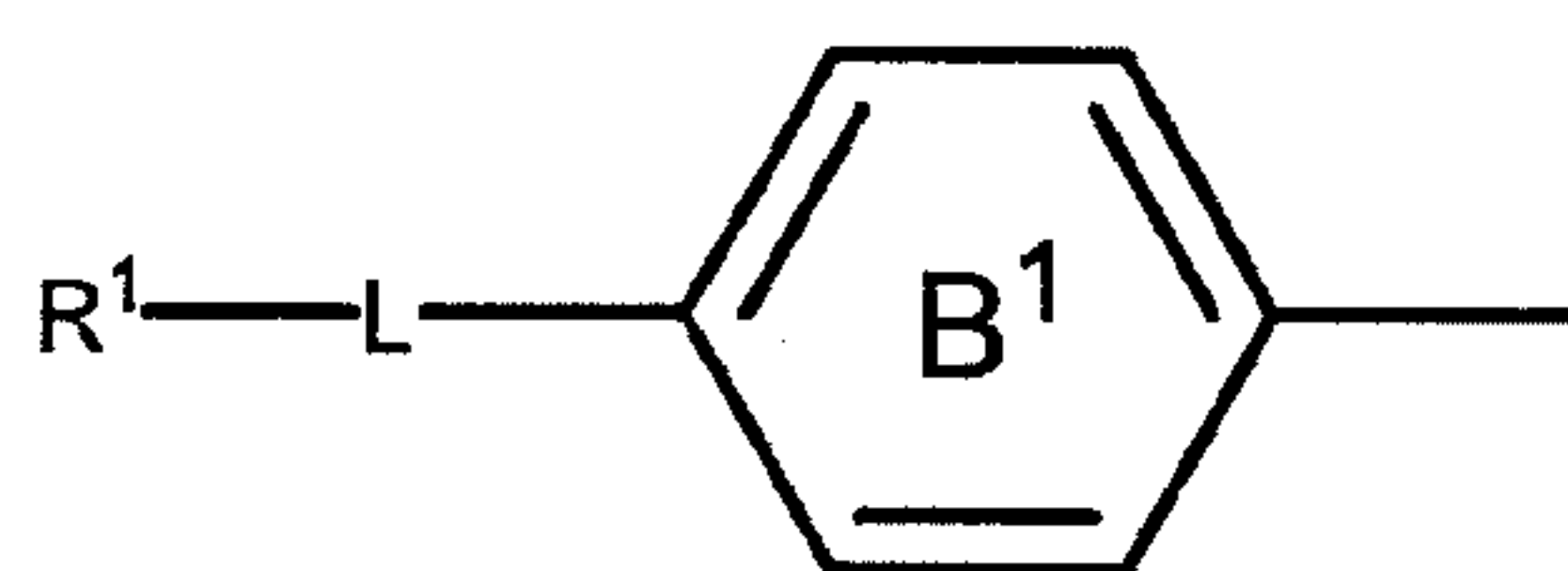
ring B² is an optionally substituted benzene ring

(preferably a benzene ring); and

ring D is a pyrrolidine ring, a pyrrole ring or a pyrazole
 5 ring, each of which is optionally substituted (preferably a
 pyrrolidine ring, a pyrrole ring or a pyrazole ring),
 or a salt thereof.

[0150]

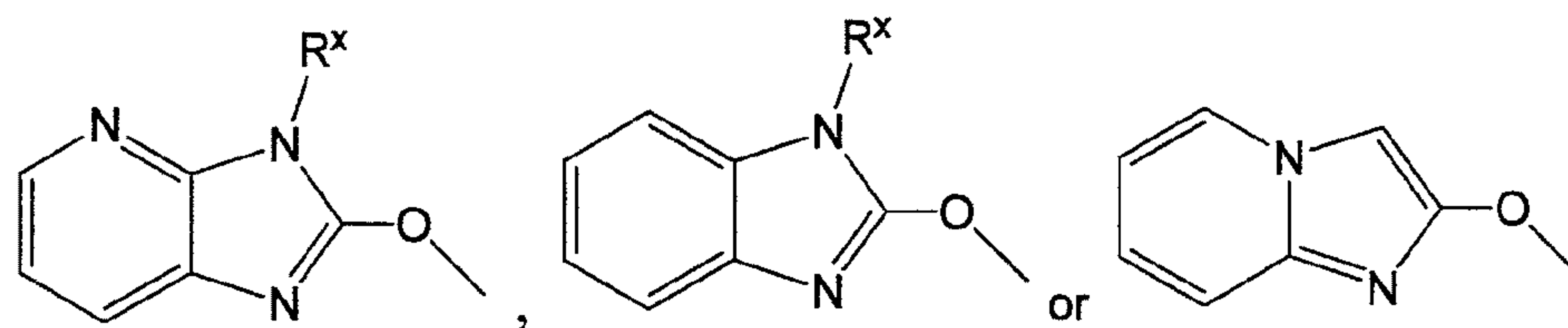
In another embodiment, the compound represented by the
 10 formula (I) or a salt thereof is preferably a compound wherein
 Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=; or Z¹
 and Z³ are -N= and the others (i.e., Z² and Z⁴) are -CH=; or Z¹
 and Z⁴ are -N= and the others (i.e., Z² and Z³) are -CH=;
 ring A is a pyridine ring, a pyrimidine ring or a pyrazine
 15 ring, each of which is optionally substituted by 1 or 2
 (preferably 1) substituents selected from a halogen atom, an
 optionally substituted C₁₋₆ alkyl group (preferably a C₁₋₂ alkyl
 group such as methyl, ethyl and the like) and an optionally
 substituted C₁₋₆ alkoxy (e.g., methoxy) [preferably a halogen
 20 atom (preferably a fluorine atom) and a methyl group];
 Y is -NR^c- wherein R^c is preferably a C₁₋₃ alkyl group (e.g.,
 methyl, ethyl, isopropyl), preferably -N(-CH₂CH₃)-; and
 R is a group represented by the formula:



25 wherein
 the partial structure:



is a group represented by the following formula:



30 wherein

R^x is an optionally substituted C₁₋₆ alkyl group
[preferably a C₁₋₆ alkyl group (preferably methyl, ethyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents selected from the group consisting of (i) a
5 hydroxy group and (ii) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy)]; and
ring B¹ is an optionally substituted benzene ring
[preferably a benzene ring optionally substituted by one substituent selected from the group consisting of a halogen
10 atom and an optionally substituted C₁₋₆ alkyl group, more preferably a halogen atom (preferably a fluorine atom) and a C₁₋₆ alkyl group (preferably methyl)] or a pyridine ring [more preferably a benzene ring],
or a salt thereof.

15 Among the embodiments of the above-mentioned formula (I), a compound wherein ring A is a pyridine ring wherein Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=, and each of -CH= for Z³ and Z⁴ has one substituent instead of a hydrogen atom, or the one of -CH= for Z³ and Z⁴ has one substituent instead of
20 a hydrogen atom, is preferable, and a compound wherein ring A is a pyridine ring wherein Z¹ is -N= and the others (i.e., Z², Z³ and Z⁴) are -CH=, and -CH= for Z⁴ has one substituent instead of a hydrogen atom, is more preferable. Examples of the substituent include a halogen atom, an optionally substituted
25 C₁₋₆ alkyl group (preferably a C₁₋₂ alkyl group such as methyl, ethyl and the like) and an optionally substituted C₁₋₆ alkoxy (e.g., methoxy) [preferable examples thereof include a halogen atom (preferably a fluorine atom) and a methyl group].
[0151]

30 In another embodiment, the compound represented by the formula (I) or a salt thereof is preferably a compound represented by the formula (I') or a salt thereof.
[0152]

As the compound represented by the formula (I) or a salt
35 thereof,

- 1-ethyl-6-methyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof;
- 1-ethyl-6-methoxy-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof;
- 1-ethyl-7-methyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof;
- 10 6-methyl-1-(1-methylethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof;
- 1-ethyl-6-fluoro-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof;
- 15 a salt thereof;
- 1,7-dimethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof; and
- 1-ethyl-7-(hydroxymethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof
- 20 b]pyridin-2-one, or a salt thereof
- are preferable.

[0153]

When the compound (I) is a salt, for example, metal salts, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids can be included. Preferable examples of metal salts, for example, include alkali metal salts such as sodium salts, potassium salts and the like; alkali earth metal salts such as calcium salts, magnesium salts, barium salts and the like; aluminum salts and the like. Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N, N'-dibenzylethylenediamine and the like.

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Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid and the like. Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine and the like. Preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid and the like. Among them, salts that are pharmacologically acceptable are preferable. For example, in the case when acidic functional group are present in the compound, for example, inorganic salts including alkali metal salts (e.g., sodium salts, potassium salts etc.), alkali earth metal salts (e.g., calcium salts, magnesium salts, barium salts etc.) and the like, ammonium salts and the like are preferable. In contrast, in the case when basic functional group are present in the compound, for example, salts with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid etc. or salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid etc. are preferable.

In the following, compound (I) and a salt thereof are generally also referred to as the compound of the present invention.

[0154]

The compound (I) can be obtained in the crystal form. Either single crystalline form or crystalline mixture can be included in the compound (I).

The compound of the formula (I) can be a pharmaceutically

acceptable co-crystal or a co-crystal salt. The term "co-crystal" or "co-crystal salt" as used herein means a crystalline material composed of two or more unique solids at room temperature, each of which has distinctive physical characteristics such as structure, melting point, and heats of fusion, hygroscopicity, solubility, and stability. A co-crystal or a co-crystal salt can be obtained according to a per se known co-crystallization method.

The compound (I) can be provided as a solvate (e.g., hydrate) or as a non-solvate and both are included in the compound (I).

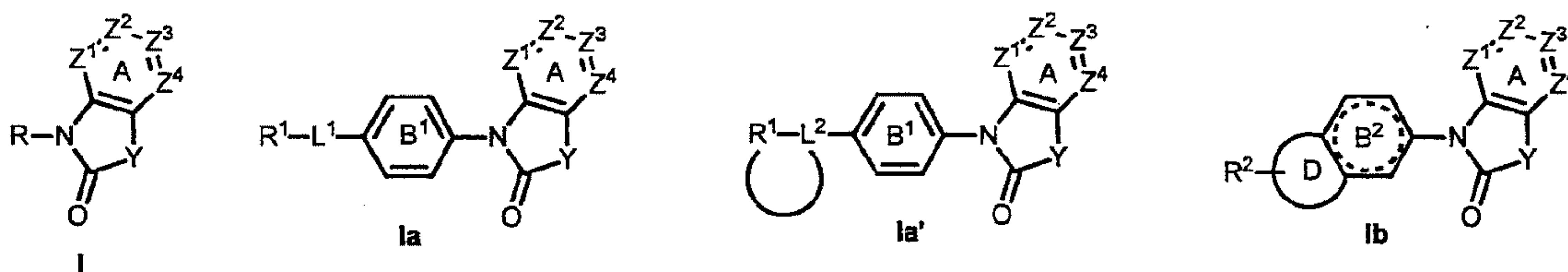
The compounds labeled with isotopes (e.g., ^2H , ^3H , ^{11}C , ^{14}C , ^{18}F , ^{35}S , ^{125}I etc.) are also included in the compound (I).

Compound (I) labeled or substituted with an isotope can be utilized as, for example, a tracer (PET tracer) used for Positron Emission Tomography (PET) and is useful in the fields of medical diagnosis and the like.

[0155]

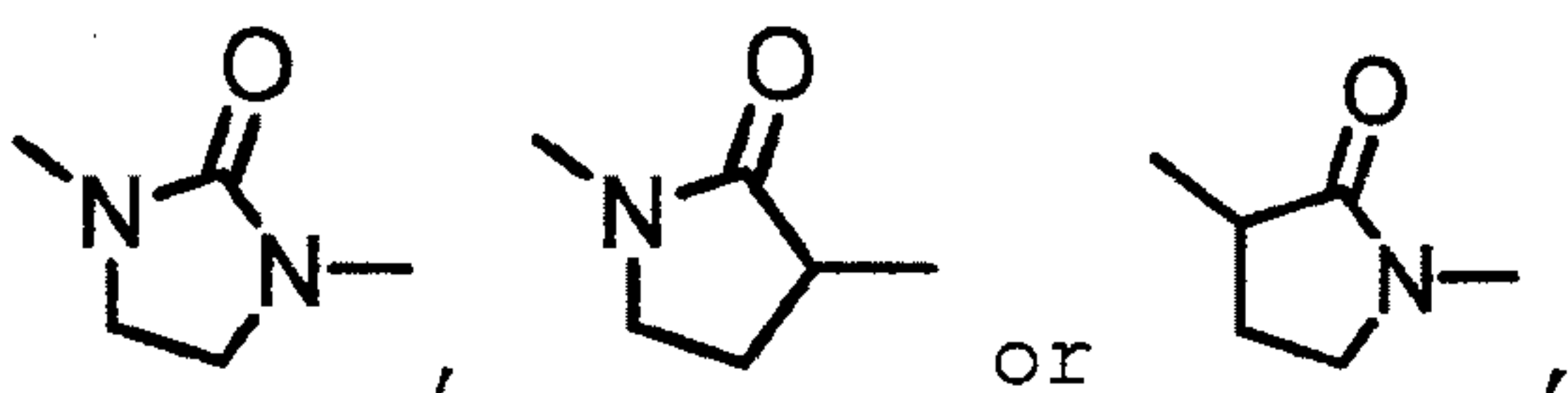
[Manufacturing method]

The methods for manufacturing compound (I), and compound (Ia), compound (Ia') and compound (Ib) encompassed in compound (I) are explained in the following.



wherein

L^1 in compound (Ia) is a sulfur atom, an oxygen atom, an optionally substituted methylene group, $-\text{CO}-$, $-\text{NR}^a-$, $-\text{CH}_2\text{O}-$, $-\text{OCH}_2-$, $-\text{NR}^a\text{COO}-$, $-\text{OCONR}^a-$, $-\text{NR}^a\text{CONR}^b-$, $-\text{NR}^a\text{COCH}_2-$, $-\text{CH}_2\text{CONR}^a-$, $-\text{NR}^a\text{CO}-$, $-\text{CONR}^a-$,



the "optionally substituted methylene group" for L^1 means the

same as the "optionally substituted methylene group" for L, L² in compound (Ia') forms, together with R¹, an optionally substituted bi- or tri-cyclic fused heterocyclic group, the "optionally substituted bi- or tri-cyclic fused heterocyclic group" formed by L² and R¹ in combination means the same as the "optionally substituted bi- or tri-cyclic fused heterocyclic group" optionally formed by L and R¹, and other symbols are each as defined above.

Compound (I) comprises compounds (Ia), (Ia') and (Ib).

10 [0156]

The compound of the present invention and starting compounds therefor can be produced by a means known per se, for example, according to the methods shown by the following schemes and the like. In the following, the "room temperature" generally means 0 - 30°C, and each symbol in the chemical structural formulas described in the schemes is, unless otherwise specified, as defined above. The compounds in the formulas also include the salts formed, and examples of such salts include those similar to the salts of compound (I) and the like. The compounds obtained in respective steps can be used for the next reaction in the form of a reaction mixture or as a crude product. They can also be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as

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25
30

recrystallization, distillation, chromatography and the like. When the compounds in the formulas are commercially available, the commercially available products can be directly used. In addition, when each ring in the formula (I) has a substituent, the corresponding precursor has the same substituent.

[0157]

When the starting compound contains an amino group, a carboxy group, a hydroxy group or a heterocyclic group, these groups may be protected with a protective group generally used in the peptide chemistry and the like. In this case, after the reaction, the target compound can be obtained by removing the

35

protective group as necessary. The protective group can be introduced or removed by a method known per se, for example, the method described in "Protective Groups in Organic Synthesis, 3rd Ed." by Theodora W. Greene, Peter G. M. Wuts, Wiley-Interscience Corporation (1999) and the like. In the formula, P¹ - P³ are each a nitrogen-protective group of an amino group or an amide group, a hydroxy-protective group, a carboxy-protective group, or a hydrogen atom, and those known per se can be used.

Examples of the nitrogen-protective group of an amino group or an amide group include a formyl group, and a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl etc.), a phenylcarbonyl group, a C₁₋₆ alkyl-oxycarbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl(Boc) etc.), an allyloxycarbonyl(Alloc) group, a phenyloxycarbonyl group, a fluorenylmethoxycarbonyl(Fmoc) group, a C₇₋₁₀ aralkyl-carbonyl group (e.g., benzylcarbonyl etc.), a C₇₋₁₀ aralkyl-oxycarbonyl group (e.g., benzyloxycarbonyl(Z) etc.), a C₇₋₁₀ aralkyl group (e.g., benzyl etc.), a 2-(trimethylsilyl)ethoxymethyl(SEM) group, a trityl group, a phthaloyl group, an N,N-dimethylaminomethylene group, a tert-butylcarbamate group, a benzylcarbamate group and the like, each of which may have substituent(s). Examples of the substituent these may have include a phenyl group, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl, ethylcarbonyl, butylcarbonyl etc.), a nitro group and the like. The number of the substituents is about 1 to 3.

[0158]

Examples of the carboxy-protective group include a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl etc.), an allyl group, a benzyl group, a phenyl group, a trityl group, a tri C₁₋₆ alkylsilyl group and the like, each of which may have substituent(s). Examples of the substituents these may have include a halogen atom (e.g.,

fluorine, chlorine, bromine, iodine etc.), a formyl group, a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl, butylcarbonyl etc.), a nitro group and the like. The number of the substituents is about 1 to 3.

5 [0159]

Examples of the hydroxy-protective group include a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl etc.), a C₇₋₁₀ aralkyl group (e.g., benzyl etc.), a formyl group, a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl etc.), a benzoyl group, a C₇₋₁₀ aralkyl-carbonyl group (e.g., benzylcarbonyl etc.), a tetrahydropyranyl group, a furyl group, a silyl group and the like, each of which may have substituent(s). Examples of the substituent these may have include a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl etc.), a phenyl group, a C₇₋₁₀ aralkyl group (e.g., benzyl etc.), a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, n-propoxy etc.), a nitro group and the like. The number of the substituents is about 1 to 4.

20 Preferable examples of P¹ - P³ include a tert-butylcarbamate group, a benzylcarbamate group, a benzyl group, a C₁₋₆ alkyl group (e.g., a methyl group, an ethyl group) and the like. In addition, P¹ - P³ themselves can sometimes be the substituent of the compound of the present invention and, for example, a tert-butylcarbamate group, a benzylcarbamate group, a benzyl group, a C₁₋₆ alkyl group (e.g., a methyl group, an ethyl group) and the like can be mentioned.

As the "leaving group" for X¹ - X¹², a halogen atom (e.g., a chlorine atom, a bromine atom, an iodine atom etc.), optionally halogenated C₁₋₆ alkylsulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy, trifluoroethanesulfonyloxy etc.), C₆₋₁₀ arylsulfonyloxy optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy etc.), 35 optionally halogenated C₁₋₆ alkylsulfonyl (e.g., methanesulfonyl,

ethanesulfonyl, trifluoroethanesulfonyl etc.) and the like are used. In addition, $X^1 - X^{12}$ also include a substituent convertible to a leaving group, and the substituent can be converted to a leaving group by a reaction known per se in a
5 desired step. For example, $X^1 - X^{12}$ may be a methylthio group convertible to a methanesulfonyl group by an oxidation reaction.

[0160]

When compound (I) contains optical isomer, stereoisomer,
10 regioisomer, rotamer or tautomer, they are also encompassed in compound (I), and each can be obtained as a single isomer by a synthetic method and separation method known per se. For example, when compound (I) is an optically active form, the racemate can be separated into (+) form and (-) form by a
15 conventional optical resolution method.

The method of optical resolution may be a method known per se, such as a fractional recrystallization method, a chiral column method, a diastereomer method etc. described in detail below.

20 1) Fractional recrystallization method

A method wherein a salt of a racemate with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine
25 etc.) is formed, which is separated by a fractional recrystallization method, and if desired, a neutralization step to give a free optical isomer.

2) Chiral column method

A method wherein a racemate or a salt thereof is applied
30 to a column for separation of an optical isomer (a chiral column) to allow separation. In the case of a liquid chromatography, for example, a mixture of the optical isomers is applied to a chiral column such as ENANTIO-OVM (manufactured by Tosoh Corporation), CHIRAL series
35 (manufactured by Daicel Chemical Industries, Ltd.) and the

like, and developed with water, various buffers (e.g., phosphate buffer, etc.) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine etc.) solely or in admixture to separate the
5 optical isomer. In the case of a gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Sciences Inc.) and the like is used to allow separation.

3) Diastereomer method

10 A method wherein a racemate is prepared into a diastereomeric mixture by chemical reaction with an optically active reagent, which is made into a single substance by a typical separation means (e.g., a fractional recrystallization method, a chromatography method etc.) and the like, and is
15 subjected to a chemical treatment such as hydrolysis and the like to separate an optically active reagent moiety, whereby an optical isomer is obtained. For example, when compound (I) contains hydroxy, or primary or secondary amino group within a molecule, the compound and an optically active organic acid
20 (e.g., MTPA [α -methoxy- α -(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid etc.) and the like are subjected to condensation reaction to give diastereomers of the ester compound or the amide compound, respectively. When compound (I) has a carboxy group, this compound and an optically active
25 amine or an optically active alcohol reagent are subjected to condensation reaction to give diastereomers of the amide compound or the ester compound, respectively. The separated diastereomer is converted to an optical isomer of the original compound by acid hydrolysis or base hydrolysis.

30 [0161]

Each step described below can be performed without solvent, or by dissolving or suspending in an appropriate solvent, where two or more kinds of solvents may be used by mixing them at an appropriate ratio. Of those recited as
35 examples of the solvent to be used in the manufacturing method

of the compound of the present invention, the following solvents are specifically used.

alcohols:

methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol,
5 2-methoxyethanol, 1-pentanol, etc.

ethers:

diethyl ether, diisopropyl ether, diphenylether,
tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, etc.

aromatic hydrocarbons:

10 benzene, chlorobenzene, toluene, xylene, etc.

saturated hydrocarbons:

cyclohexane, hexane, etc.

amides:

N,N-dimethylformamide, N,N-dimethylacetamide,
15 hexamethylphosphoric triamide, N-methylpyrrolidone, etc.

halogenated hydrocarbons:

dichloromethane, chloroform, carbon tetrachloride, 1,2-
dichloroethane, etc.

nitriles:

20 acetonitrile, propionitrile, etc.

sulfoxides:

dimethylsulfoxide, etc.

aromatic organic bases:

pyridine, lutidine, etc.

25 esters:

methyl acetate, ethyl acetate, butyl acetate, etc.

[0162]

Of those recited as examples of the base or deoxidizer to be used in the manufacturing method of the compound of the
30 present invention, the following bases and deoxidizers are specifically used.

inorganic bases:

sodium hydroxide, potassium hydroxide, magnesium hydroxide,
etc.

35 basic salts:

sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, sodium hydrogen carbonate, etc.

organic bases:

triethylamine, diisopropylethylamine, tributylamine,
5 cyclohexyldimethylamine, N¹,N²-dimethylethane-1,2-diamine,
pyridine, lutidine, 4-dimethylaminopyridine, N,N-
dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-
methyldmorpholine, 1,5-diazabicyclo[4.3.0]-5-nonene, 1,4-
diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]-7-undecene,
10 imidazole, etc.

metal alkoxides:

sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.

alkali metal hydrides:

15 sodium hydride, potassium hydride, etc.

metal amides:

sodium amide, lithiumdiisopropylamide, lithiumhexamethyl
disilazide, etc.

[0163]

20 Compound (Ia) can be produced by scheme 1. In addition,
of compounds (Ia), the following compound (Ia-I) and compound
(Ia-II) can also be produced by scheme 2.

Compound (Ia') can be produced by scheme 3. In addition,
of compounds (Ia'), the following compound (Ia'-I) and
25 compound (Ia'-II) can also be produced by scheme 4, and the
following compound (Ia'-III) can also be produced by scheme 5.

Compound (Ib) can be produced by scheme 6. In addition,
of compounds (Ib), the following compound (Ib-I) can also be
produced by scheme 7.

30 Compound (Ia-III) can be produced by scheme 8.

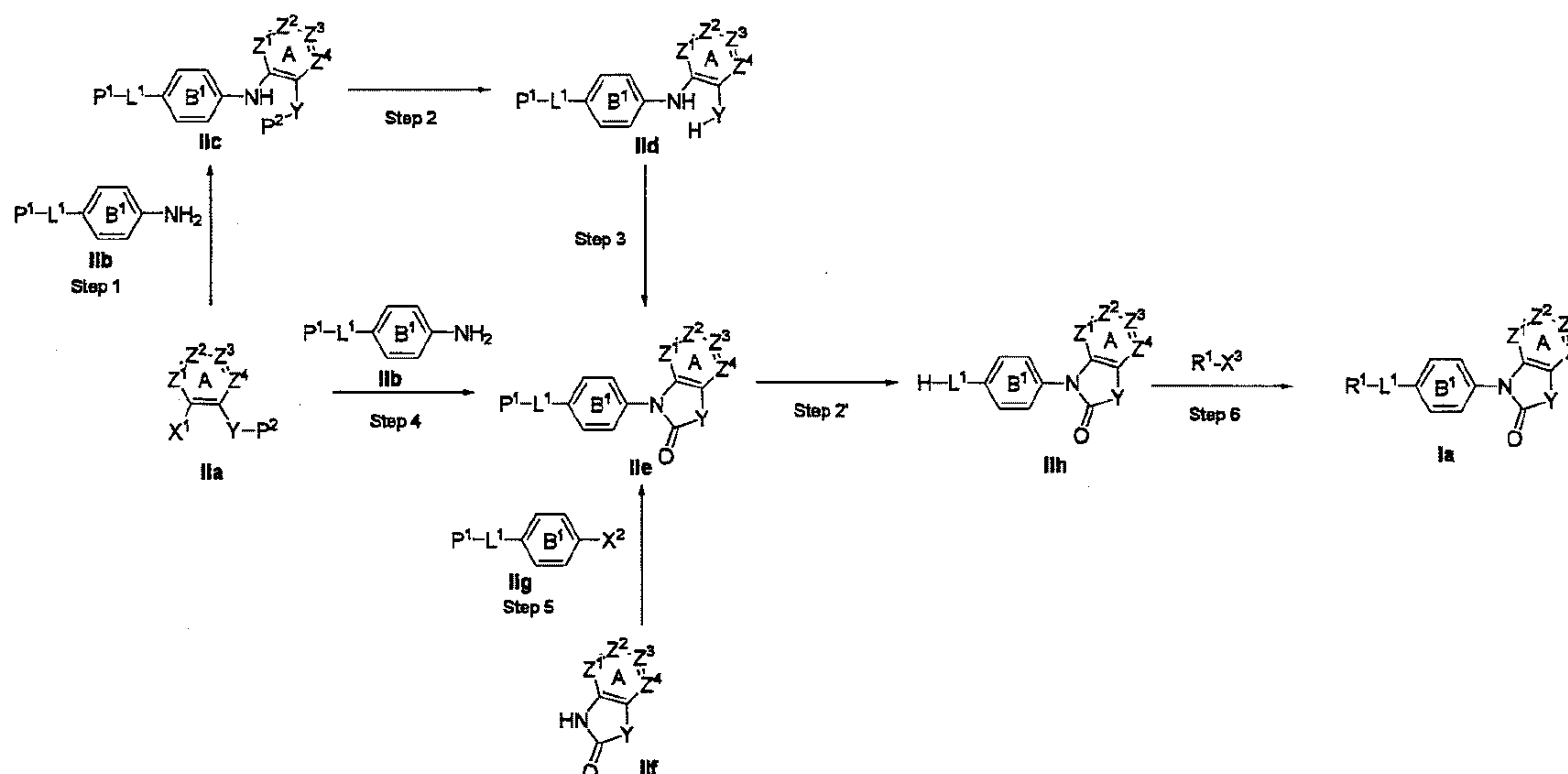
In the formulas shown in these schemes 1-8, when the
starting compound in each reaction has a hydroxy group, an
amino group and the like, these groups may be appropriately
subjected to a general protection and deprotection reactions
35 (e.g., the reaction described in step 2). The protective

groups may be selected, introduced or removed according to a method known per se, for example, the method described in "Protective Groups in Organic Synthesis, 3rd Ed." by Theodora W. Greene, Peter G. M. Wuts, Wiley-Interscience Corporation
 5 (1999), or a method analogous thereto and the like. In addition, when the starting compound in each reaction has an amino group, a compound introduced with a nitro group instead of an amino group may be used as a starting compound, and after the reaction, the nitro group may be reduced to give a
 10 desired amino group (e.g., the reaction described in step 7).

In addition, compound (I) can also be produced by an appropriate combination of the reaction of each step shown by these schemes 1-8.

[0164]

15 Scheme 1



wherein $X^1 - X^3$ are each a leaving group, and the other symbols are as defined above.

The compound of the present invention can be produced by
 20 subjecting compound (IIa) to a series of reaction steps of Steps 1, 2, 3, 2' and 6.

In addition, the compound can also be produced by subjecting compound (IIa) to a series of reaction steps in Steps 4, 2' and 6.

25 Furthermore, the compound can also be produced by

subjecting compound (II_f) to a series of reaction steps in Steps 5, 2' and 6.

[0165]

(Step 1)

5 Compound (II_c) can be produced by subjecting compound (II_a) and compound (II_b) to a substitution reaction. Compound (II_a) is generally used in about 0.2 - 5.0 mol, preferably about 0.5 - 2.0 mol, per 1 mol of compound (II_b). This reaction is advantageously performed in a solvent inert to the
10 reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the
15 like are preferable. In addition, when an acidic substance is released by the reaction, the reaction can be performed in the presence of a deoxidizer to remove the acidic substance from the reaction system. As such deoxidizer, for example, inorganic bases, basic salts, organic bases, metal alkoxides,
20 alkali metal hydrides, metal amides and the like are used. The deoxidizer is generally used in about 0.05 - 20 mol, preferably about 1 - 10 mol, per 1 mol of compound (II_b). While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 72 hr, preferably
25 30 min - 24 hr. The reaction temperature is generally 0 - 200°C, preferably 50 - 150°C. In addition, microwave irradiation may be performed to promote the reaction.

[0166]

(Step 2)

30 Compound (II_d) can be produced by removing the protective group (P²) of compound (II_c). When P² is a hydrogen atom, this step can be omitted. The protective group can be removed according to a method known per se, for example, the method described in "Protective Groups in Organic Synthesis, 3rd Ed."
35 by Theodora W. Greene, Peter G. M. Wuts, Wiley-Interscience

Corporation (1999), and the like. This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as alcohols, 5 ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min 10 - 72 hr, preferably 30 min - 24 hr. The reaction temperature is generally 0 - 200°C, preferably 0 - 50°C. In addition, microwave irradiation may be performed to promote the reaction. [0167]

(Step 3)

15 Compound (IIe) can be produced by subjecting compound (IIId) to a cyclization reaction. The reaction can be performed according to a manufacturing method known per se or a method analogous thereto and, for example, a method using a carbonating agent can be mentioned. Examples of the 20 carbonating agent include 1,1'-carbonylbis(1H-imidazole), phosgene, triphosgene, diethyl carbonate, dimethyl carbonate, di-tert-butyl dicarbonate and the like. When these carbonating agents are used, the reaction is considered to proceed via a reactive derivative of amine. The synthesis from compound 25 (IIId) to compound (IIe) sometimes proceeds via compound (IIc). The carbonating agent is generally used in about 0.2 - 5.0 mol, preferably about 0.5 - 2.0 mol, per 1 mol of compound (IIId). In addition, a base can be used to promote the reaction. Examples of the base include inorganic bases, organic bases, 30 metal alkoxides, alkali metal hydrides, metal amides and the like. The base is used in about 1.0 - 20 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (IIId). This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the 35 reaction proceeds and, for example, solvents such as ethers,

aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the like are preferable. While the reaction time varies depending
5 on the reagent and solvent to be used, it is generally 10 min - 72 hr, preferably 30 min - 24 hr. The reaction temperature is generally 0 - 200°C, preferably 0 - 100°C. In addition, microwave irradiation may be performed to promote the reaction.
[0168]

10 (Step 4)

Compound (IIe) can also be produced by subjecting compound (IIa) and compound (IIb) to a condensation reaction. This reaction can also be performed according to a manufacturing method known per se, for example, the method
15 described in Synlett, vol. 13, page 2083 (2006) and the like, or a method analogous thereto. Compound (IIa) is generally used in about 0.2 - 5.0 mol, preferably about 0.5 - 2.0 mol, per 1 mol of compound (IIb). This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is
20 not particularly limited as long as the reaction proceeds and, for example, solvents such as alcohols, ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the like are
25 preferable. In addition, when an acidic substance is released from the reaction, the reaction can be performed in the presence of a deoxidizer to remove the substance from the reaction system. As such deoxidizer, inorganic bases, basic salts, organic bases, metal alkoxides, alkali metal hydrides,
30 metal amides and the like are used. The deoxidizer is generally used in about 0.05 - 20 mol, preferably about 1 - 10 mol, per 1 mol of compound (IIb). In addition, for example, basic salts, organic bases and the like can also be used to promote the reaction. Such basic salts, organic bases and the
35 like are generally used in about 0.05 - 20 mol, preferably

about 1 - 10 mol, per 1 mol of compound (IIb). While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 200 hr, preferably 30 min - 48 hr. The reaction temperature is generally 0 - 200°C, preferably 50 - 150°C. In addition, microwave irradiation may be performed to promote the reaction.

[0169]

(Step 5)

Compound (IIe) can be produced by subjecting compound (IIf) and compound (IIg) to a substitution reaction, or a coupling reaction in the presence of a metal catalyst. Compound (IIg) is used in about 0.5 - 20 mol, preferably about 0.8 - 10 mol, per 1 mol of compound (IIf). As the metal catalyst, a metal complex having a variety of ligands is used and, for example, palladium compounds [e.g., palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) chloride, dichlorobis(triethylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), complex of palladium(II) acetate and 1,1'-bis(diphenylphosphino)ferrocene, complex of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and dichloromethane, complex of tris(dibenzylideneacetone)dipalladium(0) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (DavePhos), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (Xantphos), or dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphane (SPhos), etc.], nickel compounds [e.g., tetrakis(triphenylphosphine)nickel (0), bis(triethylphosphine)nickel (II) chloride, bis(triphenylphosphine)nickel (II) chloride, etc.], copper compounds [e.g., copper oxide, copper(I) iodide, copper sulfate, copper(II) chloride, etc.] and the like can be mentioned. The metal catalyst is used in about 0.0001 - 5 mol,

preferably about 0.001 - 1 mol, per 1 mol of compound (IIIf). This reaction is preferably performed in the presence of a base. Examples of the base include inorganic bases, organic bases, metal alkoxides, alkali metal hydrides, metal amides
5 and the like. The base is used in about 1.0 - 20 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (IIIf). To promote the reaction, for example, sodium iodide, potassium iodide and the like may be added. Such sodium iodide, potassium iodide and the like are used in about 0.05 - 100 mol,
10 preferably about 0.1 - 50 mol, per 1 mol of compound (IIIf). In addition, when a metal catalyst unstable to oxygen is used in this reaction, for example, the reaction is preferably performed in an inert gas stream such as argon gas, nitrogen gas and the like. This reaction is advantageously performed in
15 a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as alcohols, ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, nitriles, sulfoxides, esters, water and the like or a mixed solvent
20 thereof and the like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 100 hr, preferably 30 min - 50 hr. The reaction temperature is -10 to 250°C, preferably 50 to 150°C. In addition, microwave irradiation may be performed to promote
25 the reaction.

[0170]

(Step 2')

Compound (IIh) can be produced by removing the protective group (P^1) of compound (IIe). When P^1 is a hydrogen atom, this
30 step can be omitted. This reaction may be performed according to a method similar to that of the above-mentioned (Step 2).

[0171]

(Step 6)

Compound (Ia), which is the compound of the present
35 invention, can be produced by subjecting compound (IIh) and R^1 -

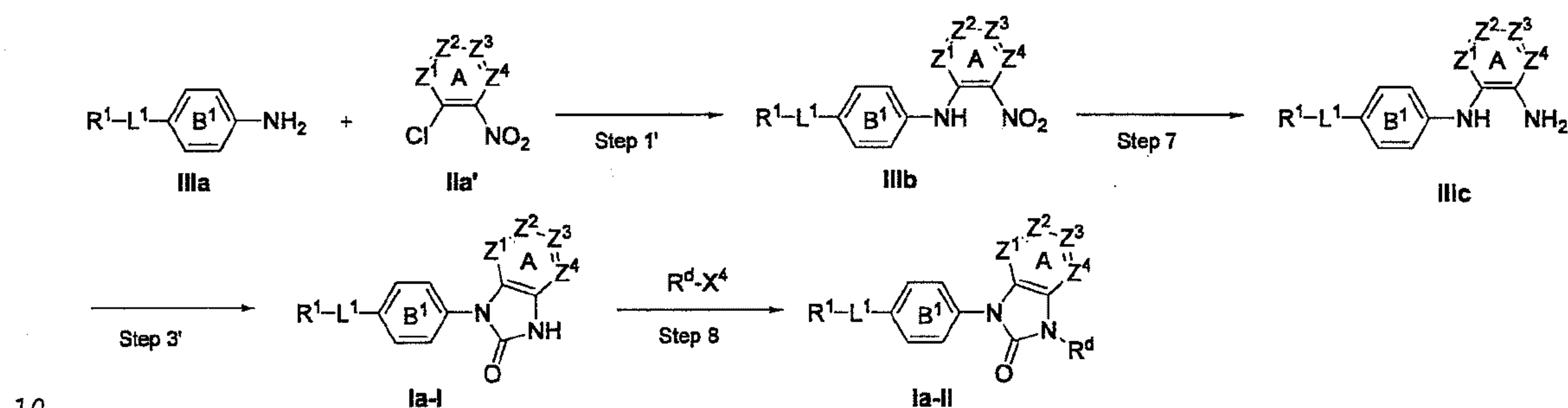
X³ to a substitution reaction in the presence of a base. R¹-X³ is used in about 0.05 - 100 mol, preferably about 0.1 - 10 mol, per 1 mol of compound (IIh). Examples of the base include inorganic bases, basic salts, organic bases, metal amides, alkali metal hydrides and the like. The base is used in about 0.5 - 10.0 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (IIh). To promote the reaction, for example, sodium iodide, potassium iodide and the like may be added. Such sodium iodide, potassium iodide and the like are used in about 0.05 - 100 mol, preferably about 0.1 - 50 mol, per 1 mol of compound (IIh). This reaction is advantageously performed in a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides and the like or a mixed solvent thereof and the like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 100 hr, preferably 30 min - 24 hr. The reaction temperature is generally -20 - 250°C, preferably 0 - 230°C. In addition, microwave irradiation may be performed to promote the reaction. [0172]

Compounds (IIa), (IIb), (IIc), (IIId), (IIe), (IIIf), (IIg) and (IIh) and R¹-X³ may be commercially available products, or can be produced according to a method known per se or a method analogous thereto. In addition, compound (IIa) can be produced according to the method described in Synlett, vol. 13, page 2083 (2006) and the like, or a method analogous thereto. Compound (IIIf) can also be produced according to the method described in Tetrahedron Letters, vol. 47, page 7567 (1993), Journal of Medicinal Chemistry, vol. 10, page 2697 (1990) and the like, or a method analogous thereto. Compound (IIh) and R¹-X³ can also be produced by a known substituent conversion reaction, condensation reaction, oxidation reaction, reduction reaction and the like, which may be used alone or in a

combination of two or more thereof. These reactions may be performed, for example, according to the method described in Shinjikken Kagaku Koza (Courses in Experimental Chemistry), vols. 14 and 15 (The Chemical Society of Japan ed.), ORGANIC
 5 FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC., (1989); Comprehensive Organic Transformations, VCH Publishers Inc. (1989) and the like.

[0173]

Scheme 2



wherein X^4 is a leaving group, and other symbols are as defined above.

Compound (Ia-I) and compound (Ia-II), which are the compounds of the present invention, can be produced by
 15 subjecting compound (IIIa) to a series of reaction steps in Steps 1', 7 and 3', and Steps 1', 7, 3' and 8, respectively.

[0174]

(Step 1')

Compound (IIIb) can be produced by reacting compound
 20 (IIIa) with compound (IIa'). Compound (IIIa) is generally used in about 0.2 - 5.0 mol, preferably about 0.5 - 2.0 mol, per 1 mol of compound (IIa'). This reaction is advantageously performed in a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and,
 25 for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the like are preferable. In addition, when an acidic substance is released by the reaction, the
 30 reaction can be performed in the presence of a deoxidizer to

remove the substance from the reaction system. As the deoxidizer, for example, inorganic bases, basic salts, organic bases, metal alkoxides, alkali metal hydrides, metal amides and the like are used. The deoxidizer is generally used in
5 about 0.05 - 20 mol, preferably about 0.1 - 10 mol, per 1 mol of compound (IIa'). In addition, for example, basic salts, organic bases and the like can also be used to promote the reaction. Such basic salts, organic bases and the like are generally used in about 0.05 - 20 mol, preferably about 0.1 -
10 10 mol, per 1 mol of compound (IIa'). While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 72 hr, preferably 30 min - 24 hr. The reaction temperature is generally 0 - 200°C, preferably 50 - 150°C. In addition, microwave irradiation may be performed to
15 promote the reaction.

[0175]

(Step 7)

Compound (IIIc) can be produced by subjecting compound (IIb) to a reduction reaction. This reaction can be performed
20 according to a method known per se such as the method described in Shinjikken Kagaku Koza (Courses in Experimental Chemistry), vols. 14 and 15 (The Chemical Society of Japan ed.), ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC. (1989); Comprehensive Organic
25 Transformations, VCH Publishers Inc. (1989) and the like, or a method analogous thereto. For example, a method using a reducing agent can be mentioned. Examples of the reducing agent include zinc, tin chloride, and complexes of hydrogen and, for example, palladium-carbon, palladium hydroxide-carbon,
30 rhodium-carbon, platinum-carbon, Raney-nickel or the like. The reducing agent is generally used in about 0.0001 - 100 mol, preferably about 0.01 - 10 mol, per 1 mol of compound (IIb). This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as
35 long as the reaction proceeds and, for example, solvents such

as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the like are preferable.

5 [0176]

(Step 3')

Compound (Ia-I), which is the compound of the present invention, can be produced by subjecting compound (IIIc) to a cyclization reaction. This reaction can be performed according to a manufacturing method known per se, for example, the method described in Australian Journal of Chemistry, vol. 4, page 775 (1982), Shinjikken Kagaku Koza (Courses in Experimental Chemistry), vols. 14 and 15 (The Chemical Society of Japan ed.), ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC. (1989); Comprehensive Organic Transformations, VCH Publishers Inc. (1989) and the like, or a method analogous thereto. For example, a method using a carbonating agent can be mentioned. Examples of the carbonating agent include 1,1'-carbonylbis(1H-imidazole), phosgene, triphosgene, diethyl carbonate, dimethyl carbonate, di-tert-butyl dicarbonate, bis(2,5-dioxopyrrolidin-1-yl)carbonate and the like. The carbonating agent is generally used in about 0.2 - 5.0 mol, preferably about 0.5 - 2.0 mol, per 1 mol of compound (IIIc). In addition, a base can be used to promote the reaction. Examples of the base include inorganic bases, organic bases, metal alkoxides, alkali metal hydrides, metal amides and the like. The base is used in about 1.0 - 20 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (IIIc). This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as alcohols, ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases, water and the like or a mixed solvent thereof and the like are

preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 72 hr, preferably 30 min - 24 hr. The reaction temperature is generally 0 - 200°C, preferably 0 - 100°C. In addition,
5 microwave irradiation may be performed to promote the reaction.
[0177]

(Step 8)

Compound (Ia-II), which is the compound of the present invention, can be produced by reacting compound (Ia-I) with R^d-
10 X⁴ in the presence of a base. The R^d-X⁴ is used in about 0.05 - 100 mol, preferably about 0.1 - 10 mol, per 1 mol of compound (Ia-I). Examples of the base include inorganic bases, basic salts, organic bases, metal amides and the like. The base is used in about 0.5 - 10.0 mol, preferably about 1.0 - 5.0 mol,
15 per 1 mol of compound (Ia-I). To promote the reaction, for example, sodium iodide, potassium iodide and the like may be added. Such sodium iodide, potassium iodide and the like are used in about 0.05 - 100 mol, preferably about 0.1 - 50 mol, per 1 mol of compound (Ia-I). This reaction is advantageously
20 performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides and the like or a mixed solvent thereof
25 and the like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 100 hr, preferably 30 min - 24 hr. The reaction temperature is generally -20 to 250°C, preferably 0 to 230°C. In addition, microwave irradiation may be performed to
30 promote the reaction.

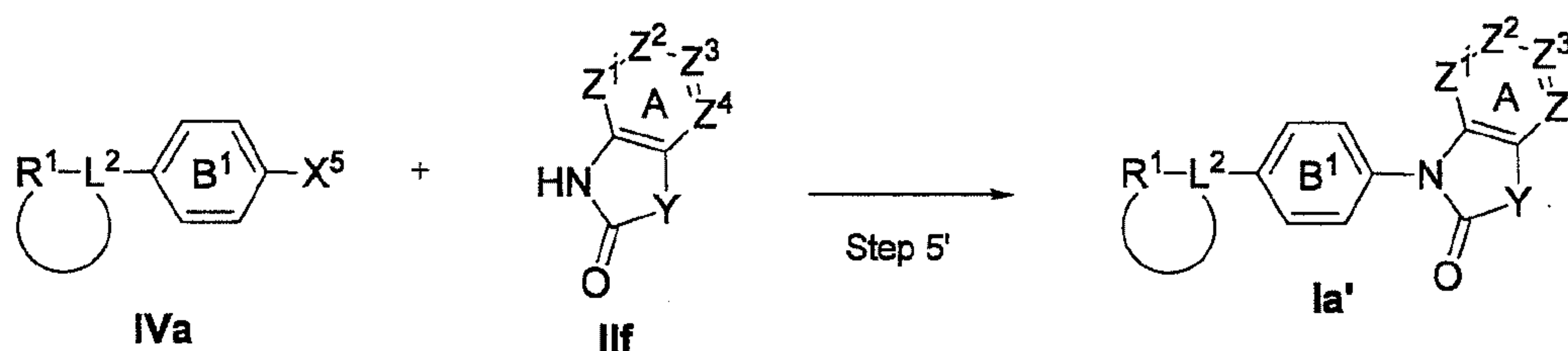
[0178]

Compounds (IIIa), (IIa'), (IIIb) and (IIIc) may be commercially available products, or can be produced according to a method known per se or a method analogous thereto. In
35 addition, R^d-X⁴ may be a commercially available product, or can

also be produced by a known substituent conversion reaction, condensation reaction, oxidation reaction, reduction reaction and the like, which may be used alone or in a combination of two or more thereof. These reactions may be performed according to, for example, the method described in Shinjikken Kagaku Koza (Courses in Experimental Chemistry), vols. 14 and 15 (The Chemical Society of Japan ed.), ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC. (1989); Comprehensive Organic Transformations, VCH Publishers Inc. (1989) and the like.

[0179]

Scheme 3



wherein X⁵ is a leaving group, and other symbols are as defined above.

Compound (Ia'), which is the compound of the present invention, can be produced by subjecting compound (IVa) to the reaction step of Step 5'.

[0180]

20 (Step 5')

Compound (Ia'), which is the compound of the present invention, can be produced by subjecting compound (IIIf) and compound (IVa) to a substitution reaction in the presence of a metal catalyst as necessary. Compound (IIIf) is used in about 0.5 - 20 mol, preferably about 0.8 - 10 mol, per 1 mol of compound (IVa). As the metal catalyst, a metal complex having a variety of ligands is used and, for example, palladium compounds [e.g., palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) chloride, dichlorobis(triethylphosphine)palladium(0),

tris(dibenzylideneacetone)dipalladium(0), complex of palladium(II) acetate and 1,1'-bis(diphenylphosphino)ferrocene, complex of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and
5 dichloromethane, complex of tris(dibenzylideneacetone)dipalladium(0) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (DavePhos), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (xantphos), or dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphane (SPhos), etc.], nickel compounds [e.g., tetrakis(triphenylphosphine)nickel (0), bis(triethylphosphine)nickel (II) chloride, bis(triphenylphosphine)nickel (II) chloride, etc.], rhodium
15 compounds [e.g., tris(triphenylphosphine)rhodium (III) chloride, etc.], cobalt compound, copper compounds [e.g., copper oxide, copper(I) iodide, copper sulfate, copper(II) chloride, etc.], platinum compound and the like can be mentioned. Of these, a palladium compound and a copper
20 compound are preferable. The metal catalyst is used in about 0.0001 - 5 mol, preferably about 0.001 - 1 mol, per 1 mol of compound (IIIf). This reaction is preferably performed in the presence of a base. Examples of the base include inorganic bases, organic bases, metal alkoxides, alkali metal hydrides,
25 metal amides and the like. The base is used in about 1.0 - 20 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (IIIf). In addition, when a metal catalyst unstable to oxygen is used in this reaction, for example, the reaction is preferably performed in an inert gas stream such as argon gas,
30 nitrogen gas and the like. This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as alcohols, ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, nitriles,
35 sulfoxides, esters, water and the like or a mixed solvent

thereof and the like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 100 hr, preferably 30 min - 50 hr. The reaction temperature is -10 to 250°C, preferably 50 to 150°C.

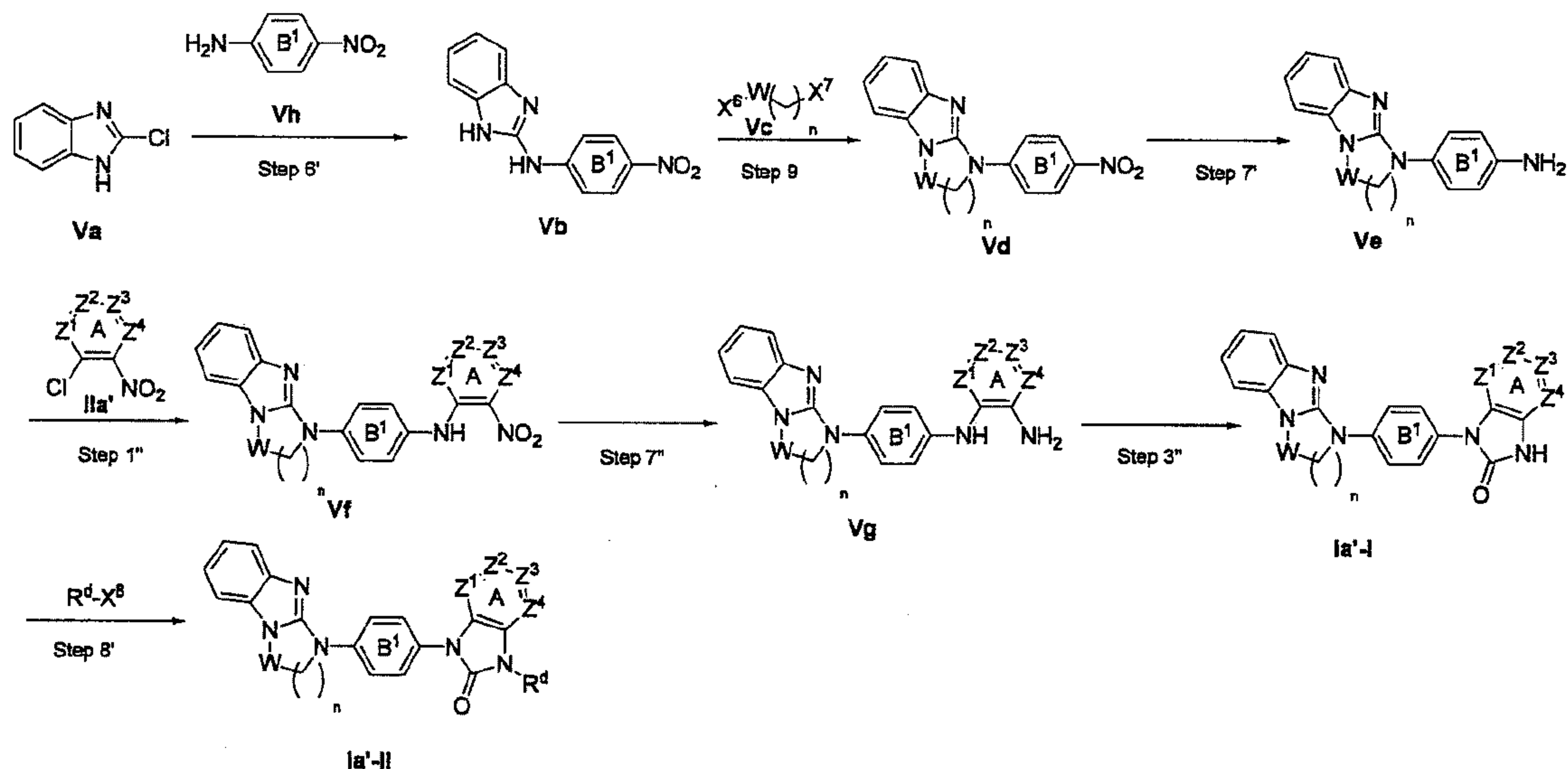
In addition, microwave irradiation may be performed to promote the reaction.

[0181]

Compound (IIIf) and compound (IVa) may be commercially available products, or can also be produced according to the method described in Shinjikken Kagaku Koza (Courses in Experimental Chemistry), vols. 14 and 15 (The Chemical Society of Japan ed.), ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC., (1989); Comprehensive Organic Transformations, VCH Publishers Inc. (1989), Heterocycles, vol. 4, page 799 (1985) and the like, or a method analogous thereto.

[0182]

Scheme 4



wherein W is an optionally substituted methylene group or a carbonyl group, $X^6 - X^8$ are each a leaving group, n is an integer of 1 to 5, and other symbols are as defined above. Examples of the substituent that the "methylene group" of the "optionally substituted methylene group" for W may have include 1 or 2 substituent selected from substituent group A.

Compound (Ia'-I) and compound (Ia'-II), which are the

compounds of the present invention, can be produced by subjecting compound (Va) to a series of reaction steps in Steps 6', 9, 7', 1'', 7'' and 3'', and Steps 6', 9, 7', 1'', 7'', 3'' and 8', respectively.

5 [0183]

(Step 6')

Compound (Vb) can be produced by subjecting compound (Va) and compound (Vh) to a substitution reaction. This reaction may be performed according to a method similar to that in
10 (Step 6) above.

[0184]

(Step 9)

Compound (Vd) can be produced by subjecting compound (Vb) and compound (Vc) to a substitution reaction. Compound (Vc) is
15 used in about 0.5 - 10.0 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (Vb). This reaction can be performed in the presence of a base to promote the reaction. Examples of the base include inorganic bases, basic salts, organic bases, metal alkoxides, alkali metal hydrides, metal amides and the
20 like. The base is used in about 0.5 - 10.0 mol, preferably 0.8 - 5.0 mol, per 1 mol of compound (Vb). In addition, to promote the reaction, for example, sodium iodide, potassium iodide and the like may be added. Such sodium iodide, potassium iodide and the like are used in about 0.05 - 100 mol, preferably
25 about 0.1 - 50 mol, per 1 mol of compound (Vc). This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides,
30 halogenated hydrocarbons, nitriles, sulfoxides and the like or a mixed solvent thereof and the like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 100 hr, preferably 30 min - 24 hr. The reaction temperature is generally -20 to 250°C,
35 preferably 0 to 230°C. In addition, microwave irradiation may

be performed to promote the reaction.

[0185]

(Step 7')

Compound (Ve) can be produced by subjecting compound (Vd)
5 to a reduction reaction. This reaction may be performed
according to a method similar to that in the above-mentioned
(Step 7).

[0186]

(Step 1'')

10 Compound (Vf) can be produced by reacting compound (Ve)
with compound (IIa'). This reaction may be performed according
to a method similar to that in the above-mentioned (Step 1').

[0187]

(Step 7'')

15 Compound (Vg) can be produced by subjecting compound (Vf)
to a reduction reaction. This reaction may be performed
according to a method similar to that in the above-mentioned
(Step 7).

[0188]

20 (Step 3'')

Compound (Ia'-I), which is the compound of the present
invention, can be produced by subjecting compound (Vg) to a
cyclization reaction. This reaction can be performed according
to a manufacturing method known per se, for example, the
25 method described in Bioorganic and Medicinal Chemistry Letters,
vol. 6, page 1702 (2009); Journal of Medicinal Chemistry, vol.
13, page 3881 (2009); ORGANIC FUNCTIONAL GROUP PREPARATIONS,
2nd edition, ACADEMIC PRESS, INC., (1989); Comprehensive
Organic Transformations, VCH Publishers Inc. (1989) and the
30 like, or a method analogous thereto and, for example, a method
using a carbonating agent can be mentioned. Examples of the
carbonating agent include 1,1'-carbonylbis(1H-imidazole),
phosgene, triphosgene, diethyl carbonate, dimethyl carbonate,
di-tert-butyl dicarbonate and the like. The carbonating agent
35 is generally used in about 0.2 - 5.0 mol, preferably about 0.5

- 2.0 mol, per 1 mol of compound (Vg). When an acidic substance is released by the reaction, the reaction can be performed in the presence of a deoxidizer to remove the substance from the reaction system. As such deoxidizer, 5 inorganic bases, basic salts, organic bases, metal alkoxides, alkali metal hydrides, metal amides and the like are used. The deoxidizer is generally used in about 0.2 - 10 mol, preferably about 0.5 - 6.0 mol, per 1 mol of compound (Vg). This reaction is advantageously performed in a solvent inert to the reaction. 10 Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the 15 like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 72 hr, preferably 30 min - 24 hr. The reaction temperature is generally 0 - 200°C, preferably 0 - 100°C. In addition, microwave irradiation may be performed to promote the reaction.

20 [0189]

(Step 8')

Compound (Ia'-II), which is the compound of the present invention, can be produced by reacting compound (Ia'-I) with R^d-X^8 in the presence of a base. This reaction may be 25 performed according to a method similar to that in the above-mentioned (Step 8).

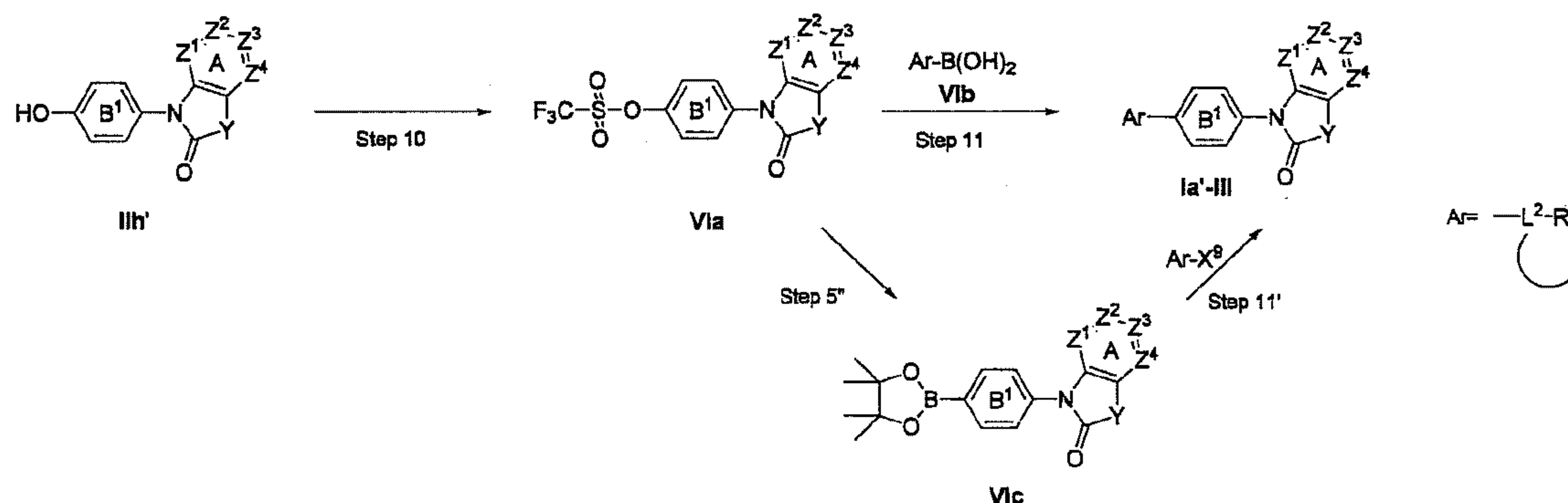
[0190]

Compounds (Va), (Vb), (Vc), (Vd), (Ve), (Vf) and (Vg) and R^d-X^8 may be commercially available products, or they can be 30 produced according to a method known per se or a method analogous thereto. In addition, compound (Vc) can also be produced according to a known substituent conversion reaction, condensation reaction, oxidation reaction, reduction reaction and the like, which may be used alone or in a combination of 35 two or more thereof. These reactions can also be performed

according to, for example, the method described in Shinjikken Kagaku Koza (Courses in Experimental Chemistry), vols. 14 and 15 (The Chemical Society of Japan ed.), ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC. (1989);
 5 Comprehensive Organic Transformations, VCH Publishers Inc. (1989), Synthesis, vol. 7, page 577 (1982), Journal of Organic Chemistry, vol. 1, page 284 (2007), Russian Journal of General Chemistry, vol. 9, page 1457 (2003) and the like. Compound (Vb) can also be produced according to the method described in
 10 Tetrahedron Letters, vol. 22, page 3747 (2006) and the like, or a method analogous thereto.

[0191]

Scheme 5



15 wherein X⁹ is a leaving group, and other symbols are as defined above.

Compound (Ia'-III), which is the compound of the present invention, can be produced by subjecting compound (IIh') to a series of reaction steps in Steps 10 and 11.

20 Compound (Ia'-III) can also be produced by subjecting compound (IIh') to a series of reaction steps in Steps 10, 5'' and 11'.

[0192]

(Step 10)

25 Compound (VIa) can be produced by reacting compound (IIh') with a trifluoromethanesulfonylating agent. Examples of the trifluoromethanesulfonylating agent include trifluoromethanesulfonylchloride, trifluoromethanesulfonic anhydride, N-phenylbis(trifluoromethanesulfonimide), N-(5-

chloropyridin-2-yl)-1,1,1-trifluoro-N-
[(trifluoromethyl)sulfonyl]methanesulfonamide and the like.
The trifluoromethanesulfonylating agent is generally used in
about 0.2 - 5.0 mol, preferably about 0.5 - 2.0 mol, per 1 mol
5 of compound (IIh'). In addition, bases such as basic salts,
organic bases and the like can be used to promote the reaction.
The base is generally used in about 0.2 - 20.0 mol, preferably
about 0.5 - 10.0 mol, per 1 mol of compound (IIh'). This
reaction is advantageously performed in a solvent inert to the
10 reaction. Such solvent is not particularly limited as long as
the reaction proceeds and, for example, solvents such as
ethers, aromatic hydrocarbons, saturated hydrocarbons, amides,
halogenated hydrocarbons, nitriles, sulfoxides, aromatic
organic bases and the like or a mixed solvent thereof and the
15 like are preferable. While the reaction time varies depending
on the reagent and solvent to be used, it is generally 10 min
- 72 hr, preferably 30 min - 24 hr. The reaction temperature
is generally 0 - 100°C, preferably 0 - 70°C.
[0193]

20 (Step 5'')

Compound (VIc) can be produced by condensing compound
(VIa) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The
condensation reaction is performed by reacting compound (VIa)
with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence
25 of a metal catalyst. The 4,4,5,5-tetramethyl-1,3,2-
dioxaborolane is used in about 0.1 - 10 mol, preferably about
0.8 - 2.0 mol, per 1 mol of compound (VIa). As the metal
catalyst, palladium compound [e.g., palladium(II) acetate,
tetrakis(triphenylphosphine)palladium(0),
30 bis(triphenylphosphine)palladium(II) chloride,
dichlorobis(triethylphosphine)palladium(0),
tris(dibenzylideneacetone)dipalladium(0), complex of
palladium(II) acetate and 1,1'-bis(diphenylphosphino)ferrocene,
complex of [1,1'-
35 bis(diphenylphosphino)ferrocene]dichloropalladium(II) and

dichloromethane, complex of tris(dibenzylideneacetone)dipalladium(0) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (DavePhos), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos),
5 (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (xantphos) or dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphane (SPhos) etc.] are preferable. The metal catalyst is used in about 0.000001 - 5.0 mol, preferably about 0.0001 - 1.0 mol, per 1 mol of compound (VIa).
10 This reaction is generally performed in the presence of a base. Examples of the base include inorganic bases, basic salts, organic bases, metal alkoxides, alkali metal hydrides, metal amides and the like. The base is used in about 1.0 - 20 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (VIa).
15 When a metal catalyst unstable to oxygen is used in these reactions, the reaction is preferably performed, for example, in an inert gas stream such as argon gas, nitrogen gas and the like. This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly
20 limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, esters, water and the like or a mixed solvent thereof and the like are preferable. While the reaction time varies depending
25 on the reagent and solvent to be used, it is generally 1 min - 200 hr, preferably 5 min - 100 hr. The reaction temperature is -10 to 250°C, preferably 0 to 150°C. In addition, microwave irradiation may be performed to promote the reaction.

[0194]

30 (Step 11)

Compound (Ia'-III), which is the compound of the present invention, can be produced by condensing compound (VIa) and compound (Vib). The condensation reaction is performed by reacting compound (VIa) with compound (Vib) in the presence of
35 a metal catalyst. Compound (Vib) is used in about 0.1 - 10 mol,

preferably about 0.8 - 2.0 mol, per 1 mol of compound (VIa).
As the metal catalyst, palladium compound [e.g., palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) chloride,
5 dichlorobis(triethylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), complex of palladium(II) acetate and 1,1'-bis(diphenylphosphino)ferrocene, complex of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and
10 dichloromethane, complex of tris(dibenzylideneacetone)dipalladium(0) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (DavePhos), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (xantphos) or dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphane (SPhos), etc.] is preferable.
The metal catalyst is used in about 0.000001 - 5.0 mol, preferably about 0.0001 - 1.0 mol, per 1 mol of compound (VIa). This reaction is generally performed in the presence of a base.
20 Examples of the base include inorganic bases, basic salts and the like. The base is used in about 1.0 - 20 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (VIa). When a metal catalyst unstable to oxygen is used in these reactions, the reaction is preferably performed, for example, in inert gas
25 stream such as argon gas, nitrogen gas and the like. This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as alcohols, ethers, aromatic hydrocarbons, saturated
30 hydrocarbons, amides, halogenated hydrocarbons, nitriles, esters, water and the like or a mixed solvent thereof and the like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 1 min - 200 hr, preferably 5 min - 100 hr. The reaction temperature is
35 -10 to 250°C, preferably 0 to 150°C. In addition, microwave

irradiation may be performed to promote the reaction.

[0195]

(Step 11')

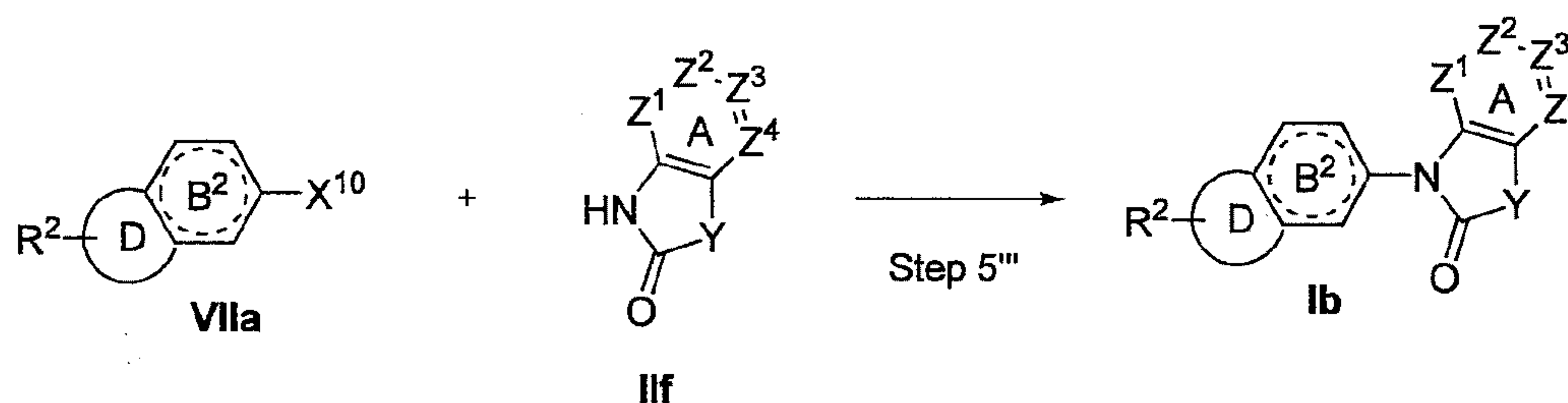
Compound (Ia'-III), which is the compound of the present invention, can be produced by reacting compound (VIc) with Ar-X⁹ in the presence of a base and a metal catalyst. This reaction may be performed according to a method similar to that in the above-mentioned (Step 11).

[0196]

Compounds (IIh'), (VIa), (VIb) and (VIc) and Ar-X⁹ may be commercially available products, or can also be produced according to a method known per se or a method analogous thereto.

[0197]

Scheme 6



wherein X¹⁰ is a leaving group, and other symbols are as defined above.

Compound (Ib), which is the compound of the present invention, can be produced by subjecting compound (VIIa) to the reaction step of Step 5'''.

[0198]

(Step 5''')

Compound (Ib), which is the compound of the present invention, can be produced by reacting compound (VIIa) with compound (IIIf) in the presence of a base and a metal catalyst. This reaction may be performed according to a method similar to that in the above-mentioned (Step 5).

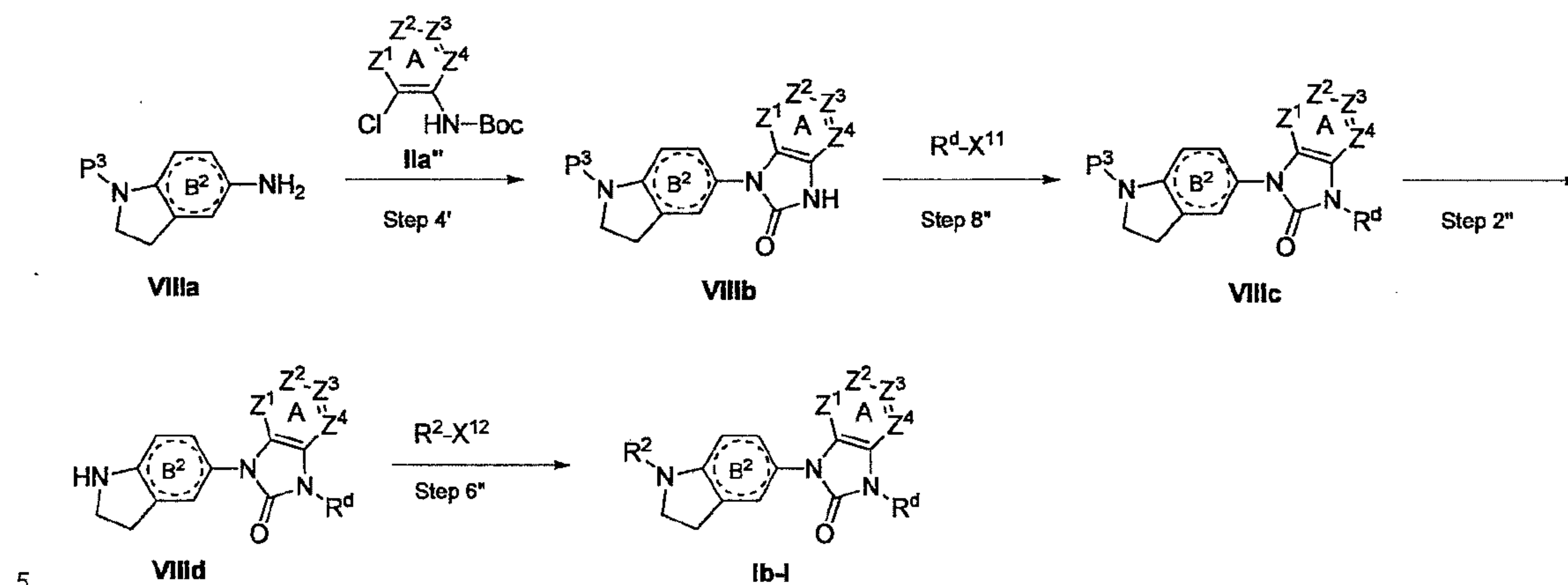
[0199]

Compound (VIIa) and compound (IIIf) may be commercially

available products, or can also be produced according to a method known per se or a method analogous thereto.

[0200]

Scheme 7



wherein X^{11} and X^{12} are each a leaving group, and other symbols are as defined above.

Compound (Ib-I), which is the compound of the present invention, can be produced by subjecting compound (VIIIa) to the reaction steps in Steps 4', 8'', 2'' and 6'''.

[0201]

(Step 4')

Compound (VIIIb) can be produced by subjecting compound (VIIIa) and compound (IIa'') to a condensation reaction, or to a coupling reaction in the presence of a metal catalyst. This reaction can also be performed according to a manufacturing method known per se, the method described in Synlett, vol. 13, page 2083 (2006) and the like, or a method analogous thereto. Compound (IIa'') is generally used in about 0.2 - 5.0 mol, preferably about 0.5 - 2.0 mol, per 1 mol of compound (VIIIa). As the metal catalyst, a metal complex having a variety of ligands is used and, for example, palladium compounds [e.g., palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) chloride, dichlorobis(triethylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), complex of

palladium(II) acetate and 1,1'-bis(diphenylphosphino)ferrocene, complex of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and dichloromethane, complex of

5 tris(dibenzylideneacetone)dipalladium(0) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (DavePhos), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (Xantphos) or dicyclohexyl(2',6'-

10 dimethoxybiphenyl-2-yl)phosphane (SPhos), etc.], nickel compounds [e.g., tetrakis(triphenylphosphine)nickel (0), bis(triethylphosphine)nickel (II) chloride, bis(triphenylphosphine)nickel (II) chloride, etc.], copper compounds [e.g., copper oxide, copper(I) iodide, copper

15 sulfate, copper(II) chloride, etc.] and the like can be mentioned. The metal catalyst is used in about 0.0001 - 5 mol, preferably about 0.001 - 1 mol, per 1 mol of compound (IIIf). This reaction is preferably performed in the presence of a base. Examples of the base include inorganic bases, organic

20 bases, metal alkoxides, alkali metal hydrides, metal amides and the like. This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as alcohols, ethers, aromatic

25 hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the like are preferable. In addition, when an acidic substance is released by the reaction, the reaction can be performed in the presence

30 of a deoxidizer to remove the substance from the reaction system. As such deoxidizer, for example, inorganic bases, basic salts, organic bases, metal alkoxides, alkali metal hydrides, metal amides and the like are used. The deoxidizer is generally used in about 0.05 - 20 mol, preferably about 1 -

35 10 mol, per 1 mol of compound (VIIIa). In addition, for

example, basic salts, organic bases and the like can be used to promote the reaction. Such basic salts, organic bases and the like are generally used in about 0.05 - 20 mol, preferably about 1 - 10 mol, per 1 mol of compound (VIIIa). While the
5 reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 200 hr, preferably 30 min - 48 hr. The reaction temperature is generally 0 - 200°C, preferably 50 - 150°C. In addition, microwave irradiation may be performed to promote the reaction.

10 [0202]

(Step 8")

Compound (VIIIc) can be produced by reacting compound (VIIIb) with R^d-X^{11} in the presence of a base. This reaction can be performed according to a method similar to that in the
15 above-mentioned (Step 8).

[0203]

(Step 2")

Compound (VIId) can be produced by removing the protective group (P^3) of compound (VIIIc). When P^3 is a
20 hydrogen atom, this step can be omitted. This reaction can be performed according to a method similar to that in the above-mentioned (Step 2).

[0204]

(Step 6")

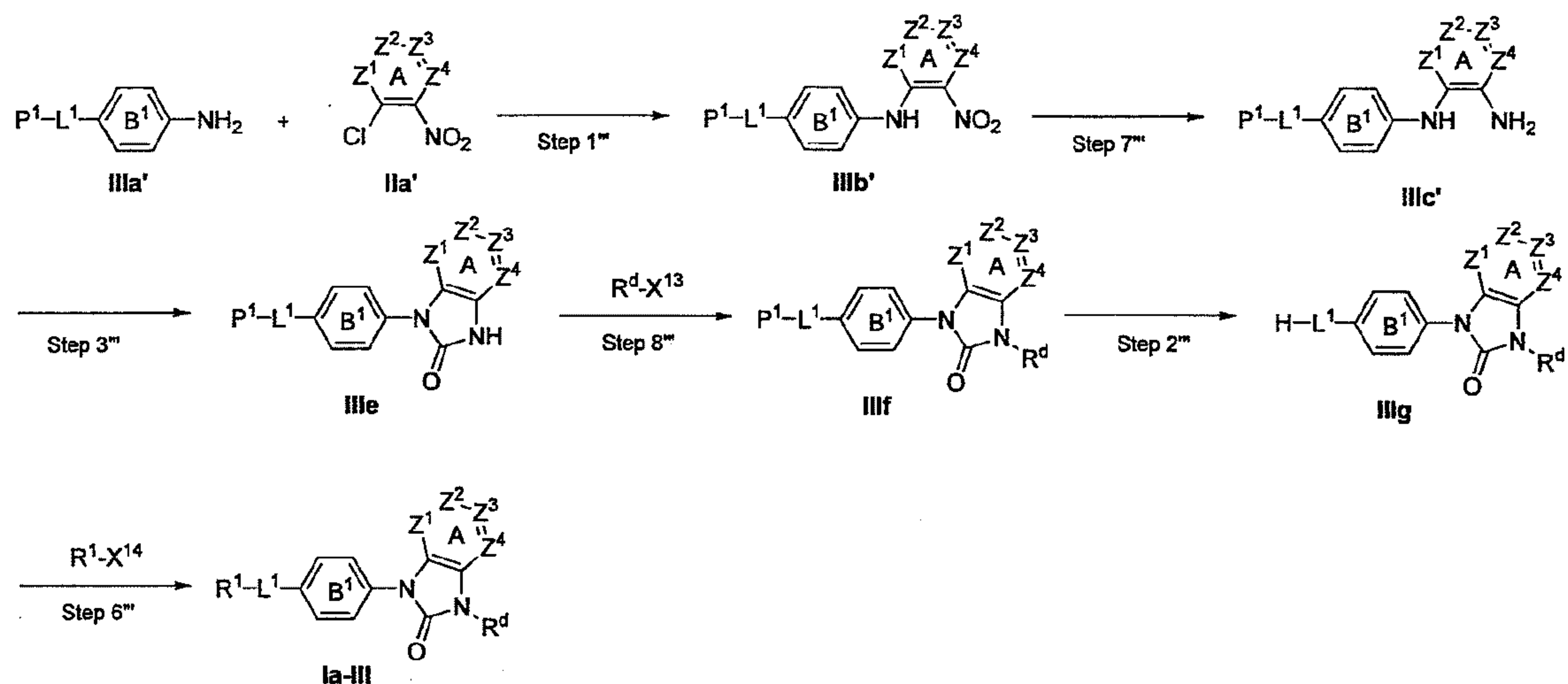
25 Compound (Ib-I), which is the compound of the present invention, can be produced by reacting compound (VIId) with R^2-X^{12} in the presence of a base. This reaction may be performed according to a method similar to that in the above-mentioned (Step 6).

30 [0205]

Compounds (VIIIa), (IIa"), (VIIIb), (VIIIc) and (VIId), and R^d-X^{11} and R^2-X^{12} may be commercially available products, or can also be produced according to a method known per se or a method analogous thereto.

[0206]

Scheme 8



wherein X^{13} and X^{14} are each a leaving group, and the other
5 symbols are as defined above.

Compound (Ia-III), which is the compounds of the present invention, can be produced by subjecting compound (IIIa') to a series of reaction steps in Steps 1''', 7''', 3''', 8''', 2''', and 6'''.

10 [0207]

(Step 1''')

Compound (IIIb') can be produced by reacting compound (IIIa') with compound (IIa'). Compound (IIIa') is generally used in about 0.2 - 5.0 mol, preferably about 0.5 - 2.0 mol,
15 per 1 mol of compound (IIa'). This reaction is advantageously performed in a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons,
20 nitriles, sulfoxides, aromatic organic bases and the like or a mixed solvent thereof and the like are preferable. In addition, when an acidic substance is released by the reaction, the reaction can be performed in the presence of a deoxidizer to remove the substance from the reaction system. As the
25 deoxidizer, for example, inorganic bases, basic salts, organic bases, metal alkoxides, alkali metal hydrides, metal amides

and the like are used. The deoxidizer is generally used in about 0.05 - 20 mol, preferably about 0.1 - 10 mol, per 1 mol of compound (IIa'). In addition, for example, basic salts, organic bases and the like can also be used to promote the
5 reaction. Such basic salts, organic bases and the like are generally used in about 0.05 - 20 mol, preferably about 0.1 - 10 mol, per 1 mol of compound (IIa'). While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 72 hr, preferably 30 min - 24 hr. The
10 reaction temperature is generally 0 - 200°C, preferably 50 - 150°C. In addition, microwave irradiation may be performed to promote the reaction.

[0208]

(Step 7''')

15 Compound (IIIc') can be produced by subjecting compound (IIIb') to a reduction reaction. This reaction can be performed according to a method known per se such as the method described in Shinjikken Kagaku Koza (Courses in Experimental Chemistry), vols. 14 and 15 (The Chemical Society
20 of Japan ed.), ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC. (1989); Comprehensive Organic Transformations, VCH Publishers Inc. (1989) and the like, or a method analogous thereto. For example, a method using a reducing agent can be mentioned. Examples of the reducing
25 agent include zinc, tin chloride, and complexes of hydrogen and, for example, palladium-carbon, palladium hydroxide-carbon, rhodium-carbon, platinum-carbon, Raney-nickel or the like. The reducing agent is generally used in about 0.0001 - 100 mol, preferably about 0.01 - 10 mol, per 1 mol of compound (IIIb').
30 This reaction is advantageously performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides,
35 aromatic organic bases and the like or a mixed solvent thereof

and the like are preferable.

[0209]

(Step 3''')

Compound (IIIe) can be produced by subjecting compound
5 (IIIc') to a cyclization reaction. This reaction can be
produced according to a manufacturing method known per se, for
example, the method described in Australian Journal of
Chemistry, vol. 4, page 775 (1982), Shinjikken Kagaku Koza
(Courses in Experimental Chemistry), vols. 14 and 15 (The
10 Chemical Society of Japan ed.), ORGANIC FUNCTIONAL GROUP
PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC. (1989);
Comprehensive Organic Transformations, VCH Publishers Inc.
(1989) and the like, or a method analogous thereto. For
example, a method using a carbonating agent can be mentioned.
15 Examples of the carbonating agent include 1,1'-carbonylbis(1H-
imidazole), phosgene, triphosgene, diethyl carbonate, dimethyl
carbonate, di-tert-butyl dicarbonate, bis(2,5-dioxopyrrolidin-
1-yl)carbonate and the like. The carbonating agent is
generally used in about 0.2 - 5.0 mol, preferably about 0.5 -
20 2.0 mol, per 1 mol of compound (IIIc'). In addition, a base
can be used to promote the reaction. Examples of the base
include inorganic bases, organic bases, metal alkoxides,
alkali metal hydrides, metal amides and the like. The base is
used in about 1.0 - 20 mol, preferably about 1.0 - 5.0 mol,
25 per 1 mol of compound (IIIc'). This reaction is advantageously
performed in a solvent inert to the reaction. Such solvent is
not particularly limited as long as the reaction proceeds and,
for example, solvents such as alcohols, ethers, aromatic
hydrocarbons, saturated hydrocarbons, amides, halogenated
30 hydrocarbons, nitriles, sulfoxides, aromatic organic bases,
water and the like or a mixed solvent thereof and the like are
preferable. While the reaction time varies depending on the
reagent and solvent to be used, it is generally 10 min - 72 hr,
preferably 30 min - 24 hr. The reaction temperature is
35 generally 0 - 200°C, preferably 0 - 100°C. In addition,

microwave irradiation may be performed to promote the reaction.

[0210]

(Step 8''')

Compound (IIIIf) can be produced by reacting compound
5 (IIIe) with R^d-X^{13} in the presence of a base. R^d-X^{13} is used in
about 0.05 - 100 mol, preferably about 0.1 - 10 mol, per 1 mol
of compound (IIIe). Examples of the base include inorganic
bases, basic salts, organic bases, metal amides and the like.
The base is used in about 0.5 - 10.0 mol, preferably about 1.0
10 - 5.0 mol, per 1 mol of compound (IIIe). To promote the
reaction, for example, sodium iodide, potassium iodide and the
like may be added. Such sodium iodide, potassium iodide and
the like are used in about 0.05 - 100 mol, preferably about
0.1 - 50 mol, per 1 mol of compound (IIIe). This reaction is
15 advantageously performed in a solvent inert to the reaction.
Such solvent is not particularly limited as long as the
reaction proceeds and, for example, solvents such as ethers,
aromatic hydrocarbons, saturated hydrocarbons, amides,
halogenated hydrocarbons, nitriles, sulfoxides and the like or
20 a mixed solvent thereof and the like are preferable. While the
reaction time varies depending on the reagent and solvent to
be used, it is generally 10 min - 100 hr, preferably 30 min -
24 hr. The reaction temperature is generally -20 to 250°C,
preferably 0 to 230°C. In addition, microwave irradiation may
25 be performed to promote the reaction.

[0211]

(Step 2''')

Compound (IIIg) can be produced by removing the
protective group (P^1) of compound (IIIIf). When P^1 is a
30 hydrogen atom, this step can be omitted. This reaction may be
performed according to a method similar to that of the above-
mentioned (Step 2).

[0212]

(Step 6''')

35 Compound (Ia-III), which is the compound of the present

invention, can be produced by subjecting compound (IIIg) and R^1-X^{14} to a substitution reaction in the presence of a base. R^1-X^{14} is used in about 0.05 - 100 mol, preferably about 0.1 - 10 mol, per 1 mol of compound (IIIg). Examples of the base include inorganic bases, basic salts, organic bases, metal amides, alkali metal hydrides and the like. The base is used in about 0.5 - 10.0 mol, preferably about 1.0 - 5.0 mol, per 1 mol of compound (IIIg). This reaction is advantageously performed in a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, solvents such as ethers, aromatic hydrocarbons, saturated hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides and the like or a mixed solvent thereof and the like are preferable. While the reaction time varies depending on the reagent and solvent to be used, it is generally 10 min - 100 hr, preferably 30 min - 24 hr. The reaction temperature is generally -20 - 250°C, preferably 0 - 230°C. In addition, microwave irradiation may be performed to promote the reaction.

[0213]

Compounds (IIIa'), (IIa'), (IIIb'), (IIIc'), (IIIe), (IIIIf) and (IIIg) may be commercially available products, or can be produced according to a method known per se or a method analogous thereto. In addition, R^d-X^{13} and R^1-X^{14} may be commercially available products, or can also be produced by a known substituent conversion reaction, condensation reaction, oxidation reaction, reduction reaction and the like, which may be used alone or in a combination of two or more thereof. These reactions may be performed according to, for example, the method described in Shinjikken Kagaku Koza (Courses in Experimental Chemistry), vols. 14 and 15 (The Chemical Society of Japan ed.), ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd edition, ACADEMIC PRESS, INC. (1989); Comprehensive Organic Transformations, VCH Publishers Inc. (1989) and the like.

35

[0214]

Compound (I) obtained by the above-mentioned methods can be isolated and purified by, for example, general separation means such as recrystallization, distillation, chromatography and the like. When the thus-obtained compound (I) of the present invention is in a free form, it can be converted to a salt thereof by a known method or a comparable method (e.g., neutralization etc.). Alternatively, when it is obtained as a salt, it can be converted to a free form or other salt by a known method or a comparable method.

In any of the above-mentioned manufacturing methods and steps, compound (I) can be synthesized by known protection and deprotection reactions, acylation reaction, alkylation reaction, hydrogenation reaction, oxidation reaction, reduction reaction, carbon chain extension reaction, substituent exchanging reactions and the like, which may be used alone or in a combination of two or more thereof.

[0215]

Compound (I) may be used as a prodrug. A prodrug of compound (I) means a compound converted to compound (I) by a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound converted to compound (I) by oxidation, reduction, hydrolysis, etc. due to an enzyme, a compound converted to compound (I) by hydrolysis etc. due to gastric acid, and the like.

A prodrug of compound (I) may be a compound obtained by subjecting an amino group in compound (I) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (I) to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation, etc.); a compound obtained by subjecting a hydroxy group in compound (I) to acylation, alkylation, phosphorylation

or boration (e.g., a compound obtained by subjecting a hydroxy group in the compound (I) to acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation, etc.); a
5 compound obtained by subjecting a carboxy group in compound (I) to esterification or amidation (e.g., a compound obtained by subjecting a carboxy group in compound (I) to ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification,
10 pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonyl ethyl esterification or methylamidation, etc.) and the like. Any one of these compounds can be produced
15 from compound (I) by a method known *per se*. In addition, a prodrug of compound (I) may also be a compound converted into compound (I) under physiological conditions, such as those described in IYAKUJIN no KAIHATSU (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198,
20 Published by HIROKAWA SHOTEN (1990).
[0216]

The compound of the present invention has an excellent PDE10A inhibitory activity and is useful for the following diseases and symptoms in mammals (e.g., humans, cows, horses,
25 dogs, cats, monkeys, mice, rats, etc. particularly in humans):

psychotic disorder (e.g., brief psychotic disorder, shared psychotic disorder);

psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, obesity, inhalants, opioids, or
30 phencyclidine;

delusional disorder;

anxiety disorder;

movement disorder;

mood disorder;

35 major depressive disorder;

a major depressive disorder superimposed on a psychotic disorder comprising a delusional disorder or schizophrenia;
major depressive episode of the mild, moderate or severe type;

- 5 manic or mixed mood episode;
hypomanic mood episode;
depressive episode with atypical features;
depressive episode with melancholic features;
depressive episode with catatonic features;
10 mood episode with postpartum onset;
post-stroke depression;
dysthymic disorder;
minor depressive disorder;
autism;
15 drug addiction;
neurodegenerative disorder;
neurodegeneration associated with cerebral trauma;
neurodegeneration associated with stroke;
neurodegeneration associated with cerebral infarct;
20 hypoglycemia-induced neurodegeneration;
neurodegeneration associated with epileptic seizure;
neurodegeneration associated with neurotoxin poisoning;
multi-system atrophy;
Alzheimer's disease;
25 dementia;
multi-infarct dementia;
alcoholic dementia or other drug-related dementia;
dementia associated with intracranial tumors or cerebral trauma;
30 dementia associated with Huntington's disease or Parkinson's disease;
AIDS-related dementia;
frontotemporal dementia;
delirium;
35 amnestic disorder;

post-traumatic stress disorder;
mental retardation;
learning disorder (e.g., reading disorder, mathematics
disorder, or a disorder of written expression);
5 attention-deficit/hyperactivity disorder;
age-related cognitive decline;
premenstrual dysphoric disorder;
post-psychotic depressive disorder of schizophrenia;
bipolar disorders comprising bipolar I disorder, and
10 bipolar II disorder;
cyclothymic disorder;
Parkinson's disease;
Huntington's disease;
paranoid;
15 schizophrenia (e.g., paranoid schizophrenia, disorganized
schizophrenia, catatonic schizophrenia, undifferentiated
schizophrenia, residual schizophrenia);
schizophreniform disorder;
schizoaffective disorder of the delusional type or the
20 depressive type;
personality disorder of the paranoid type;
personality disorder of the schizoid type;
obesity;
metabolic syndrome;
25 non-insulin dependent diabetes mellitus (NIDDM);
glucose intolerance;

[0217]

In particular, the compound of the present invention is
useful for preventing or treating schizophrenia.

30 [0218]

Since the compound of the present invention demonstrates
excellent metabolic stability, superior therapeutic effects on
the aforementioned diseases are expected even at a low dosage.

The compound of the present invention shows low toxicity
35 and can be administered safely, as it is, or in a dosage form

which is manufactured according to a per se known method for manufacturing pharmaceutical formulations (e.g., methods described in Japanese Pharmacopoeia) such as tablets (inclusive of sugar coated tablet, film coated tablet, sublingual tablet, orally disintegrable tablet, and buccal), pills, powders, granules, capsules (inclusive of soft capsule, and microcapsule), troches, syrups, liquid dosage forms, emulsions, controlled-release preparations (e.g., quick-release preparation, sustained-release preparation, sustained-release microcapsule), aerosols, films (e.g., orally disintegrable film, adhesive film for application to oral-cavity mucosa), injections (e.g., subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection), drip infusion, percutaneous absorbent, ointment, lotion, patch, suppositories (e.g., rectal suppository, vaginal suppository), pellets, transnasal preparations, pulmonary preparations (inhalant), eye drops and the like, in an oral or parenteral route (e.g., intravenous, intramuscular, subcutaneous, intraorgan, intranasal, intradermal, ophthalmic instillation, intracerebral, intrarectal, intravaginal, intraperitoneal, directly to lesion).

The compound of the present invention can be administered orally or non-orally (e.g., including local, rectal and venous routes).

[0219]

Here, as a pharmaceutical acceptable carrier, common organic or inorganic carrier substances are used as formulation raw materials. Carriers are added as vehicles, lubricants, binders and disintegrants in the solid formulations; and as solvents, solubilizing agents, suspending agents, isotonization agents, buffers and soothing agents in the liquid formulations. If desired, formulation additives such as antiseptics, antioxidants, colorants, sweeteners, etc. can be used.

[0220]

Favorable examples of the vehicles are as follows:

lactose, sucrose, D-mannitol, D-sorbitol, starch, α -starch,
dextrin, crystalline cellulose, low-substituted hydroxypropyl
5 cellulose, sodium carboxymethylcellulose, gum Arabic, pullulan,
light silicic anhydride, synthetic aluminum silicate and
magnesium metasilicic aluminate.

Favorable examples of the lubricants include magnesium
stearate, calcium stearate, talc and colloidal silica.

10 [0221]

Favorable examples of the binders are as follows: α -
starch, sucrose, gelatin, gum Arabic, methylcellulose,
carboxymethylcellulose, sodium carboxymethylcellulose,
crystalline cellulose, D-mannitol, trehalose, dextrin,
15 pullulan, hydroxypropylcellulose, hydroxypropyl methyl
cellulose and polyvinylpyrrolidone.

[0222]

Favorable examples of the disintegrants are as follows:

lactose, sucrose, starch, carboxymethylcellulose, calcium
20 carboxymethylcellulose, croscarmellose sodium, sodium
carboxymethyl starch, light silicic anhydride and low-
substituted hydroxypropylcellulose.

[0223]

Favorable examples of the solvents are as follows: water

25 for injection, physiological saline, Linger solution, alcohol,
propylene glycol, polyethylene glycol, sesame oil, corn oil,
olive oil and cottonseed oil.

[0224]

Favorable examples of the solubilizing agents are as

30 follows: polyethylene glycol, propylene glycol, D-mannitol,
trehalose, benzylbenzoate, ethanol, tris-aminomethane,
cholesterol, triethanolamine, sodium carbonate, sodium citrate,
sodium salicylate and sodium acetate.

[0225]

35 Favorable examples of the suspending agents are as

follows: surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylamino propionic acid, lecithin, benzalkonium chloride, benzethonium chloride, and glycerin monostearate; hydrophilic polymers such as polyvinyl alcohol, 5 polyvinyl pyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose; polysorbates, and polyoxyethylene-hardened castor oil.

[0226]

10 Favorable examples of the isotonization agents include sodium chloride, glycerin, D-mannitol, D-sorbitol and glucose.

Favorable examples of the buffers include buffer solutions of phosphates, acetates, carbonates and citrates.

Favorable examples of the soothing agents include benzyl 15 alcohol.

Favorable examples of the antiseptics include para-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Favorable examples of the antioxidants include sulfites 20 and ascorbates.

[0227]

Favorable examples of the colorants include water soluble edible tar dyes (e.g., edible dyes such as Food Red No. 2 and No. 3, Food Yellow No. 4 and No. 5, Food Blue No. 1 and 2); 25 water insoluble lake dyes (e.g., aluminum salts of the aforementioned water soluble edible tar dyes), natural dyes (e.g., β -carotene, chlorophyll, red iron oxide).

Favorable examples of the sweeteners include sodium saccharin, dipotassium glycyrrhizate, aspartame and stevia.

30 [0228]

The medical compositions of the present invention can be manufactured by the common methods in the field of formulation technology, for example, methods listed in the Japanese pharmacopoeia. Specific manufacturing methods for formulations 35 are described in detail below.

The content of the compound of the present invention in the medical compositions of the present invention varies based on the dosage forms, dosages of the compound of the present invention, etc. For example, the content approximately ranges
5 from 0.01 to 100 wt% and preferably from 0.1 to 95 wt% relative to the entire amount of the composition.

[0229]

The dosage of the compound of the present invention depends upon injection targets, administration routes, target
10 diseases, symptoms, etc. For example, in the case of oral administration in patients with schizophrenia (adults, bodyweight of approximately 60 kg), generally a single dose ranges from approximately 0.1 to 20 mg/kg bodyweight, preferably from approximately 0.2 to 10 mg/kg bodyweight,
15 further preferably from approximately 0.5 to 10 mg/kg bodyweight, and this dosage is preferably administered once daily or several times daily (e.g., 3 times).

[0230]

The compounds can be administered as the sole active
20 agent or in combination with other pharmaceutical agents such as other agents used in the treatment of psychosis, especially schizophrenia and bipolar disorder, obsessive-compulsive disorder, major depression, Parkinson's disease, Alzheimer's disease, cognitive impairment and/or memory loss, e.g.,
25 nicotinic $\alpha 7$ agonists, nicotinic $\alpha 7$ partial agonists, nicotinic $\alpha 7$ positive allosteric modulators, PDE2 inhibitors, PDE4 inhibitors, PDE5 inhibitors, other PDE inhibitors, calcium channel blockers, muscarinic m1 and m2 modulators, adenosine receptor modulators, ampakines, Glycine transporter
30 1 inhibitors, NMDA-R modulators, mGluR modulators, dopamine modulators, serotonin modulators, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, triple reuptake inhibitors, cannabinoid modulators, and
35 cholinesterase inhibitors (e.g., donepezil, rivastigimine, and

galantamine). In such combinations, each active ingredient can be administered either in accordance with their usual dosage range or a dose below their usual dosage range, and can be administered either simultaneously or sequentially.

5 Drugs suitable in combination with the compounds of the present invention include, but are not limited to, other suitable schizophrenia drugs such as Haloperidol, Clozapine, Olanzapine, Risperidone, Aripiprazole, Ziprasidone, Paliperidone, and Quetiapine fumarate; bipolar disorder drugs,
10 including, but not limited to, Lithium, Olanzapine, Aripiprazole, and Valproic acid; Parkinson's disease drugs, including, but not limited to, Levodopa, Bromocriptine, Pergolide, Pramipexole, Tolcapone, Procyclidine, Trihexyphenidyl, and Benztropine; agents used in the treatment
15 of major depression, including, but not limited to, Amitriptyline, Protriptyline, Desipramine, Nortriptyline, Paroxetine, Fluoxetine, Sertraline, Bupropion, Escitalopram, Mirtazapine, Venlafaxine, Duloxetine; agents used in the treatment of Alzheimer's disease, including, but not limited
20 to, Galantamine, Tacrine, Donepezil, Rivastigmine, Memantine, Neotropin, Selegiline, Estrogen and Iodoquinol; agents used in the treatment of dementia, including, but not limited to, Thioridazine, Haloperidol, Risperidone, Tacrine, Donepezil, and Rivastigmine; agents used in the treatment of epilepsy,
25 including, but not limited to, Phenytoin, Phenobarbital, Carbamazepine, Valproic acid, Ethosuximide, Gabapentin, Phenobarbital, Solfeton and Felbatol; agents used in the treatment of multiple sclerosis, including, but not limited to, Tolterodine, Oxybutynin, Oxycodone, Interferon beta-1b,
30 Interferon beta-1a, Azathioprine, Methotrexate and Glatiramer; agents used in the treatment of Huntington's disease, including, but not limited to, Amitriptyline, Protriptyline, Desipramine, Nortriptyline, Paroxetine, Fluoxetine, Setraline, Tetrabenazine, Haloperidol, Chlorpromazine, Thioridazine,
35 Sulpiride, Quetiapine, Clozapine, and Risperidone; agents

useful in the treatment of diabetes, including, but not limited to, PPAR ligands (e.g. agonists, antagonists, such as Rosiglitazone, Troglitazone and Pioglitazone), insulin secretagogues (e.g., sulfonylurea drugs, such as Glyburide, 5 Glimepiride, Chlopropamide, Tolbutamide, and Glipizide, and non-sulfonyl secretagogues), α -glucosidase inhibitors (such as Acarbose, Miglitol, and Voglibose), insulin sensitizers (such as the PPAR- γ agonists, e.g., the glitazones; biguanides, PTP-1B inhibitors, DPP-IV inhibitors, and 11beta-HSD inhibitors), 10 hepatic glucose output lowering compounds (such as glucagon antagonists and metformin, e.g., Glucophage and Glucophage XR), insulin and insulin derivatives (both long and short acting forms and formulations of insulin); and antiobesity drugs, including, but not limited to, β -3 agonists, CB-1 agonists, 15 neuropeptide Y5 inhibitors, Ciliary Neurotrophic Factor and derivatives (e.g., Axokine), appetite suppressants (e.g., Sibutramine), and lipase inhibitors (e.g., Orlistat).

[0231]

The form of administration of concomitant drugs with the 20 compound of the present invention is not particularly limited and is acceptable as long as the compound of the present invention is combined with concomitant drugs at the time of administration. Examples of such forms of administration are as follows:

25 (1) administration of a single formula obtained by simultaneous formulation of the compound of the present invention with a concomitant drug,

(2) simultaneous administration via the same administration route for two kinds of formulas obtained by 30 independent formulations of the compound of the present invention and a concomitant drug,

(3) administrations at different times via the same administration route for two kinds of formulas obtained by independent formulations of the compound of the present 35 invention and a concomitant drug,

(4) simultaneous administration via different administration routes for two kinds of formulas obtained by independent formulations of the compound of the present invention and a concomitant drug,

5 (5) administrations at different times via different administration routes for two kinds of formulas obtained by independent formulations of the compound of the present invention and a concomitant drug (For example, administration in the order of the composition of the present invention and
10 then a concomitant drug, or administration in the reversed order). These forms of administration are summarized below and abbreviated as a concomitant agent of the present invention.
[0232]

When administering the concomitant agent of the present
15 invention, a concomitant drug and the compound of the present invention can be administered at the same time, but the compound of the present invention can be administered after a concomitant drug is administered or after the compound of the present invention is administered, a concomitant drug can be
20 administered. When administering at different times, the time difference depends upon the active ingredients to be administered, drug forms and methods of administration. For example, when a concomitant drug is administered first, the compound of the present invention can be administered within 1
25 min to 3 days, preferably within 10 min to 1 day and more preferably within 15 min to 1 hour after the concomitant drug is administered. However, if the compound of the present invention is administered first, a concomitant drug can be administered within 1 min to 1 day, preferably within 10 min.
30 to 6 hours and more preferably within 15 min to 1 hour after the compound of the present invention is administered.
[0233]

If there are no problems with side effects of the concomitant drugs, any dosages can be set. A daily dosage as a
35 concomitant drug depends upon dosages, administration subjects,

administration routes, target diseases, symptoms, etc. For example, in the case of oral administration in patients with schizophrenia (adults, bodyweight of approximately 60 kg), a normal daily dosage ranges from about 0.1 to 20 mg/kg bodyweight, preferably from about 0.2 to 10 mg/kg bodyweight and more preferably from about 0.5 to 10 mg/kg bodyweight. It is preferable that this dosage is administered once daily to several times daily (e.g., 3 times).

If the compound of the present invention is used in combination with a concomitant drug, the respective dosages can be reduced within a safe range with consideration of the opposite effects of the respective drugs.

[0234]

The concomitant agent of the present invention exhibits low toxicity. For example, the compound of the present invention or(and) the aforementioned concomitant drug can be combined with a pharmaceutically acceptable carrier according to the known method to prepare a medical composition such as tablets (including sugar-coated tablets and film-coated tablets), powder agents, granular agents, capsules (including soft capsules), liquids, injection solutions, suppositories, sustained-release agents, etc. These compositions can be administered safely orally or non-orally (e.g., including local, rectal and venous routes).

[0235]

The pharmaceutically acceptable carriers that can be used for manufacturing the concomitant agent of the present invention can be the same as those used in the medical composition of the present invention as mentioned above.

[0236]

A mixing ratio between the compound of the present invention and a concomitant drug in the concomitant agent of the present invention can be selected appropriately based on the administration subjects, administration routes and diseases.

The aforementioned concomitant drugs can be combined at an appropriate proportion if two or more drugs are combined.

A dosage of the concomitant drug can be selected appropriately based on the dosages used clinically. In addition, a mixing ratio between the compound of the present invention and a concomitant drug can be selected appropriately based on the administration subjects, administration routes, target diseases, symptoms, combinations, etc. For example, if the administration subject is humans, a concomitant drug can be used in an amount ranging from 0.01 to 100 parts by weight relative to 1 part by weight of the compound of the present invention.

[0237]

For example, the content of the compound of the present invention in the concomitant agent of the present invention varies with the drug form of formulations. Generally, it is present in a range from about 0.01 to 99.9 wt%, preferably from about 0.1 to 50 wt% and more preferably from about 0.5 to 20 wt% relative to the entire formula.

[0238]

The content of a concomitant drug in the concomitant agent of the present invention varies with the drug form of formulations. Generally it is present in a range from about 0.01 to 99.9 wt%, preferably from about 0.1 to 50 wt% and more preferably from about 0.5 to 20 wt% relative to the entire formula.

[0239]

The content of an additive such as carriers in the concomitant agent of the present invention varies with the drug form of formulations. Generally it is present in a range from about 1 to 99.99 wt% and preferably from about 10 to 90 wt% relative to the entire formula.

[0240]

When the compound of the present invention and a concomitant drug are formulated independently, the same

contents can be applied.

[0241]

Since the dosages may fluctuate under various conditions as mentioned above, a dosage less than the aforementioned dosages may be sufficient or it may be necessary to administer at a dosage exceeding the range.

[0242]

Examples

The present invention is explained in detail by referring to the following Reference Examples, Examples, Formulation Examples, and Experimental Examples. These examples are mere embodiments, which do not limit the present invention, and can be modified within the range not deviating from the scope of the present invention.

The "room temperature" in the following Reference Examples and Examples is generally about 10°C to about 35°C. % in the yield means mol/mol%, % of solvent used for chromatography means % by volume, and % used for others means wt%. In proton NMR spectrum, OH and NH protons and the like that cannot be identified since they are broad bands are not recorded in the data. In silica gel chromatography, Kiesselgel 60 manufactured by Merck & Co., Inc. was used, and Chromatorex NH manufactured by Fuji Silysia Chemical Ltd. was used in basic silica gel chromatography.

Other abbreviations used in the text mean the following.

s: singlet
d: doublet
dd: doublet of doublets
dt: doublet of triplets
t: triplet
tt: triplet of triplets
td: triplet of doublets
q: quartet
septet: septet
m: multiplet

br: broad
J: coupling constant
Hz: Hertz
CDCl₃: deuterated chloroform
5 DMSO-d₆: deuterated dimethyl sulfoxide
¹H NMR: proton nuclear magnetic resonance
HPLC: high performance liquid chromatography
THF: tetrahydrofuran
DMF: N,N-dimethylformamide
10 DMSO: dimethyl sulfoxide
DMA: N,N-dimethylacetamide
DIEA: diisopropylethylamine
NMP: N-methylpyrrolidone
Boc₂O: di-tert-butyl dicarbonate
15 DMAP: 4-dimethylaminopyridine
TEA: triethylamine
NaHMDS: sodiumbis(trimethylsilyl)amide
mCPBA: meta-chloroperbenzoic acid
DMTMM: 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-
20 methylmorpholinium chloride n-hydrate
CDI: 1,1'-carbonylbis(1H-imidazole)
DBU: 1,8-diazabicyclo[5.4.0]-7-undecene
Pd(Ph₃P)₄: tetrakis(triphenylphosphine)palladium(0)
Pd₂(dba)₃: tris(dibenzylideneacetone)dipalladium(0)
25 TBAF: tetra-n-butylammonium fluoride
TMEDA: tetramethylethylenediamine
IPE: diisopropyl ether
DME: 1,2-dimethoxyethane
DIPEA: N,N-diisopropylethylamine
30 LC-MS: liquid chromatography-mass spectrometry spectrum
ESI: electrospray-ionization method
aq.: aqueous solution
sat.: saturated
rt: room temperature

35 [0243]

All reagents and solvents were of commercial quality and used without further purification. Column chromatography was performed using Merck silica gel 60 (230-400 mesh). The compounds and/or intermediates were purified by preparative
5 high performance liquid chromatography (prep. HPLC) using a Gilson High through Put purification system.

The columns were reversed phase YMC CombiPrep Pro C18, S-5 μm , 19 x 50 mm. A gradient elution was used (flow rate 20 mL/min), typically starting with 5% acetonitrile/95% water and
10 progressing to 100% acetonitrile over a Period of 7 minutes. All solvents contained 0.1% trifluoroacetic acid (TFA).

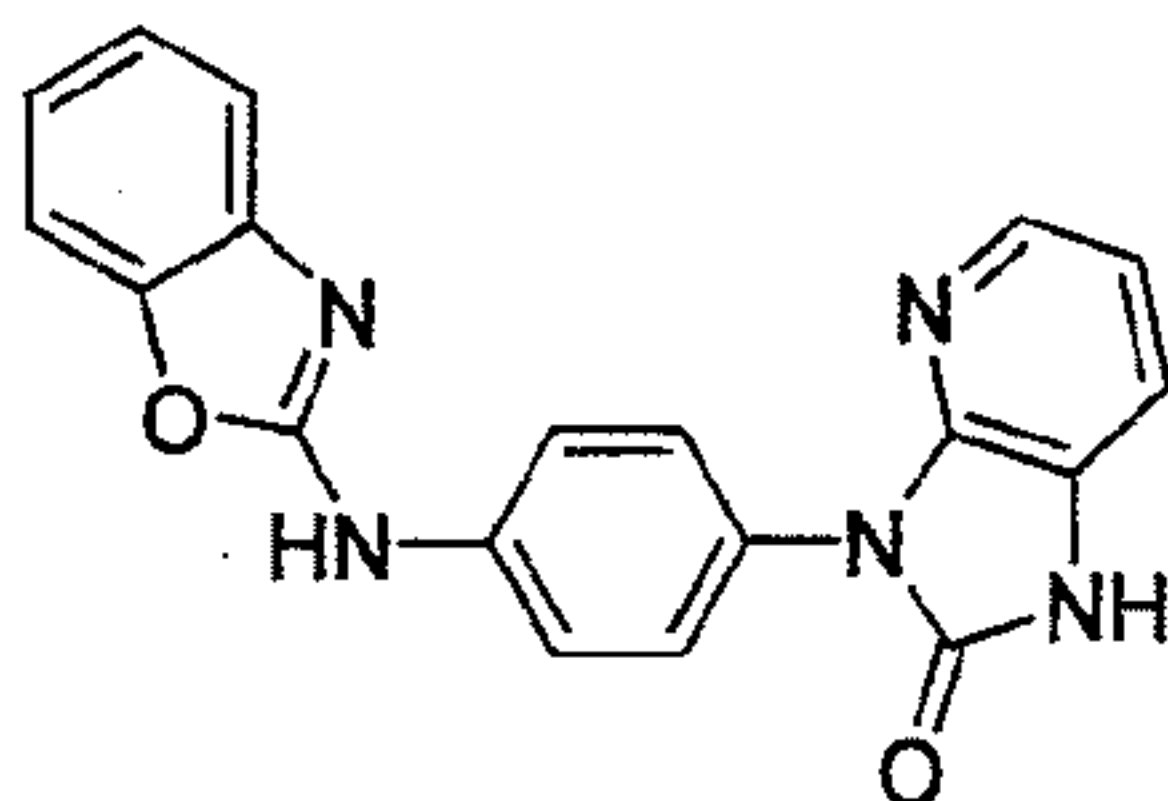
Mass spectrometric analysis was performed according to liquid chromatography/mass spectroscopy (LCMS) methods. The method employed a Waters LC-MS System (Agilent HP1100 HPLC and
15 a Micromass ZMD mass spectrometer for the LCMS instrument, a CAPCELL PAK C18, UG120, S-3 μm , 1.5 x 35 mm for the chromatography column), and a solvent system that was a 5-95% gradient of acetonitrile in water with 0.04% TFA over a 3.60 min period (flow rate 0.5 mL/min molecular weight range 200-
20 800; cone Voltage 20 V; column temperature 40°C). All masses were reported as those of the protonated parent ions.

Example

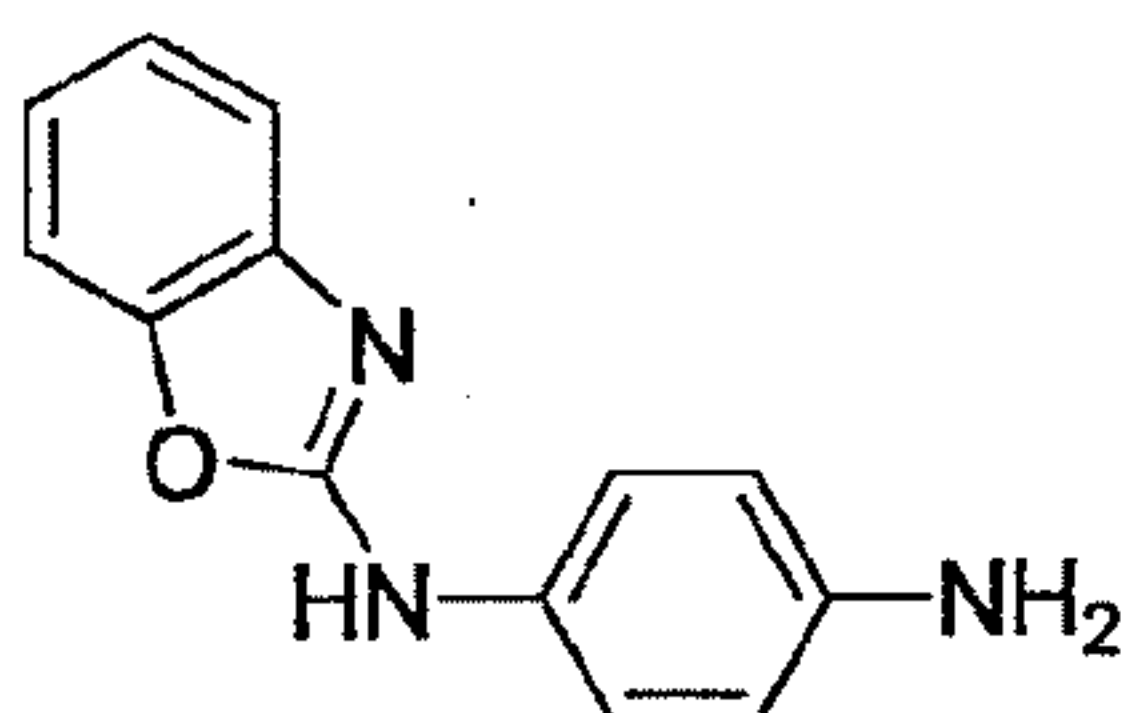
[0244]

25 Example 1

3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



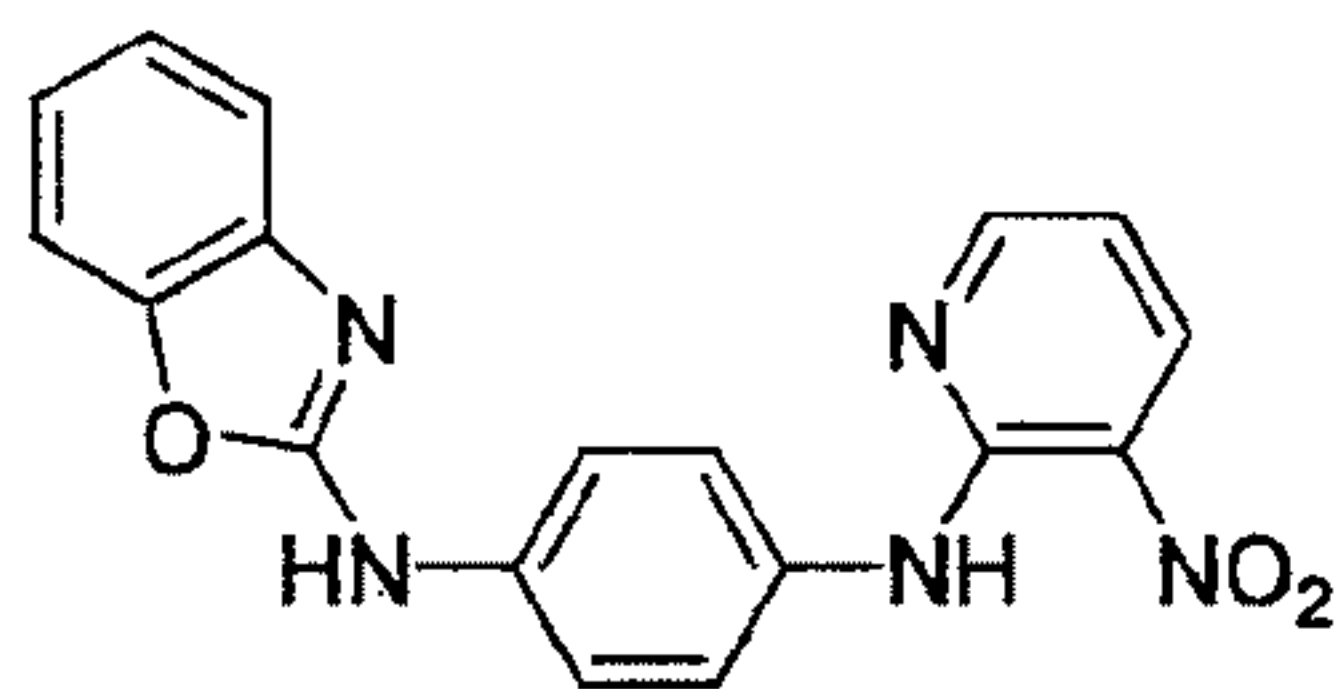
1a) N-(1,3-benzoxazol-2-yl)benzene-1,4-diamine



To a solution of benzene-1,4-diamine (5.0 g) in NMP (30 mL) was added dropwise, over 0.5 h, a solution of 2-chlorobenzo[d]oxazole (6.03 g) in NMP (50 mL). After the addition was complete, the mixture was stirred at ambient temperature for 1 h. After this time, the reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with brine (150 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 1:19 methanol/methylene chloride) to afford N-(1,3-benzoxazol-2-yl)benzene-1,4-diamine (9.20 g) as an off-white solid. MS (ESI⁺): [M+H]⁺ 226.

15 [0245]

1b) N-(1,3-benzoxazol-2-yl)-N'-(3-nitropyridin-2-yl)benzene-1,4-diamine

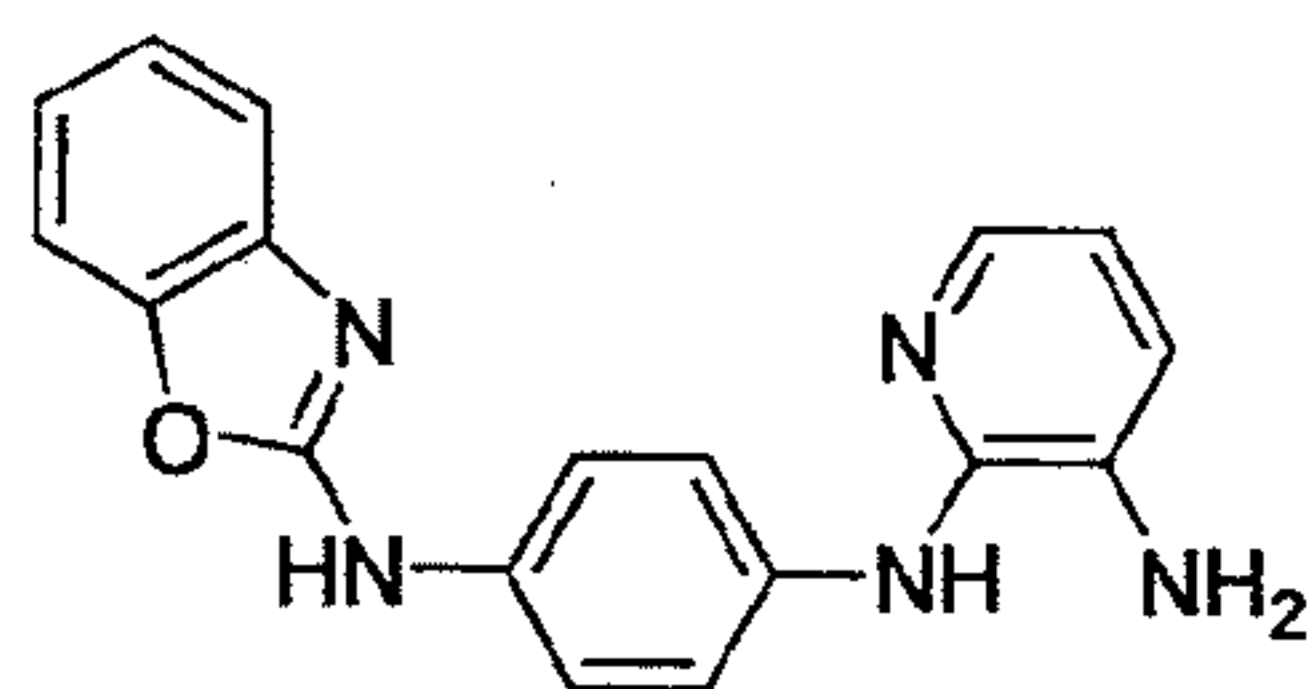


A mixture of N-(1,3-benzoxazol-2-yl)benzene-1,4-diamine (0.50 g) and 2-chloro-3-nitropyridine (0.352 g) in NMP (3.0 mL) was stirred at 140°C for 1.5 h. After this time, the reaction mixture was cooled to ambient temperature, diluted with water (50 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 1:9 ethyl acetate/methylene chloride) to afford N-(1,3-benzoxazol-2-yl)-N'-(3-nitropyridin-2-yl)benzene-1,4-diamine (0.335 g) as a red solid.

MS (ESI+): $[M+H]^+$ 348.

[0246]

1c) N^2 -[4-(1,3-benzoxazol-2-ylamino)phenyl]pyridine-2,3-diamine

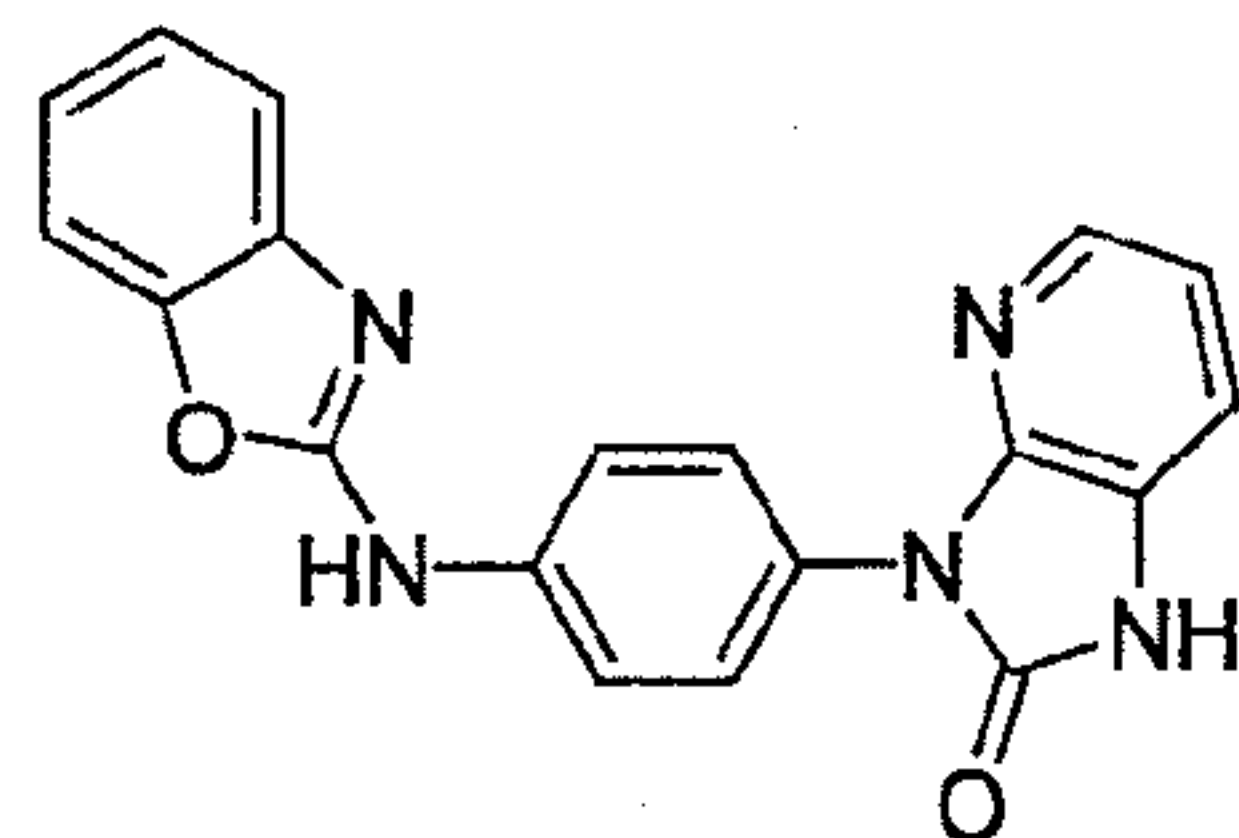


5 A solution of N-(1,3-benzoxazol-2-yl)-N'-(3-nitropyridin-2-yl)benzene-1,4-diamine (0.330 g) in methanol (20 mL) was treated with palladium on carbon (0.060 g, 10% wt on activated carbon) and the mixture was hydrogenated (1 atm H_2) for 1 h. After this time, the reaction mixture was filtered through
10 diatomaceous earth. The filtrate was concentrated under reduced pressure to afford N^2 -[4-(1,3-benzoxazol-2-ylamino)phenyl]pyridine-2,3-diamine (0.294 g) as a yellow solid.

MS (ESI+): $[M+H]^+$ 318.

15 [0247]

1d) 3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



To a mixture of N^2 -[4-(1,3-benzoxazol-2-ylamino)phenyl]pyridine-2,3-diamine (0.080 g) and
20 triethylamine (0.0638 g) in THF (1.5 mL) at 0°C, was added dropwise a solution of triphosgene (0.030 g) in THF (0.6 mL). The reaction mixture was stirred at 0°C for 0.5 h. The cold bath was removed and the stirring continued at ambient
25 temperature for another 0.5 h. After this time, a saturated aqueous solution of sodium bicarbonate was added. The organic layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (50 mL),

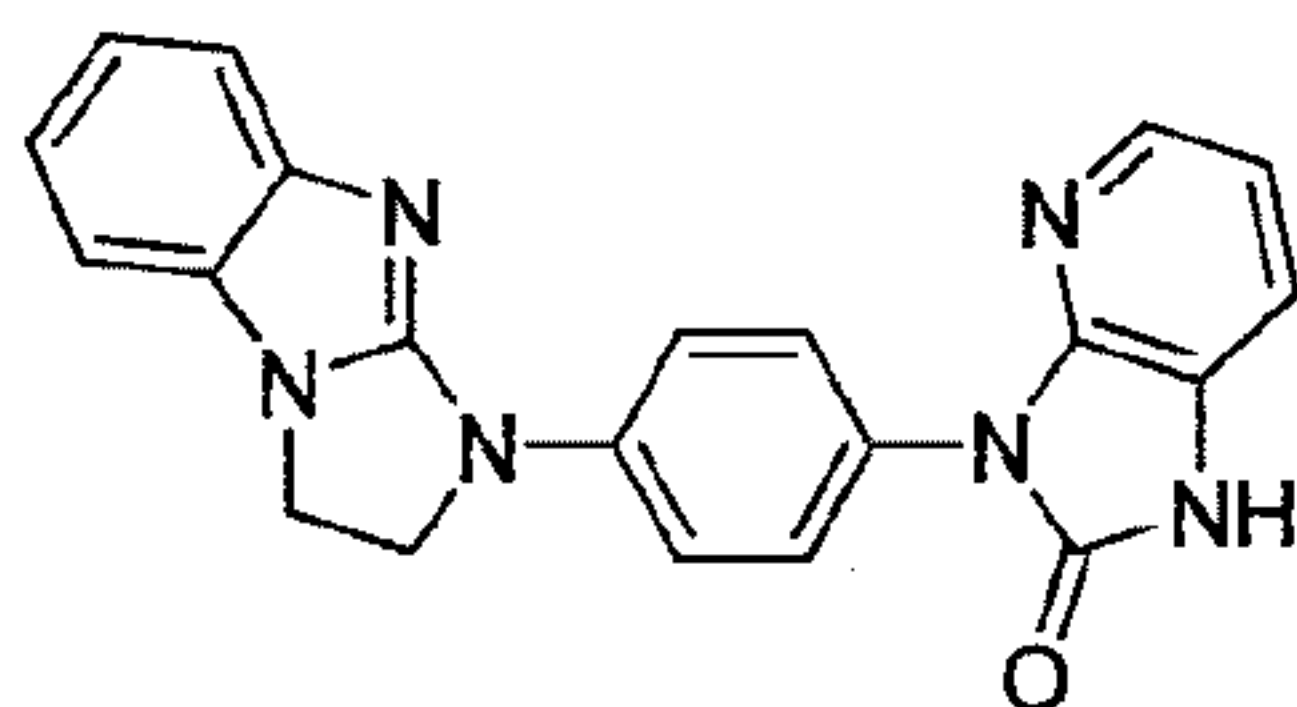
dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 0.3:5:95 ammonium hydroxide/methanol/methylene chloride) to afford 3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (0.038 g) as a white solid.

MS (ESI+): $[\text{M}+\text{H}]^+$ 344.

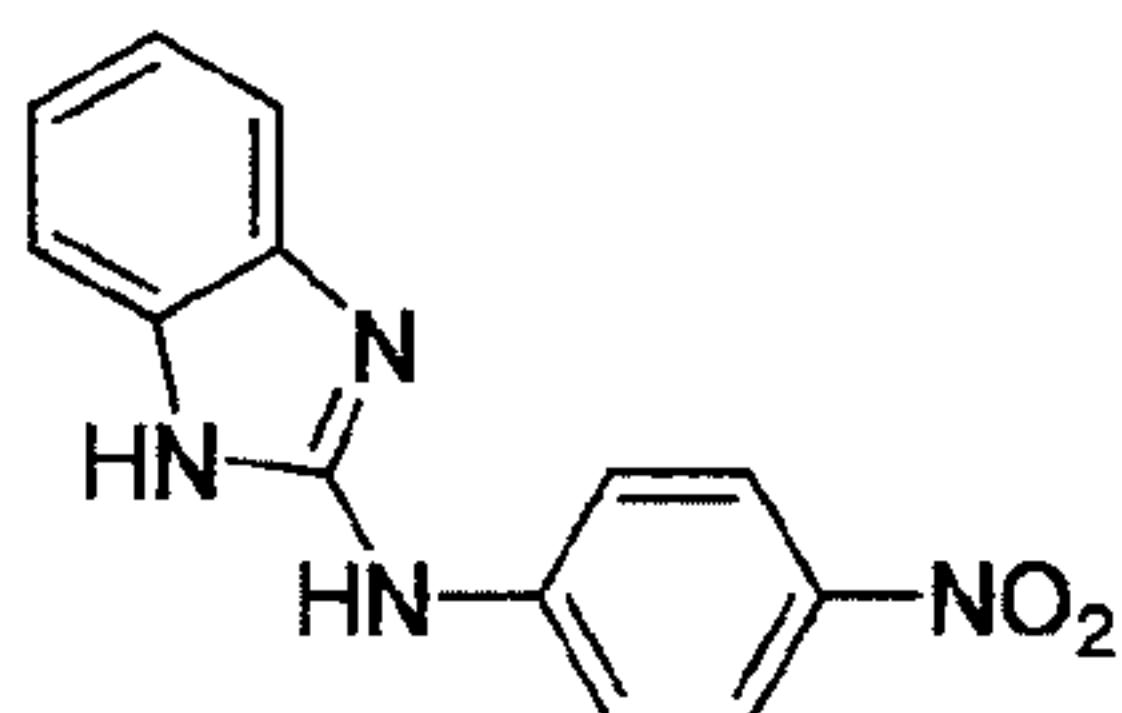
^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.08 (1H, dd, $J = 8.0, 5.5$ Hz), 7.15 (1H, dt, $J = 7.5, 1.0$ Hz), 7.24 (1H, dt, $J = 7.5, 1.0$ Hz), 7.39 (1H, dd, $J = 7.5, 1.5$ Hz), 7.48 (1H, d, $J = 7.5$ Hz), 7.52 (1H, d, $J = 8.0$ Hz), 7.60–7.63 (2H, m), 7.88–7.91 (2H, m), 7.93 (1H, dd, $J = 5.0, 1.5$ Hz), 10.79 (1H, s), 11.34 (1H, s).
[0248]

Example 2

3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



2a) N-(4-nitrophenyl)-1H-benzimidazol-2-amine



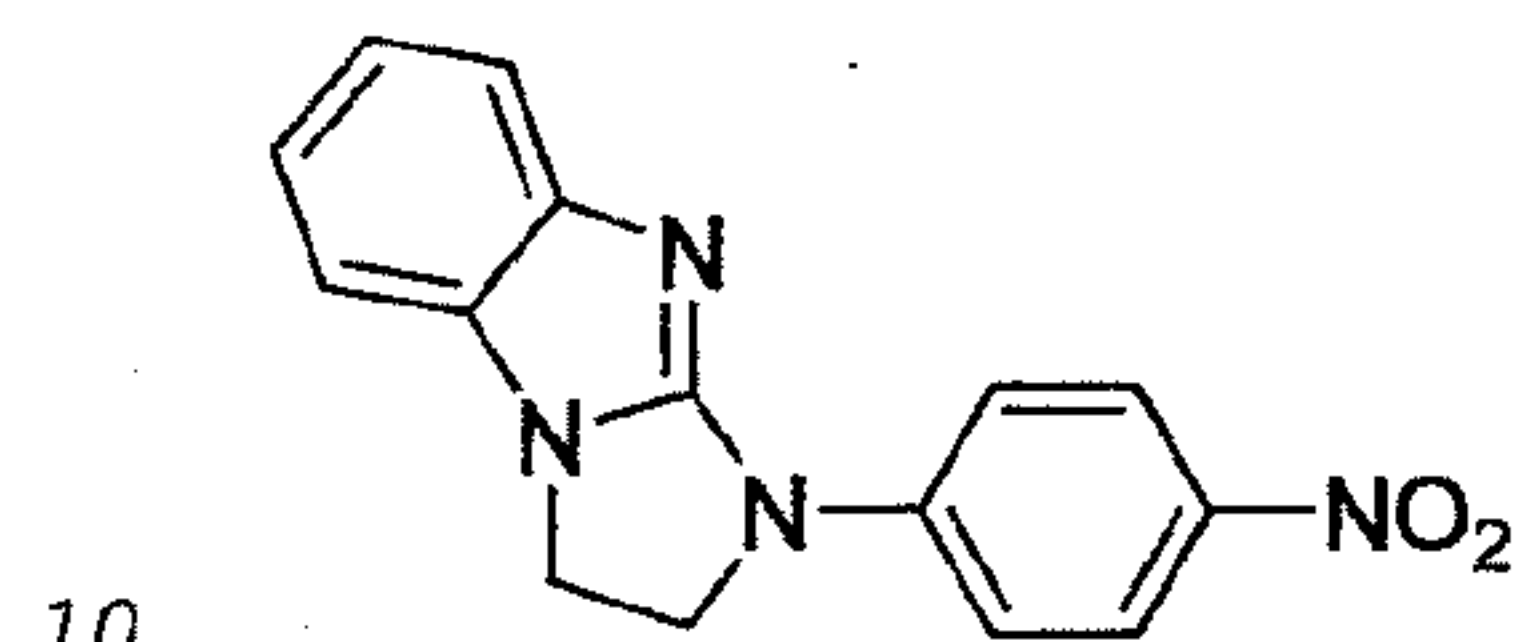
A mixture of 2-chlorobenzimidazole (10.0 g) and 4-nitroaniline (9.05 g) in NMP (130 mL) was stirred at 120°C for 3 days. After this time, the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (750 mL) and washed with water (750 mL). The aqueous layer was extracted with ethyl acetate (750 mL) and the combined organic extracts were washed with water (3×750 mL) then brine (750 mL), dried over sodium sulfate, and filtered and the filtrate was concentrated under reduced pressure. The residue obtained was triturated with 1:1 ethyl acetate/heptane (200 mL) and the

solid that formed was collected by filtration to afford N-(4-nitrophenyl)-1H-benzimidazol-2-amine (4.00 g) as an orange solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.06–7.08 (2H, m), 7.36–7.37 (1H, m), 7.45–7.46 (1H, m), 8.00 (1H, d, *J* = 9.0 Hz), 8.23–8.25 (2H, m), 10.43 (1H, brs), 11.31 (1H, brs).

[0249]

2b) 1-(4-nitrophenyl)-2,3-dihydro-1H-imidazo[1,2-a]benzimidazole

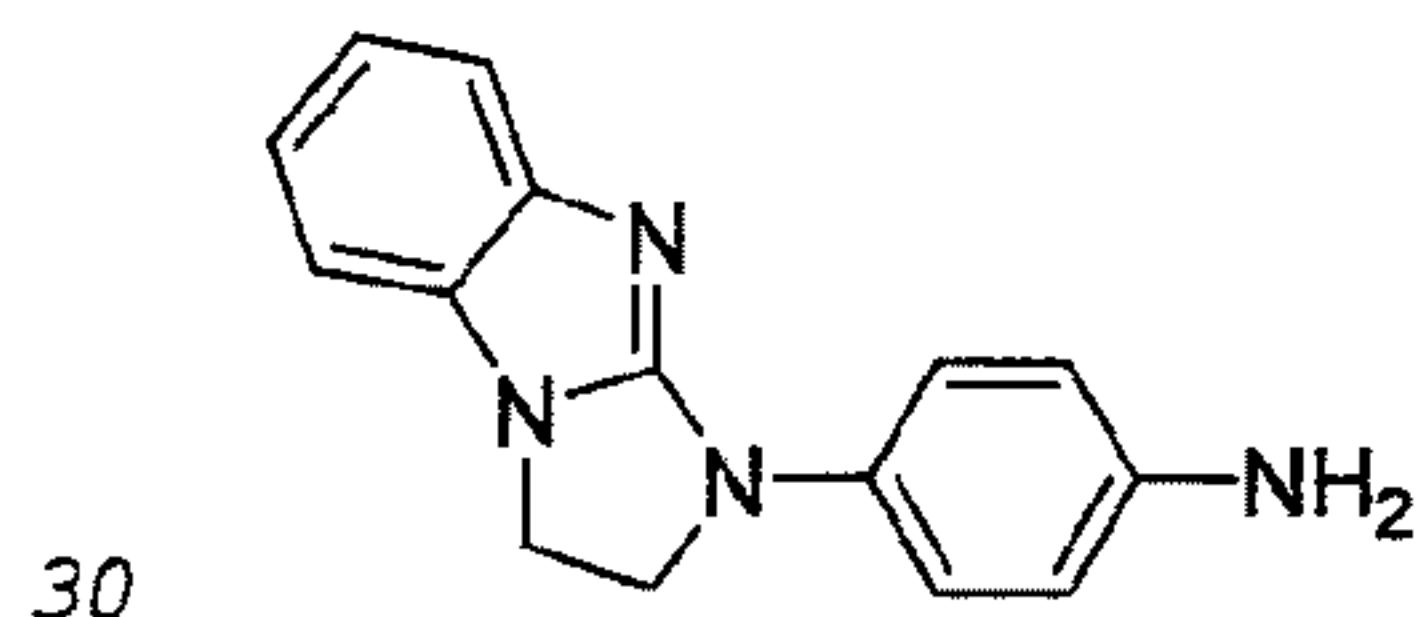


A mixture of N-(4-nitrophenyl)-1H-benzimidazol-2-amine (1.00 g) in DMF (20 mL) at ambient temperature was treated with a 60% dispersion of sodium hydride in mineral oil (393 mg) then stirred for 5 min. The mixture was treated with a solution of 1,2-dibromoethane (738 mg) in DMF (1 mL) then stirred at ambient temperature for 1 h. After this time, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL), diluted with water (80 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with 5% aqueous lithium chloride (2 × 50 mL) then brine (50 mL), dried over sodium sulfate, and filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, heptane to 1:1 ethyl acetate/heptane) to afford 1-(4-nitrophenyl)-2,3-dihydro-1H-imidazo[1,2-a]benzimidazole (63 mg) as a yellow solid.

MS (ESI⁺): [M+H]⁺ 281.

[0250]

2c) 4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)aniline

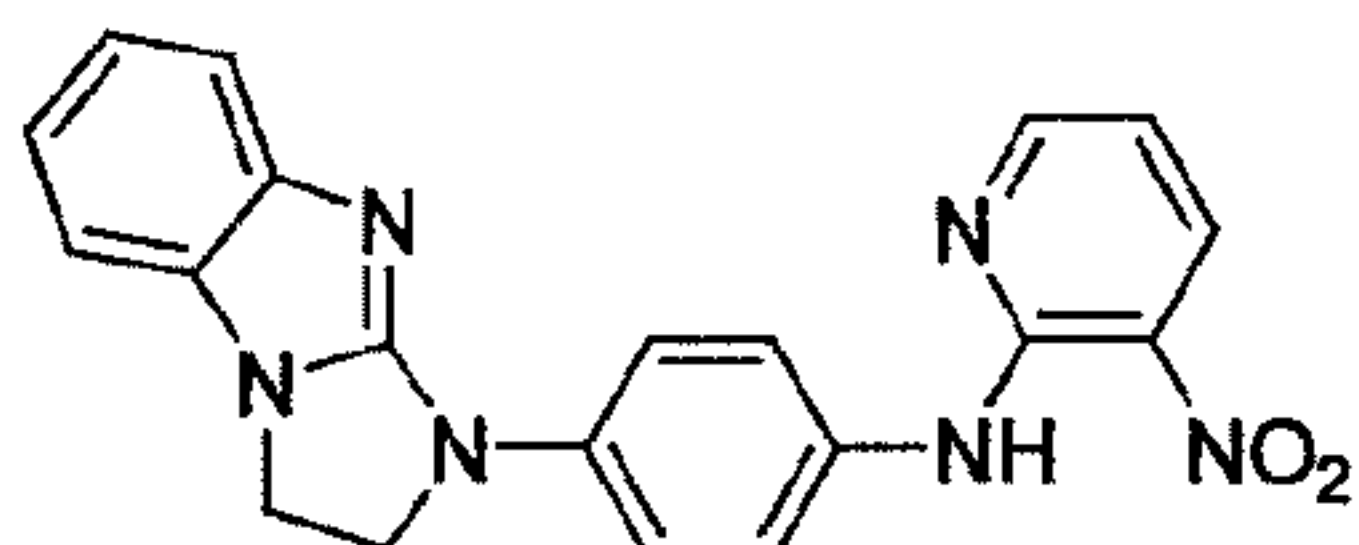


Same procedure of example 1c) with 1-(4-nitrophenyl)-2,3-dihydro-1H-imidazo[1,2-a]benzimidazole (61 mg) gave 4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)aniline (55 mg) as an off-white solid.

5 MS (ESI⁺): [M+H]⁺ 251.

[0251]

2d) N-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-3-nitropyridin-2-amine

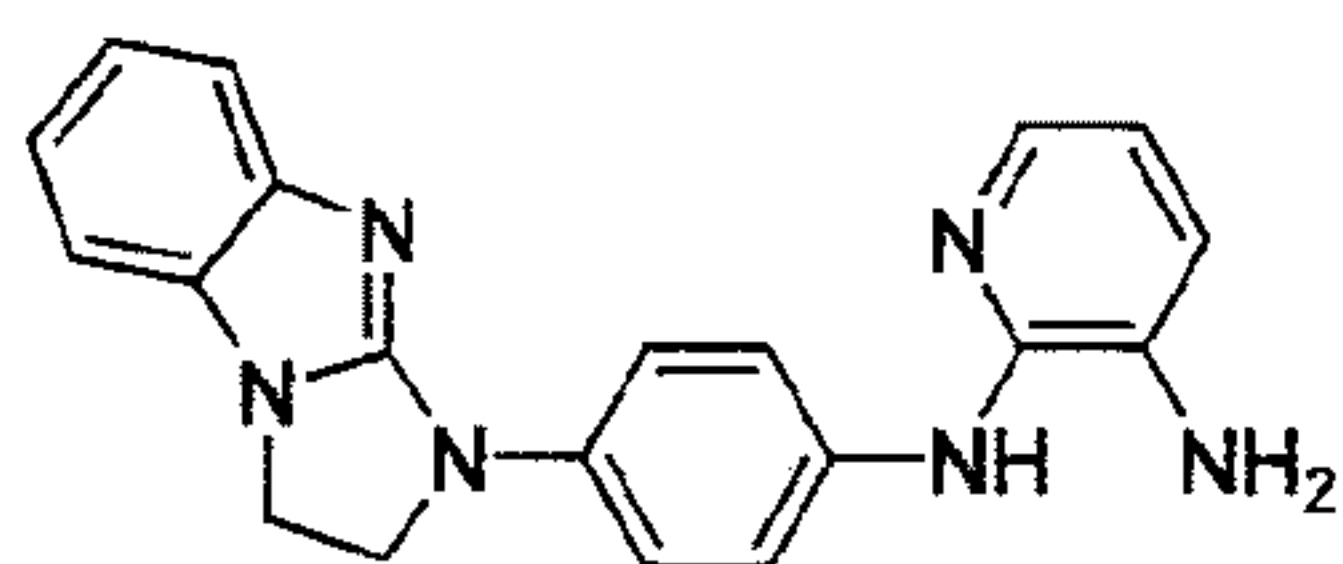


10 A mixture of 4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)aniline (55 mg) and 2-chloro-3-nitropyridine (35 mg) in NMP (3 mL) was stirred at 140°C overnight. After this time, the reaction mixture was cooled to ambient temperature, diluted with water (50 mL) and extracted
15 with ethyl acetate (2 × 75 mL). The combined organic layers were washed with water (50 mL) then brine (50 mL), dried over sodium sulfate, and filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 1:9 ethyl
20 acetate/methylene chloride) to afford N-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-3-nitropyridin-2-amine (34 mg) as a dark brown solid.

MS (ESI⁺): [M+H]⁺ 373.

[0252]

25 2e) N²-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]pyridine-2,3-diamine

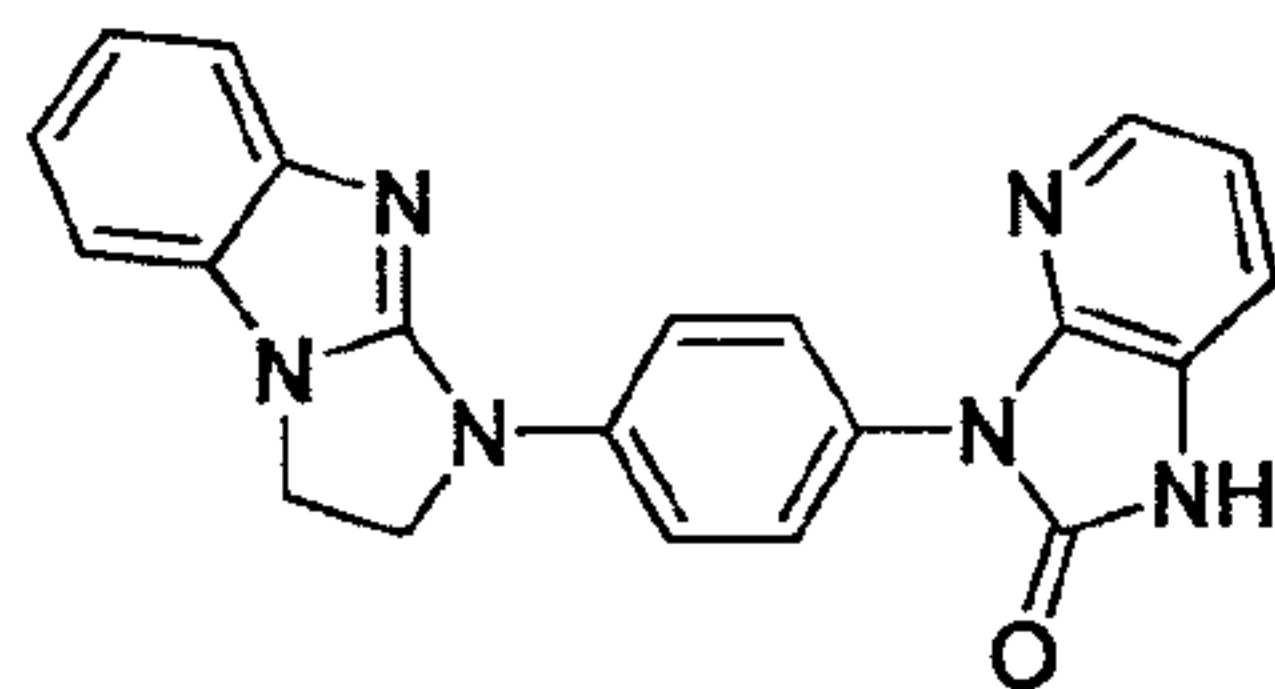


Same procedure of example 1c) with N-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-3-nitropyridin-2-amine
30 (34 mg) gave N²-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]pyridine-2,3-diamine (20 mg) as a yellow solid.

MS (ESI+): $[M+H]^+$ 343.

[0253]

2f) 3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



5

A mixture of N^2 -[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]pyridine-2,3-diamine (20 mg) and 1,1'-carbonyldiimidazole (19 mg) in THF (5 mL) was stirred at ambient temperature overnight. After this time, the solids
10 that formed were collected by filtration to afford 3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (12 mg) as off-white crystals.

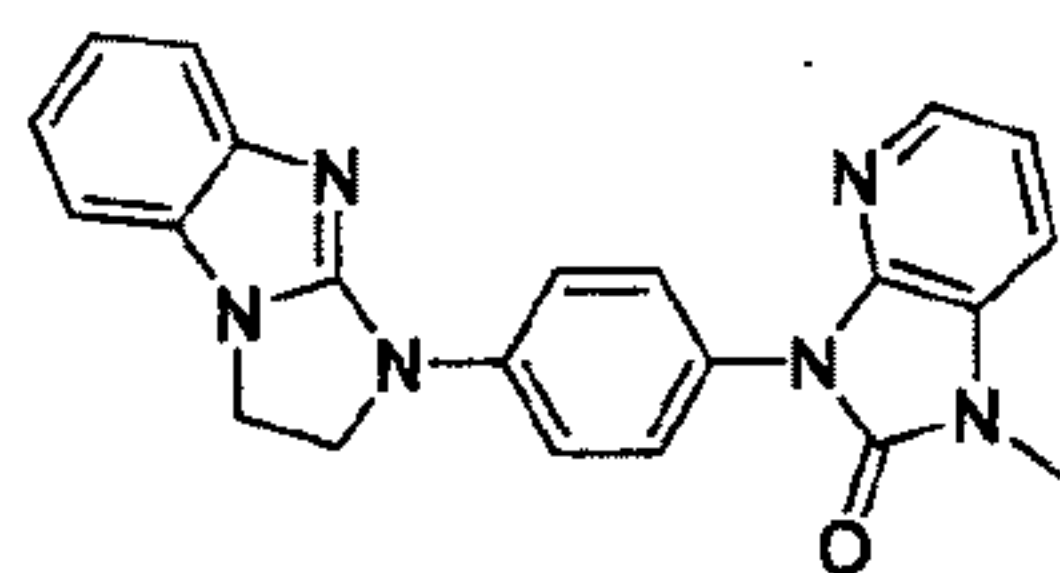
MS (ESI+): $[M+H]^+$ 369.

15 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 4.38-4.41 (2H, m), 4.59-4.63 (2H, m), 7.06-7.10 (3H, m), 7.29-7.31 (1H, m), 7.39 (1H, dd, J = 7.5, 1.0 Hz), 7.43-7.45 (1H, m), 7.65 (2H, d, J = 9.0 Hz), 7.93-7.95 (3H, m), 11.34 (1H, brs).

[0254]

20 Example 3

3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



To a mixture of 3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (57 mg) and methyl iodide (0.012 mL) in DMF
25 (2.0 mL) was added sodium hydride (62 mg) (60% in mineral oil) at 0°C. The mixture was stirred at 0°C for 1 h, and then added H_2O . The precipitate was collected and washed with MeOH to give
30 3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-

1-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (43 mg) as white powder.

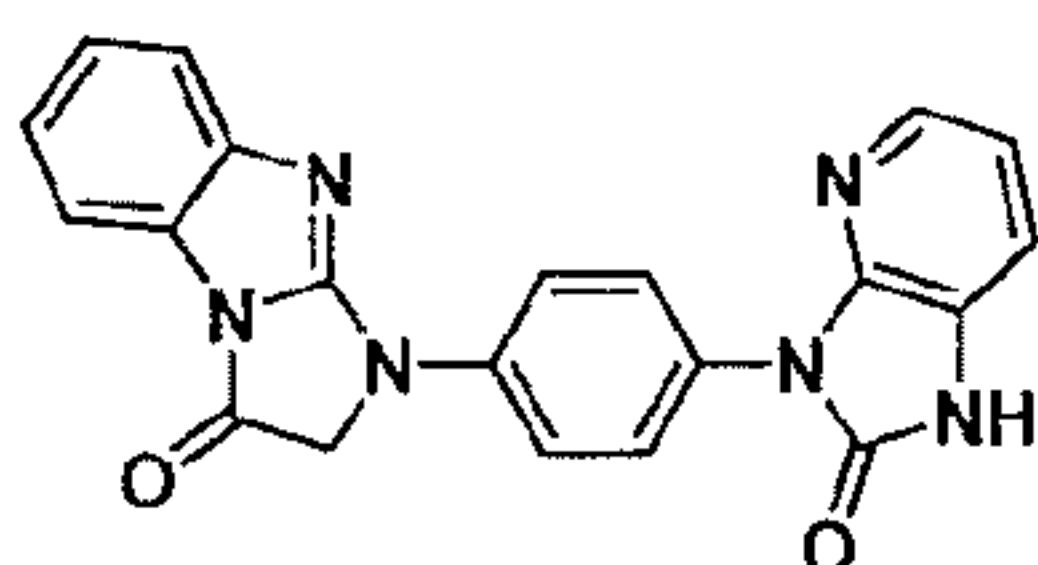
MS (ESI⁺): [M+H]⁺ 383.0.

¹H NMR (300 MHz, DMSO-d₆) δ 3.44 (3H, s), 4.33-4.46 (2H, m),
 5 4.53-4.71 (2H, m), 7.01-7.12 (2H, m), 7.13-7.22 (1H, m), 7.24-7.35 (1H, m), 7.39-7.50 (1H, m), 7.55-7.74 (3H, m), 7.82-8.15 (3H, m).

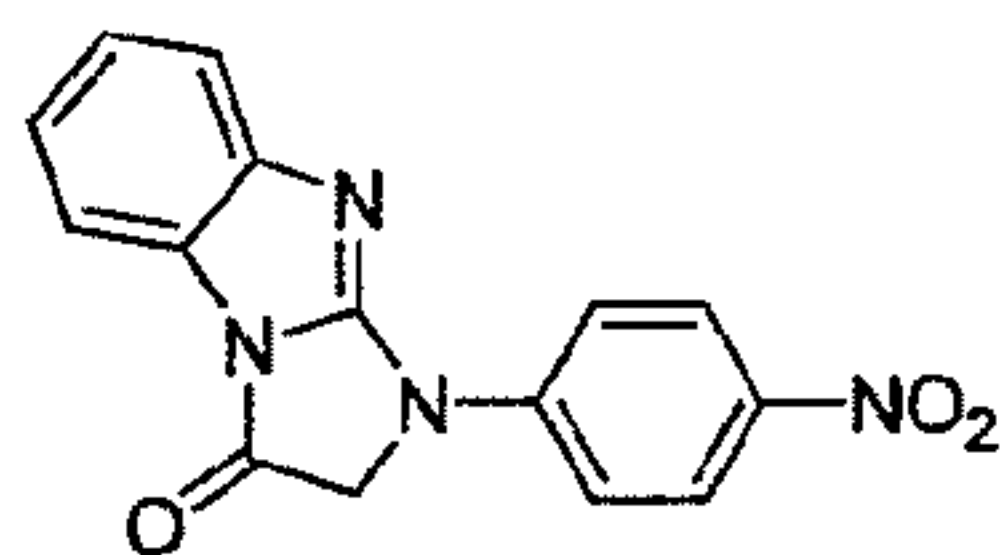
[0255]

Example 4

10 1-[4-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one



4a) 1-(4-nitrophenyl)-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one



15

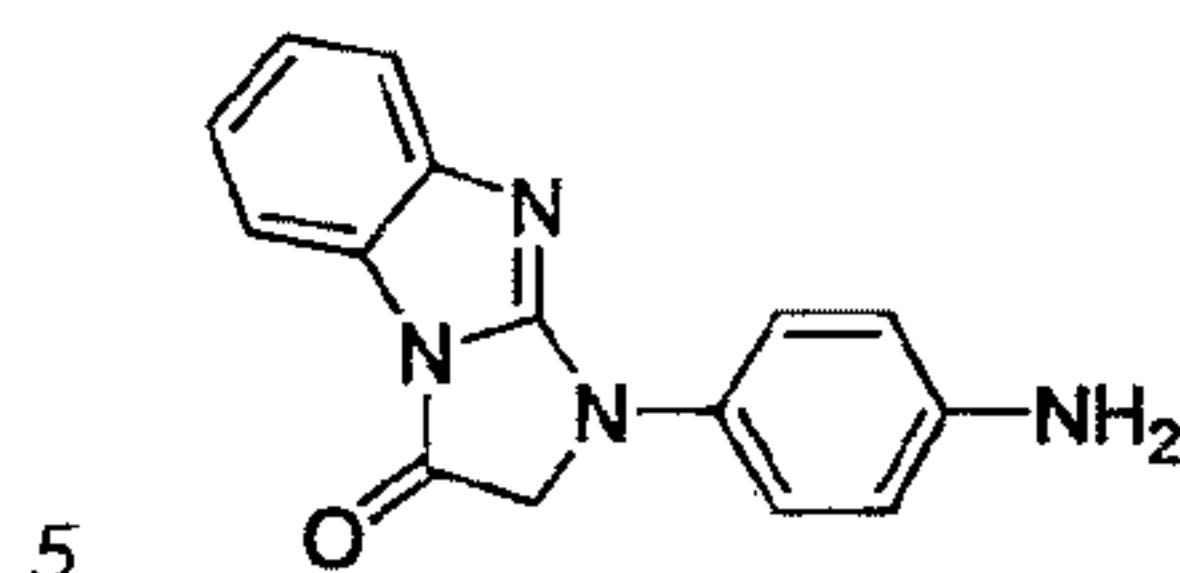
A mixture of N-(4-nitrophenyl)-1H-benzimidazol-2-amine (947 mg) and N,N-diisopropylethylamine (1.45 g) in THF (10 mL) at -78°C was treated dropwise with a solution of bromoacetyl bromide (826 mg) in THF (2.0 mL) then the resulting mixture
 20 was allowed to warm to ambient temperature overnight. After this time, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layers were washed with brine (50 mL), dried over sodium sulfate, and filtered and the filtrate was concentrated under
 25 reduced pressure. The residue obtained was purified by chromatography (silica, heptane to 2:3 ethyl acetate/heptane) to afford 1-(4-nitrophenyl)-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (92 mg) as a yellow solid.

¹H NMR (300 MHz, CDCl₃) δ 4.84 (2H, s), 7.31 (1H, d, J = 7.8
 30 Hz), 7.40 (1H, td, J = 7.8, 1.2 Hz), 7.63 (1H, d, J = 9.6 Hz), 7.81 (1H, d, J = 7.5 Hz), 7.91 (2H, d, J = 9.3 Hz), 8.36 (2H,

d, $J = 9.0$ Hz).

[0256]

4b) 1-(4-aminophenyl)-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one

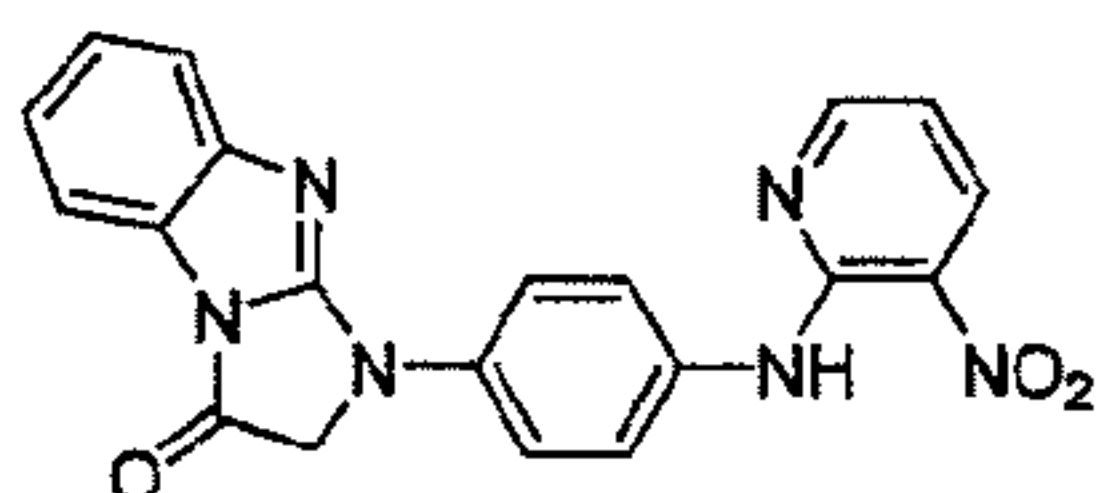


Same procedure of example 1c) with 1-(4-nitrophenyl)-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (92 mg) gave 1-(4-aminophenyl)-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (82 mg) as a yellow solid.

10 MS (ESI+): $[M+H]^+$ 265.

[0257]

4c) 1-{4-[(3-nitropyridin-2-yl)amino]phenyl}-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one

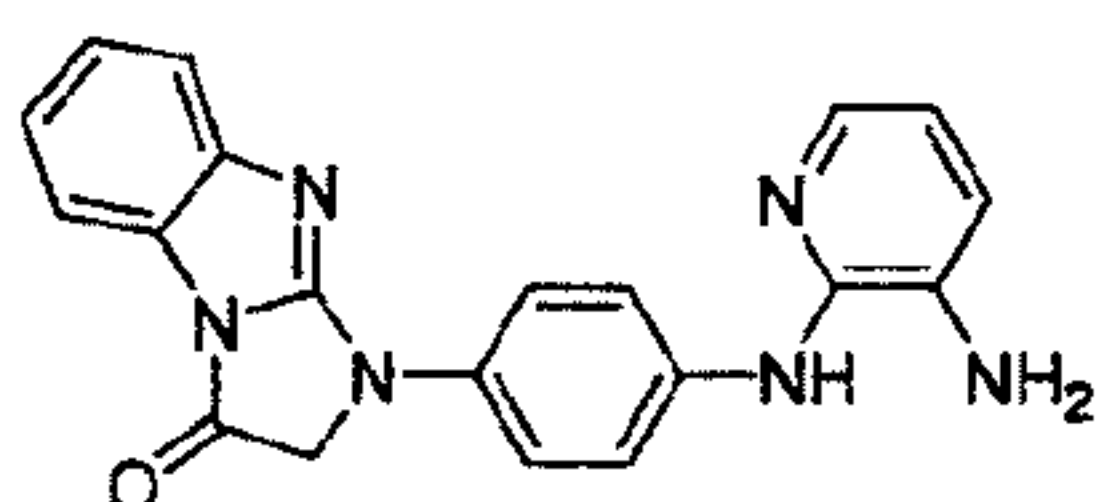


15 Same procedure of example 2d) with 1-(4-aminophenyl)-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (82 mg) gave 1-{4-[(3-nitropyridin-2-yl)amino]phenyl}-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (7 mg) as a yellow solid.

MS (ESI+): $[M+H]^+$ 387.

20 [0258]

4d) 1-{4-[(3-aminopyridin-2-yl)amino]phenyl}-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one

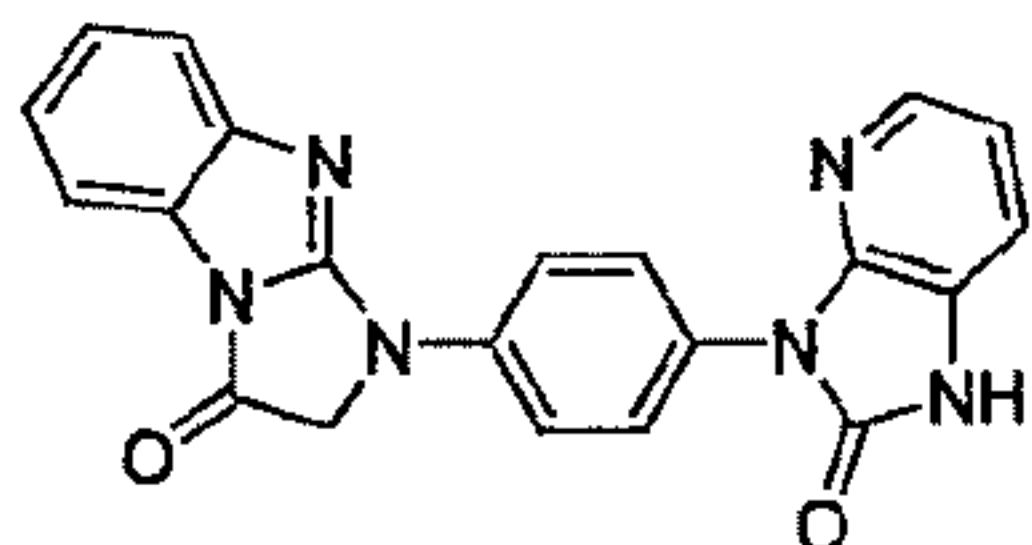


Same procedure of example 1c) with 1-{4-[(3-nitropyridin-2-yl)amino]phenyl}-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (7 mg) gave 1-{4-[(3-aminopyridin-2-yl)amino]phenyl}-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (7 mg) as a yellow solid.

MS (ESI+): $[M+H]^+$ 357.

[0259]

4e) 1-[4-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one



5 Same procedure of example 2f) with 1-{4-[(3-aminopyridin-2-yl)amino]phenyl}-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (7 mg) gave 1-[4-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1,2-dihydro-3H-imidazo[1,2-a]benzimidazol-3-one (4 mg) as yellow crystals.

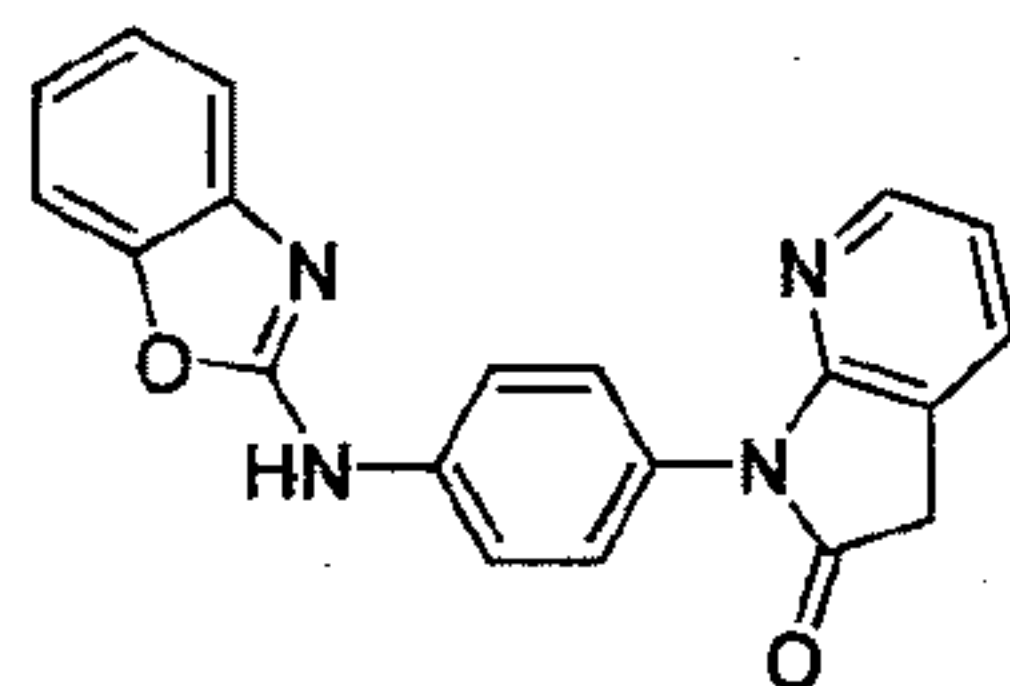
10 MS (ESI⁺): [M+H]⁺ 383.

¹H NMR (500 MHz, CDCl₃) δ 4.80 (2H, s), 7.08 (1H, dd, *J* = 8.0, 5.5 Hz), 7.33-7.36 (3H, m), 7.59 (1H, d, *J* = 8.0 Hz), 7.78 (1H, d, *J* = 8.0 Hz), 7.81-7.83 (3H, m), 7.92 (2H, d, *J* = 9.5 Hz), 8.09 (1H, dd, *J* = 5.0, 1.0 Hz).

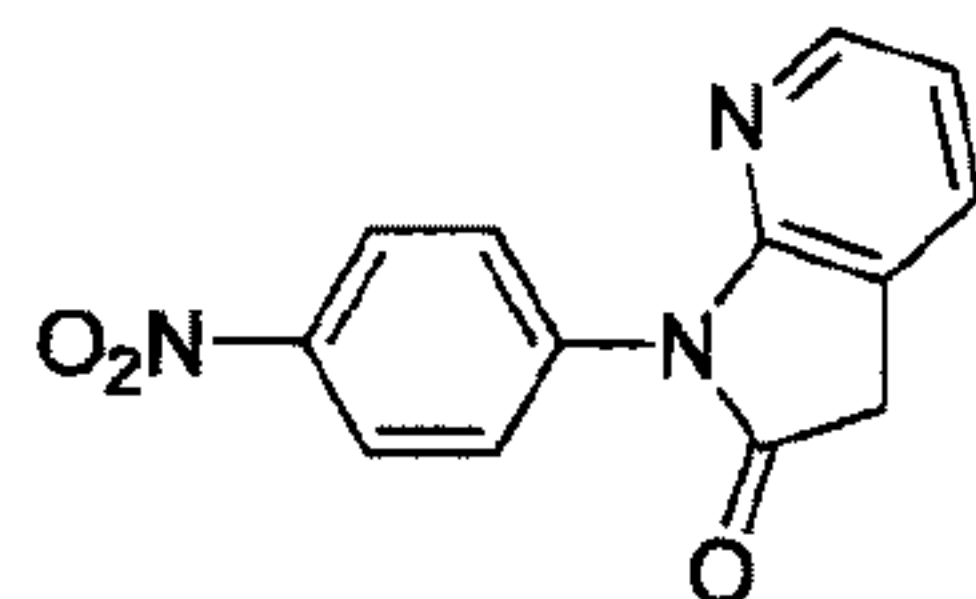
[0260]

Example 5

1-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one



20 5a) 1-(4-nitrophenyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one



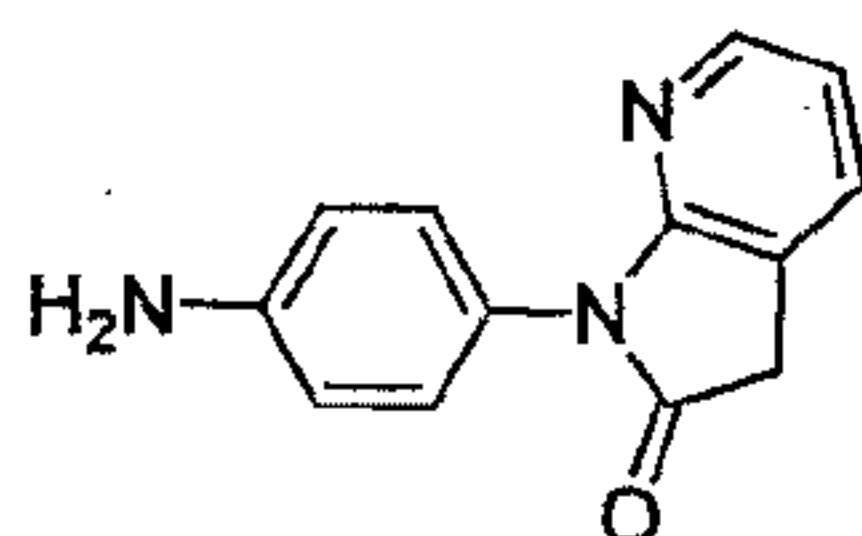
A mixture of 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (431 mg), 1-bromo-4-nitrobenzene (778 mg), copper(I) iodide (122 mg),
 25 *N*¹,*N*²-dimethylethane-1,2-diamine (113 mg) and potassium iodide (1.36 g) in 1,4-dioxane (10 mL) was sparged with argon for 5 min then heated overnight at 95°C. After this time, the reaction mixture was cooled to ambient temperature, diluted

with ethyl acetate (100 mL), filtered through diatomaceous earth and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, heptane to 1:1 ethyl acetate/heptane) to afford 1-(4-nitrophenyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (207 mg) as a white solid.

MS (ESI+): $[M+H]^+$ 256.

[0261]

5b) 1-(4-aminophenyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one
10 one

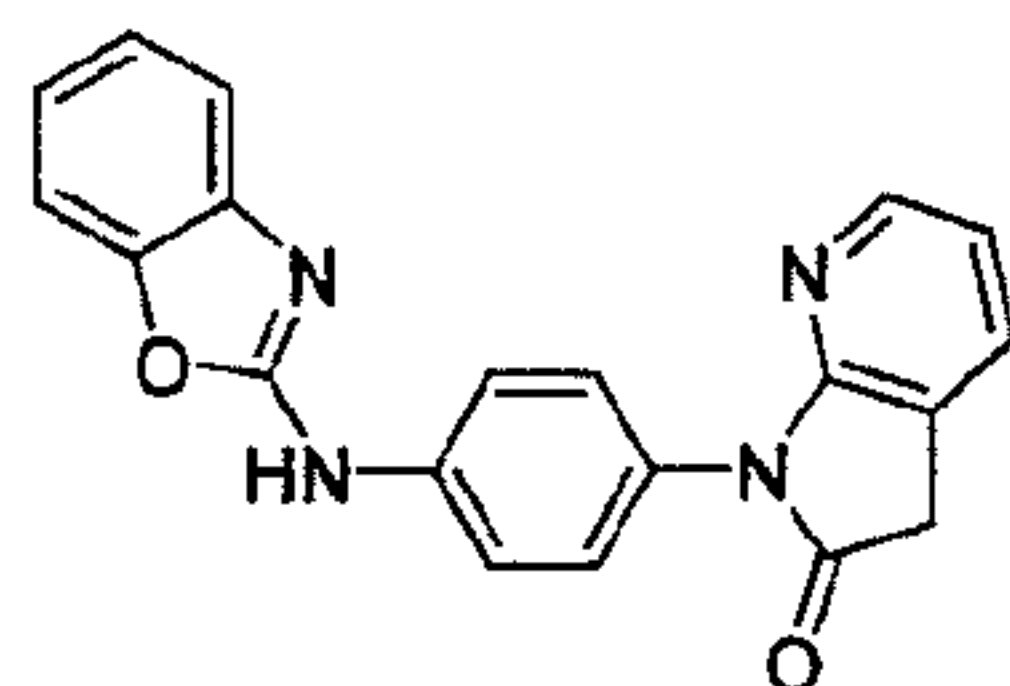


Same procedure of example 1c) with 1-(4-nitrophenyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (145 mg) gave 1-(4-aminophenyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (120 mg) as a yellow solid.

MS (ESI+): $[M+H]^+$ 226.

[0262]

5c) 1-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one



Same procedure of example 1a) with 1-(4-aminophenyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (120 mg) and 2-chlorobenzo[d]oxazole (98 mg) gave 1-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (126 mg) as yellow crystals.

MS (ESI+): $[M+H]^+$ 343.

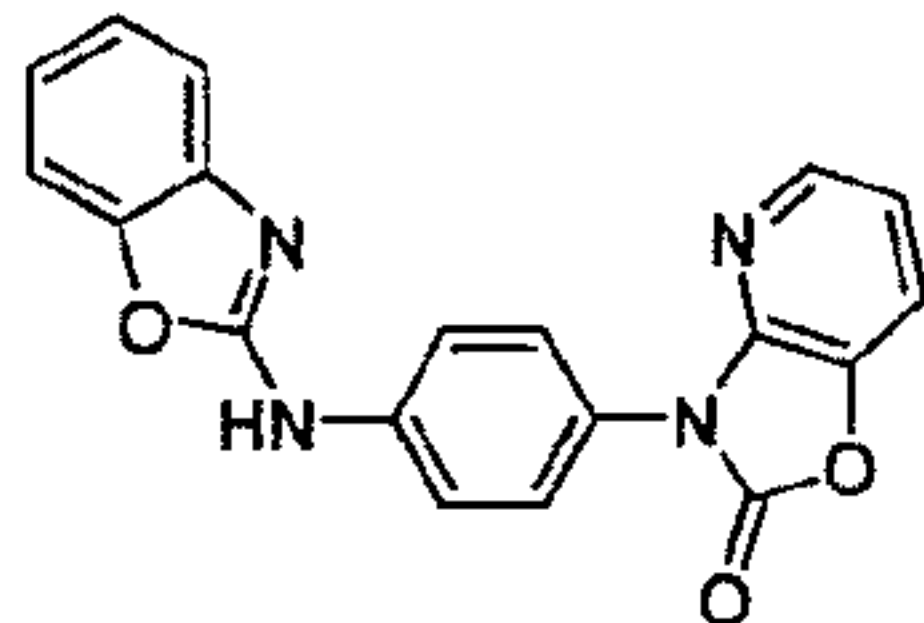
^1H NMR (500 MHz, DMSO- d_6) δ 3.80 (2H, s), 7.08 (1H, dd, J = 7.5, 5.5 Hz), 7.15 (1H, td, J = 8.0, 1.5 Hz), 7.24 (1H, td, J = 7.5, 1.0 Hz), 7.45-7.49 (3H, m), 7.52 (1H, d, J = 8.0 Hz), 7.70 (1H, dd, J = 7.0, 1.0 Hz), 7.87 (2H, d, J = 9.0 Hz), 8.08-8.09 (1H,

m), 10.79 (1H, brs).

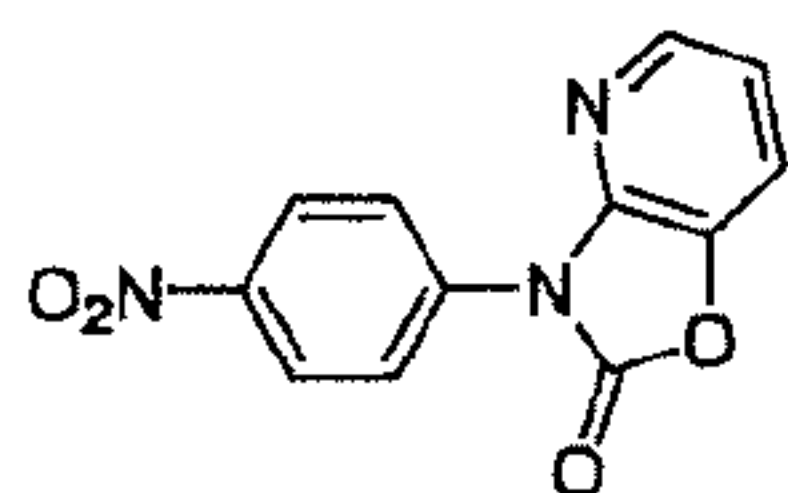
[0263]

Example 6

3-[4-(1,3-benzoxazol-2-ylamino)phenyl][1,3]oxazolo[4,5-b]pyridin-2(3H)-one



6a) 3-(4-nitrophenyl)[1,3]oxazolo[4,5-b]pyridin-2(3H)-one

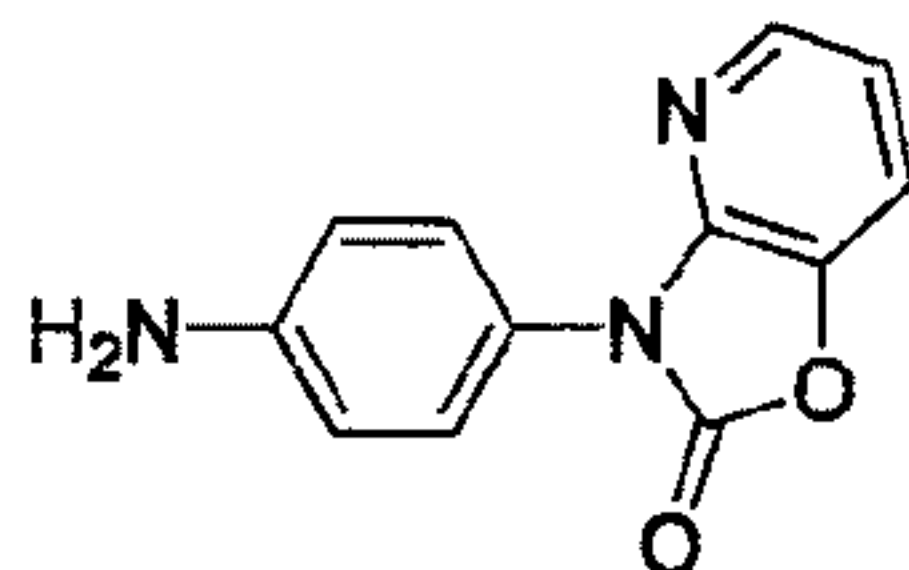


A solution of oxazolo[4,5-b]pyridin-2(3H)-one (200 mg) in
 10 DMF (3.5 mL) was treated with a 60% dispersion of sodium
 hydride in mineral oil (62 mg) and the resulting mixture
 stirred at ambient temperature for 5 min. The mixture was
 treated with 1-fluoro-4-nitrobenzene (248 mg) then stirred at
 100°C for 17 h. After this time, the reaction mixture was
 15 cooled to ambient temperature, diluted with ethyl acetate (100
 mL), washed with water (2 × 50 mL), 5% aqueous lithium
 chloride (50 mL) then brine (50 mL), dried over sodium sulfate,
 and filtered and the filtrate was concentrated under reduced
 pressure. The residue obtained was purified by chromatography
 20 (silica, heptane to 1:1 ethyl acetate/heptane) to afford 3-(4-
 nitrophenyl)[1,3]oxazolo[4,5-b]pyridin-2(3H)-one (73 mg) as a
 yellow solid.

MS (ESI⁺): [M+H]⁺ 258.

[0264]

25 6b) 3-(4-aminophenyl)[1,3]oxazolo[4,5-b]pyridin-2(3H)-one



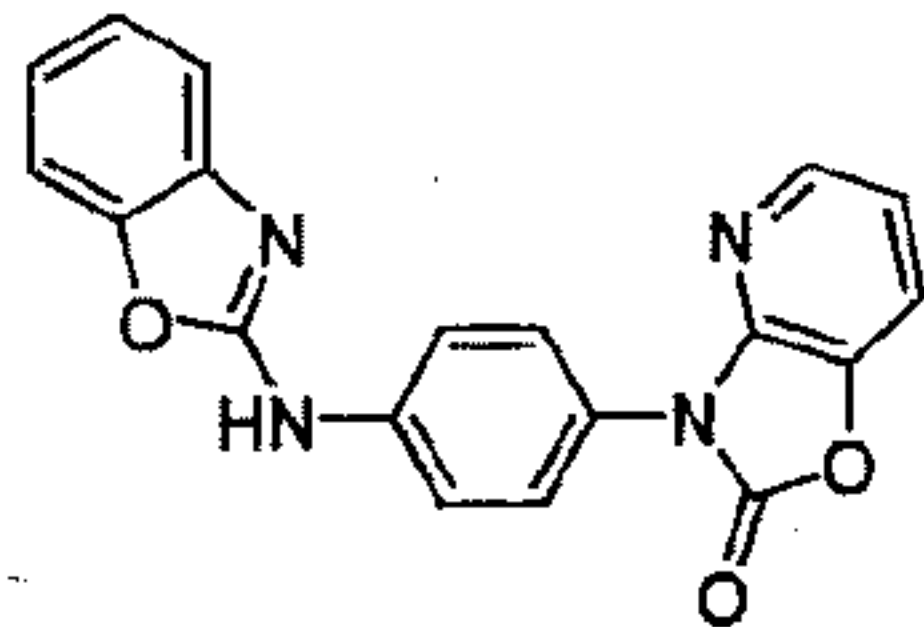
Same procedure of example 1c) with 3-(4-
 nitrophenyl)[1,3]oxazolo[4,5-b]pyridin-2(3H)-one (70 mg) gave
 3-(4-aminophenyl)[1,3]oxazolo[4,5-b]pyridin-2(3H)-one (55 mg)

as an off-white solid.

MS (ESI⁺): [M+H]⁺ 228.

[0265]

6c) 3-[4-(1,3-benzoxazol-2-ylamino)phenyl][1,3]oxazolo[4,5-b]pyridin-2(3H)-one



Same procedure of example 1a) with 3-(4-aminophenyl)[1,3]oxazolo[4,5-b]pyridin-2(3H)-one (50 mg) and 2-chlorobenzo[d]oxazole (40 mg) gave 3-[4-(1,3-benzoxazol-2-ylamino)phenyl][1,3]oxazolo[4,5-b]pyridin-2(3H)-one (58 mg) as brown crystals.

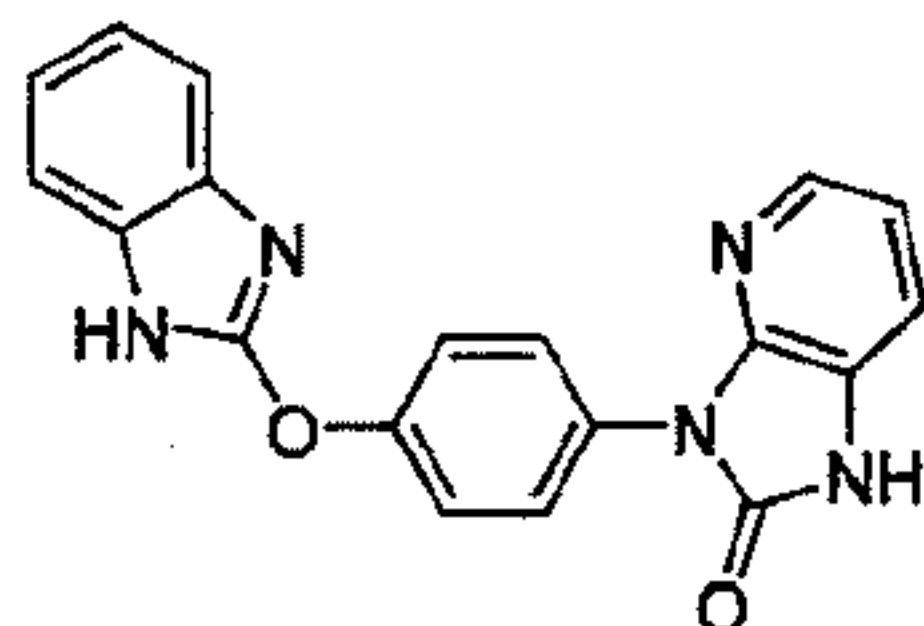
MS (ESI⁺): [M+H]⁺ 345.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.15–7.18 (1H, m), 7.23–7.27 (2H, m), 7.49 (1H, dd, *J* = 7.5, 0.5 Hz), 7.52 (1H, d, *J* = 8.0 Hz), 7.68–7.71 (2H, m), 7.81 (1H, dd, *J* = 8.0, 1.5 Hz), 7.92–7.95 (2H, m), 8.11 (1H, dd, *J* = 5.5, 1.5 Hz), 10.88 (1H, s).

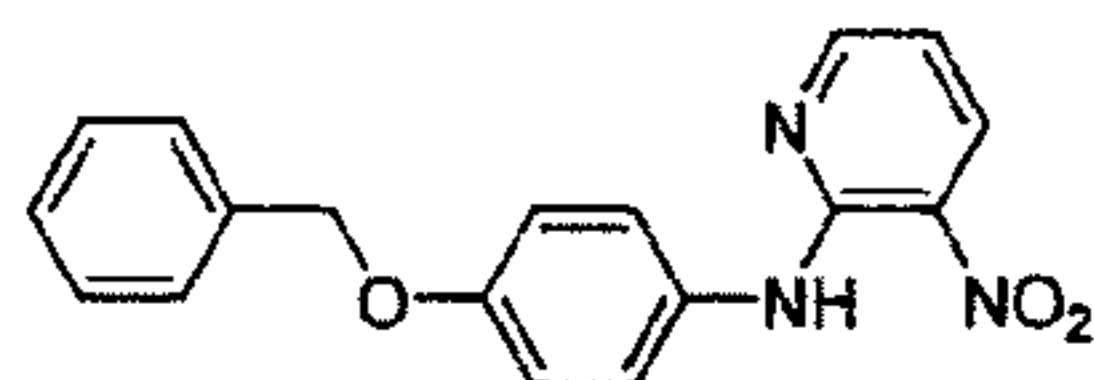
[0266]

Example 7

3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



7a) N-[4-(benzyloxy)phenyl]-3-nitropyridin-2-amine



A mixture of 2-chloro-3-nitropyridine (2.0 g), 4-(benzyloxy)aniline hydrochloride (3.6 g), and cesium carbonate (12.3 g) in NMP (50 mL) was heated at 100°C for 5 h. After cooling to rt, the mixture was partitioned between AcOEt and H₂O. The organic layer was washed with brine, dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (SiO₂, hexane/AcOEt=1/1) to give N-[4-

WO 2011/163355

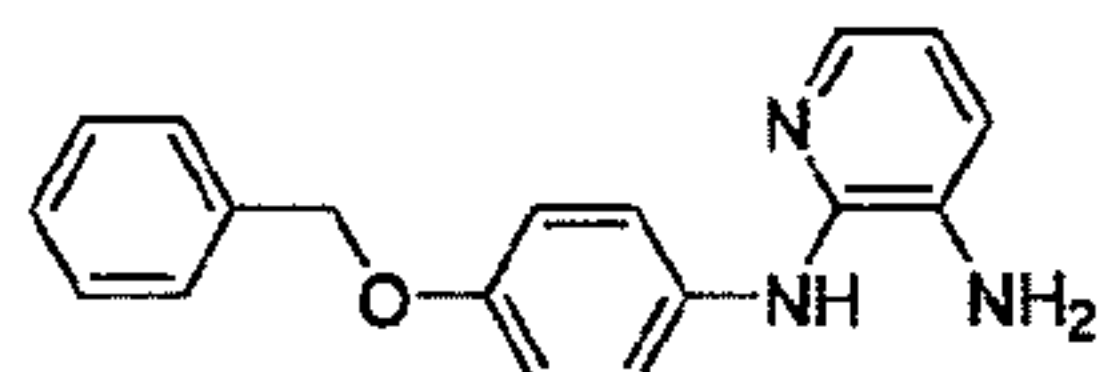
PCT/US2011/041443

(benzyloxy)phenyl]-3-nitropyridin-2-amine (3.04 g) as a brown solid.

MS (ESI+): $[M+H]^+$ 322.0.

[0267]

5 7b) N^2 -[4-(benzyloxy)phenyl]pyridine-2,3-diamine

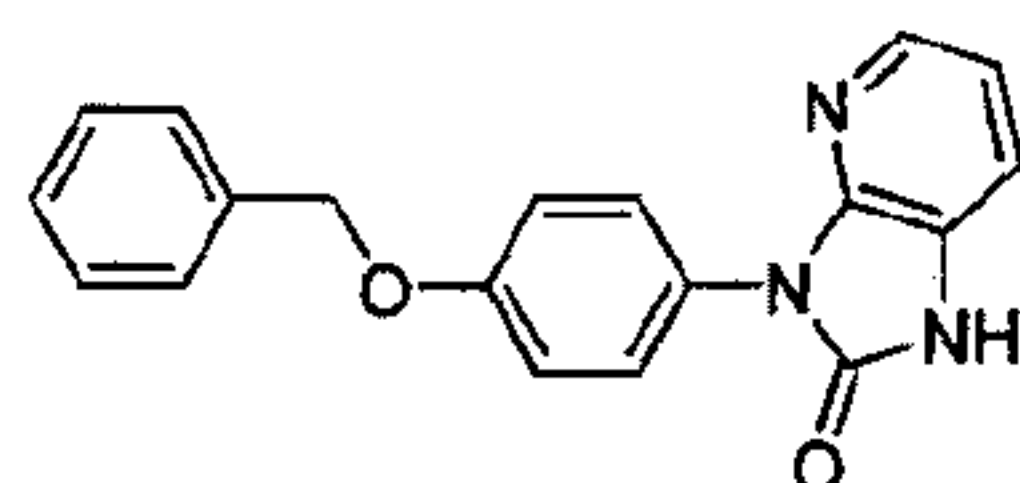


A mixture of *N*-[4-(benzyloxy)phenyl]-3-nitropyridin-2-amine (1.5 g), Fe (2.6 g), and $CaCl_2$ (260 mg) in EtOH (30 mL) and H_2O (6.0 mL) was heated at 100°C for 6 h. After cooling to
 10 rt, the precipitate was removed by Celite, and the filtrate was concentrated. The residue was partitioned between AcOEt and sat. $NaHCO_3$ aq. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (SiO_2 , hexane/AcOEt=3/2 to 1/1). The
 15 obtained solid was rinsed with iPr_2O -hexane to give N^2 -[4-(benzyloxy)phenyl]pyridine-2,3-diamine (1.0 g) as a pale pink solid.

MS (ESI+): $[M+H]^+$ 292.1.

[0268]

20 7c) 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

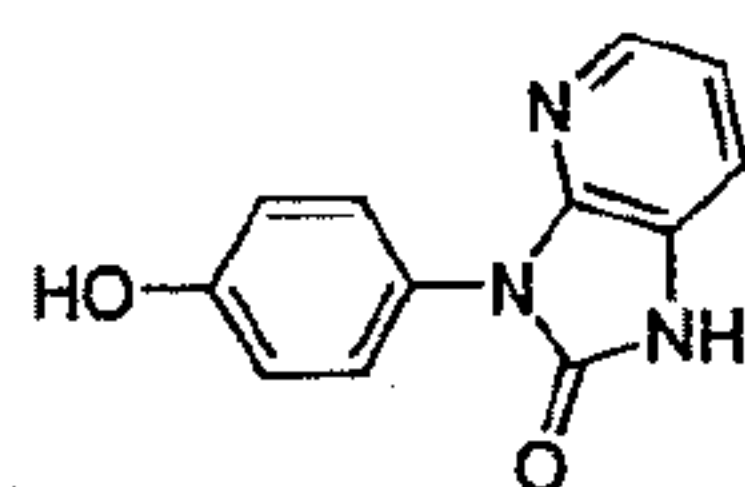


A mixture of N^2 -[4-(benzyloxy)phenyl]pyridine-2,3-diamine (1.0 g), CDI (668 mg), and DBU (1.2 mL) in THF (25 mL) was
 25 heated at 60°C overnight. After cooling to rt, the mixture was partitioned between AcOEt and H_2O . The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (SiO_2 , hexane/AcOEt=97/3 to 9/1) to give 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-
 30 imidazo[4,5-b]pyridin-2-one (993 mg) as a pale brown solid.

MS (ESI+): $[M+H]^+$ 318.0.

[0269]

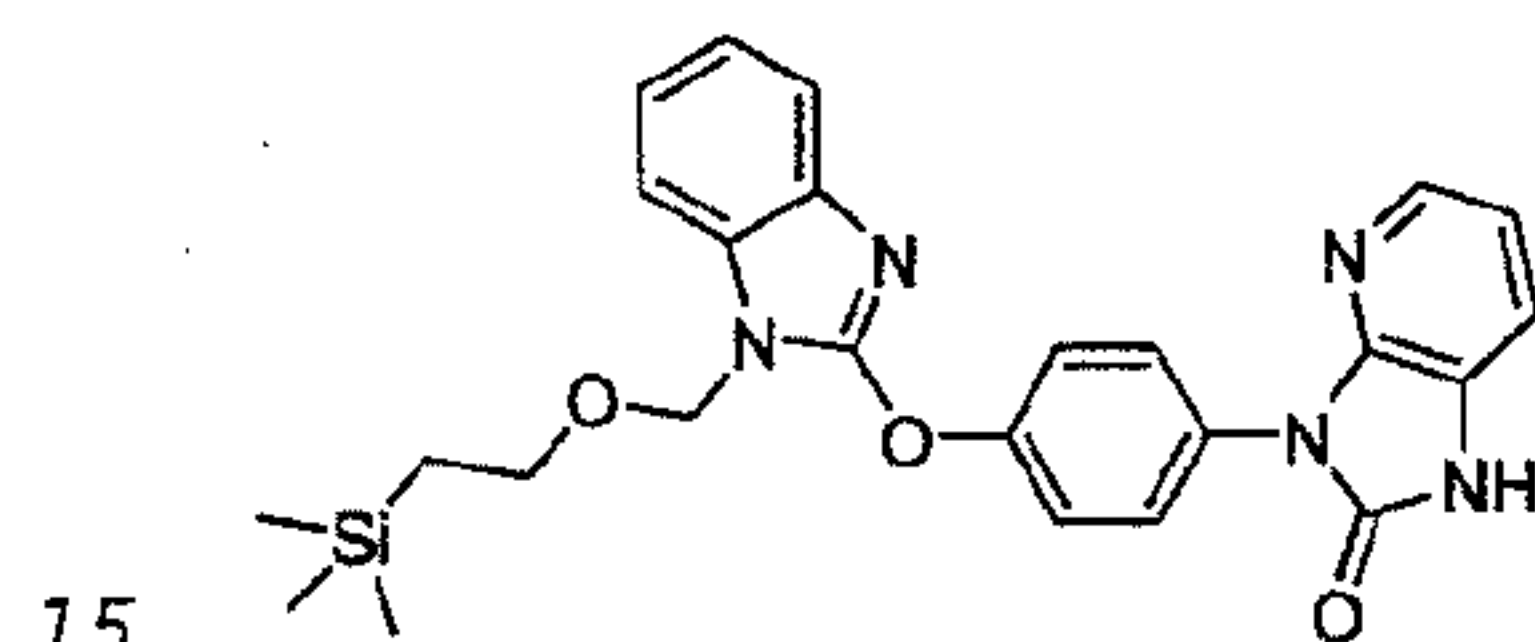
7d) 3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (500 mg) and Pd-C (100 mg) in MeOH (30 mL) was stirred at room temperature for 5.5 h. The mixture was filtered by Celite, and the filtrate was concentrated. The resulting solid was rinsed with i -Pr₂O to give 3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (370 mg) as a pale brown solid.

[0270]

7e) 3-{4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

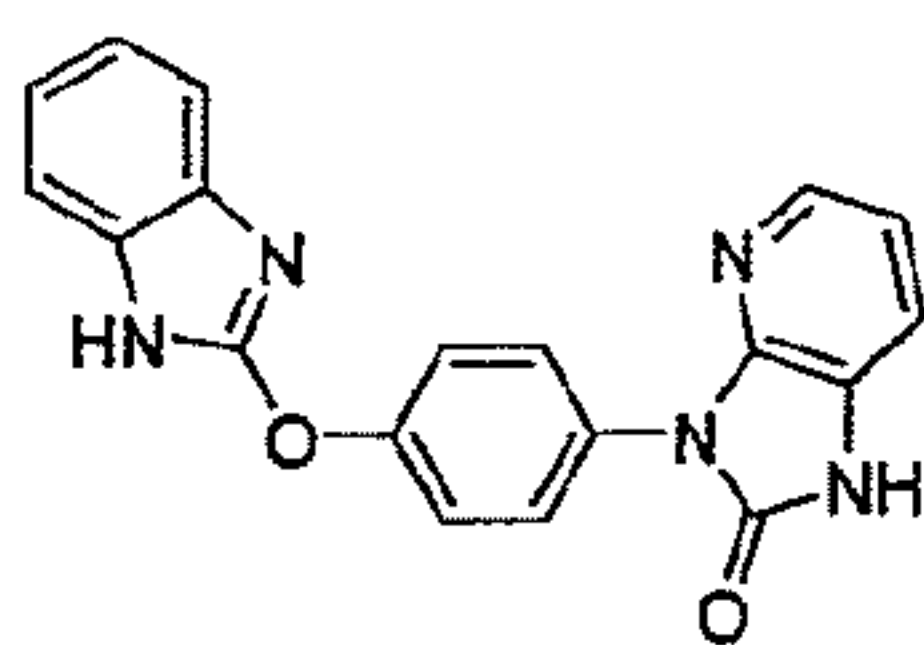


3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (370 mg), 2-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazole (507 mg) and cesium carbonate (1.17 g) in DMF (10 mL) was heated at 100°C for 4 h. After cooling to rt, the mixture was partitioned between AcOEt and H₂O. The organic layer was washed with brine, dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (SiO₂, hexane/AcOEt=1/1 to 0/1) to give 3-{4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (560 mg) as white crystals.

MS (ESI⁺): [M+H]⁺ 474.0.

[0271]

7f) 3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-[4-((1-([2-(trimethylsilyl)ethoxy)methyl]-1H-benzimidazol-2-yl)oxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (300 mg), 1 M TBAF in THF (6.3 mL), and TMEDA
 5 in THF (20 mL) was heated at 50°C for 24 h. After cooling to rt, the mixture was partitioned between AcOEt and H₂O. The organic layer was washed with brine, dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (SiO₂, hexane/AcOEt=1/3 then AcOEt/MeOH=95/5). The obtained product
 10 was recrystallized from MeOH-iPr₂O to give 3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (75 mg) as white crystals.

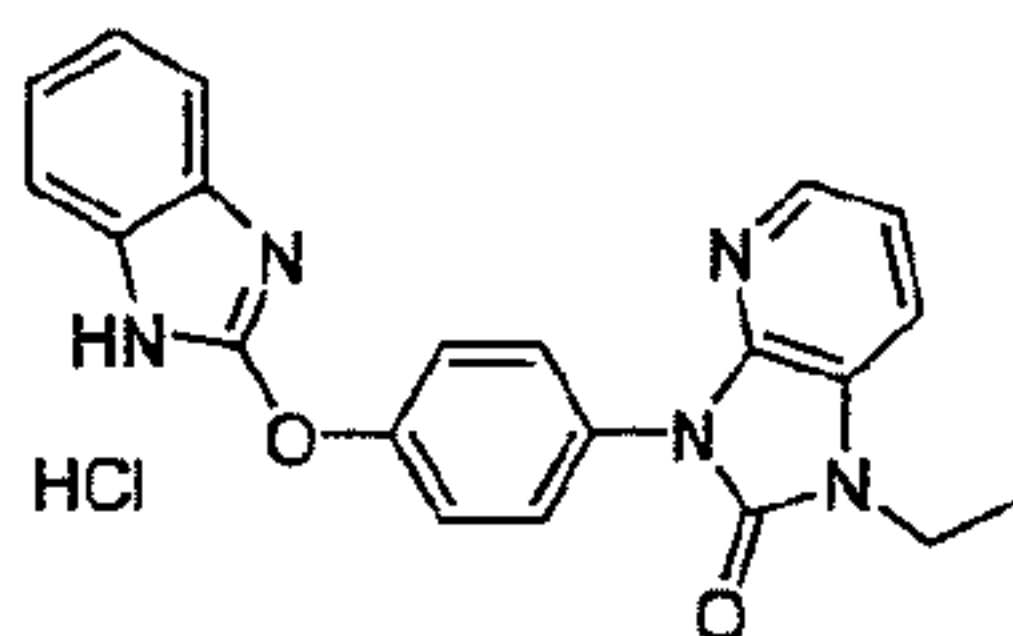
MS (ESI⁺): [M+H]⁺ 343.9.

¹H NMR (300 MHz, DMSO-d₆) δ 7.11 (3 H, dd, J = 5.7, 3.8 Hz),
 15 7.32 - 7.47 (3 H, m), 7.54 (2 H, d, J = 8.0 Hz), 7.74 (2 H, d, J = 8.3 Hz), 7.95 (1 H, d, J = 4.9 Hz), 12.04 (2 H, brs).

[0272]

Example 8

3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1-ethyl-1,3-dihydro-2H-
 20 imidazo[4,5-b]pyridin-2-one hydrochloride



2-Chloro-1-([2-(trimethylsilyl)ethoxy)methyl]-1H-benzimidazole (1.861 g) was added to a solution of 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
 25 (1.4 g) and sodium hydride (0.263 g) in DMF(dry) (10 mL) at room temperature. The mixture was heated at 200 °C for 1 h under microwave irradiation. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluted with 5% - 50%
 30 EtOAc in hexane) to give 1-ethyl-3-[4-((1-([2-(trimethylsilyl)ethoxy)methyl]-1H-benzimidazol-2-

yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.60 g) as a colorless solid. A mixture of 1-ethyl-3-{4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (194 mg) and 2 M HCl in EtOH (6.0 mL) was stirred at 70°C for 4 h. After cooling to room temperature, the solvent was removed in vacuo. The residue was recrystallized from EtOH-ether to give 3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one hydrochloride (154 mg).

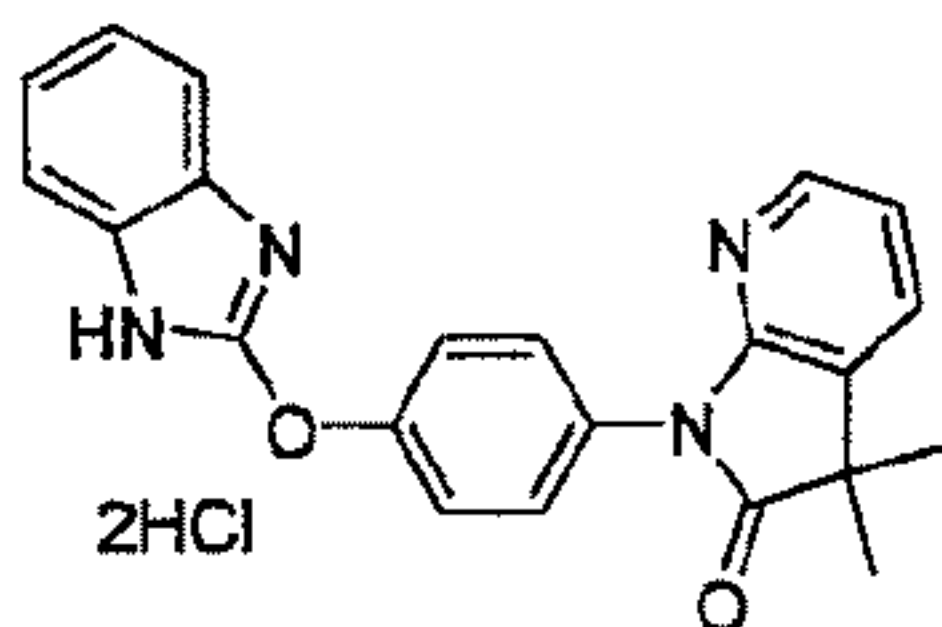
10 MS (ESI+): $[M+H]^+$ 372.1.

^1H NMR (300 MHz, DMSO- d_6) δ 1.17-1.43 (3H, m), 3.78-4.15 (2H, m), 7.12-8.06 (10H, m), 8.62 (2H, brs).

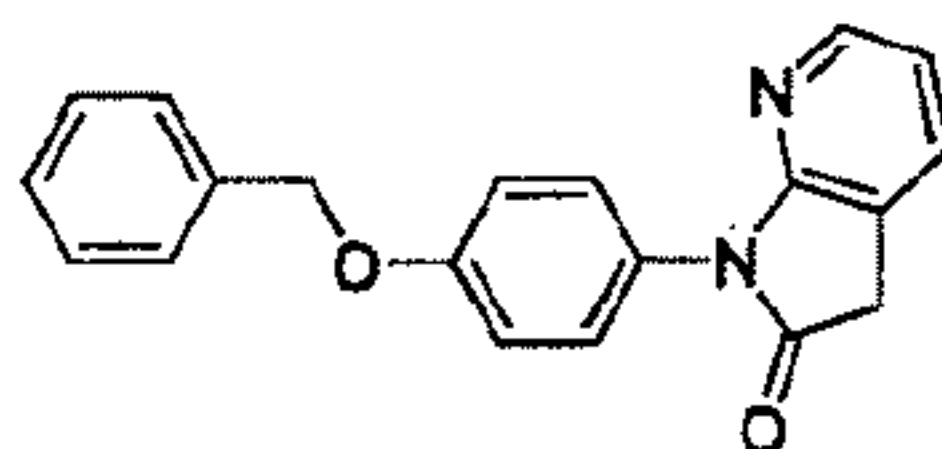
[0273]

Example 9

15 1-[4-(1H-benzimidazol-2-yloxy)phenyl]-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride



9a) 1-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one



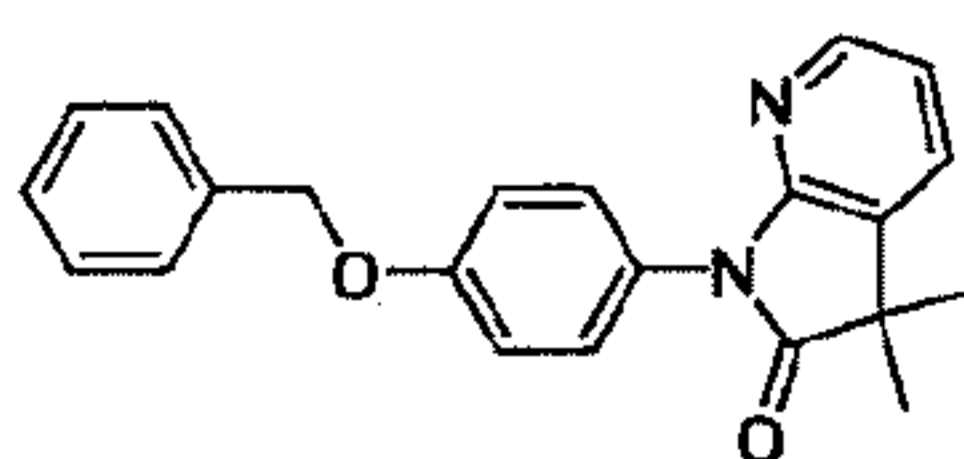
20

A mixture of 4-(benzyloxy)aniline hydrochloride (2.21 g), 4-methylbenzenesulfonic acid hydrate (0.178 g), and (2-chloropyridin-3-yl)acetic acid (*Journal of Medicinal Chemistry*, 1990, 33, 2697 - 2706.) (1.61 g) in 1-pentanol (15 mL) was stirred at 140°C for 24 h. After cooling to room temperature, the mixture was added to SiO_2 , and the mixture was concentrated and purified by column chromatography (silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (1.39 g) as a pale yellow solid.

30 MS (ESI+): $[M+H]^+$ 317.0.

[0274]

9b) 1-[4-(benzyloxy)phenyl]-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one

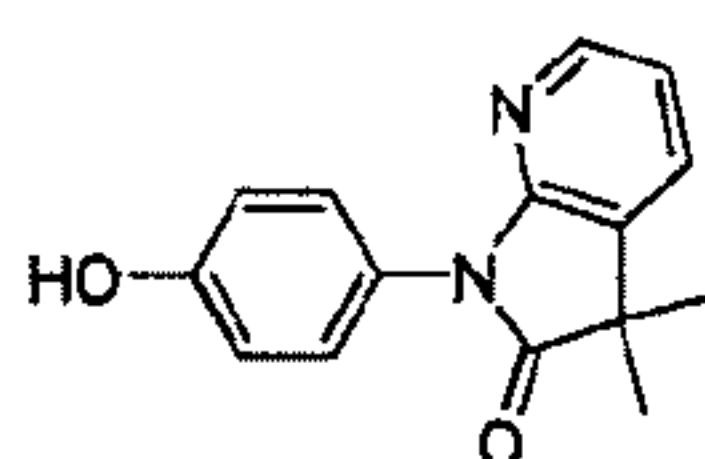


5 A mixture of 1-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (350 mg), iodomethane (0.145 mL), and sodium hydride (49 mg) (60% in mineral oil) in DMF (5 mL) was stirred at 0°C to room temperature overnight. The mixture was quenched with water at room temperature and extracted with
10 EtOAc. The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-[4-(benzyloxy)phenyl]-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (198 mg)
15 as an orange solid.

MS (ESI⁺): [M+H]⁺ 345.4.

[0275]

9c) 1-(4-hydroxyphenyl)-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one



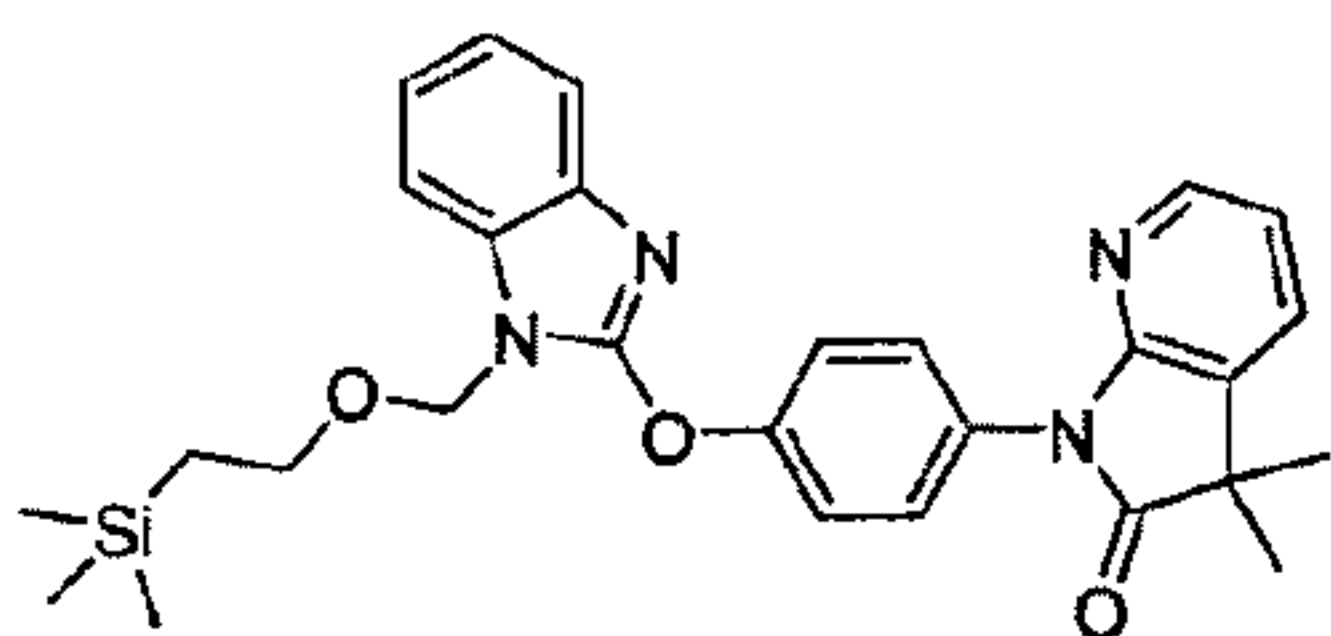
20

Same procedure of example 1c) with 1-[4-(benzyloxy)phenyl]-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (198 mg) gave 1-(4-hydroxyphenyl)-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (139 mg)
25 as a white solid.

MS (ESI⁺): [M+H]⁺ 255.4.

[0276]

9d) 3,3-dimethyl-1-{4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-pyrrolo[2,3-
30 b]pyridin-2-one

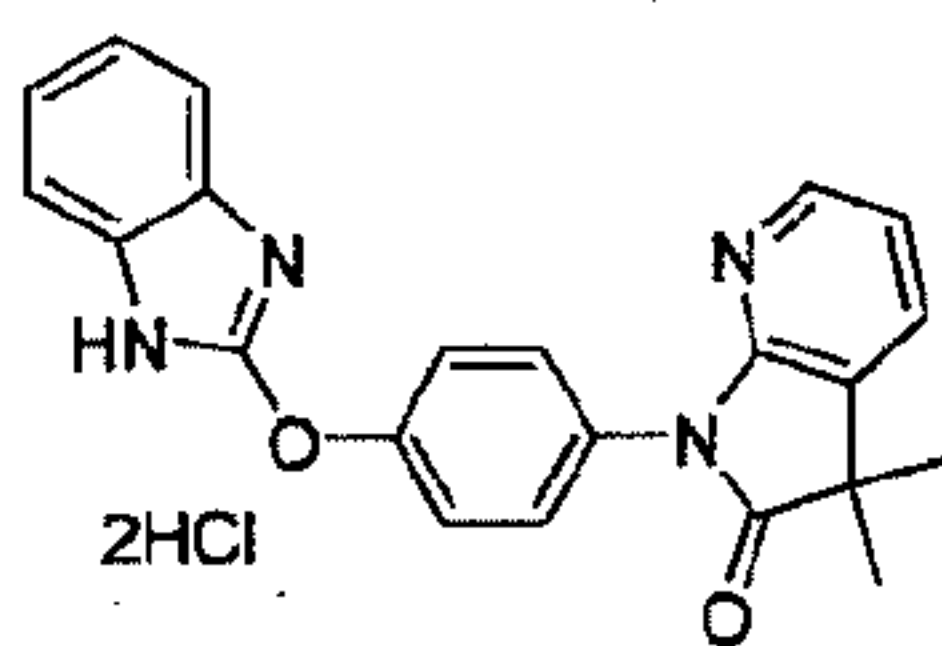


Same procedure of example 7e) with 1-(4-hydroxyphenyl)-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (139 mg) and 2-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazole (155 mg) gave 3,3-dimethyl-1-{4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (258 mg) as white crystals.

MS (ESI+): $[M+H]^+$ 501.1.

10 [0277]

9e) 1-[4-(1H-benzimidazol-2-yloxy)phenyl]-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride



A mixture of 3,3-dimethyl-1-{4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (258 mg) and 2N HCl in EtOH (5 mL) in EtOH (5 mL) was stirred at 60°C for 10 h. After cooling to room temperature, the solvent was removed. The residue was recrystallized from EtOH-AcOEt to give 1-[4-(1H-benzimidazol-2-yloxy)phenyl]-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride (152 mg).

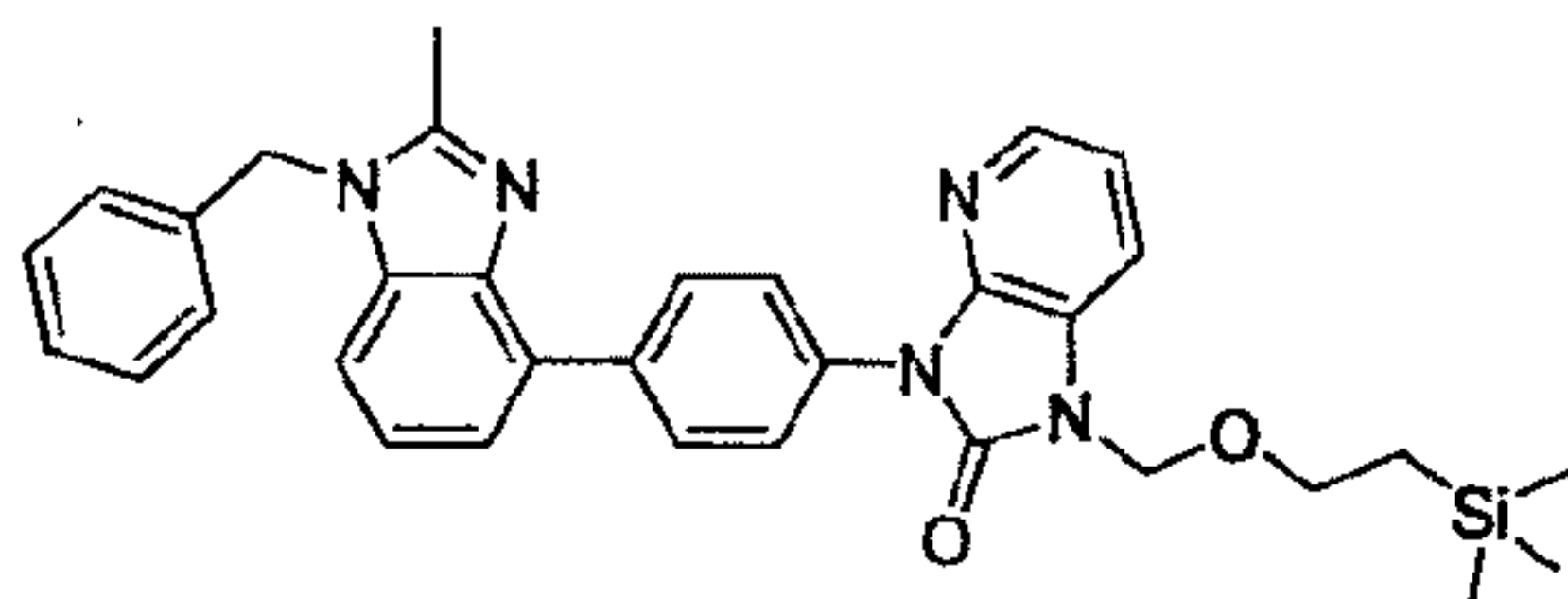
MS (ESI+): $[M+H]^+$ 371.0.

^1H NMR (300 MHz, DMSO- d_6) δ 1.45 (6H, s), 7.12-7.23 (3H, m), 7.38-7.48 (2H, m), 7.49-7.72 (4H, m), 7.87 (1H, dd, J = 7.4, 1.7 Hz), 8.13 (1H, dd, J = 5.3, 1.9 Hz), 8.67 (3H, brs).

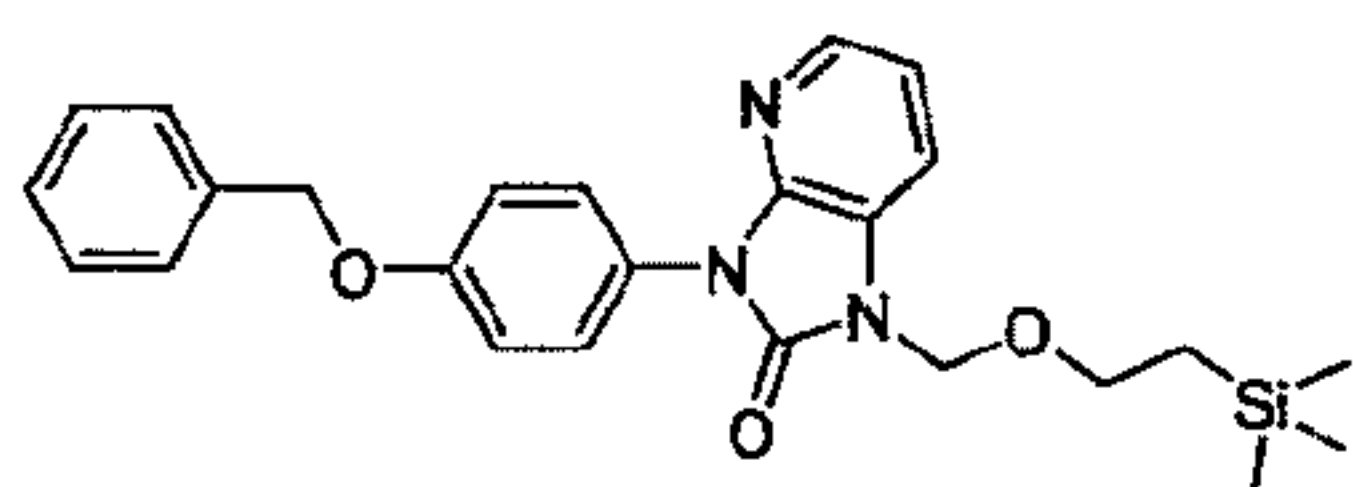
[0278]

Example 10

3-[4-(1-benzyl-2-methyl-1H-benzimidazol-4-yl)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



10a) 3-[4-(benzyloxy)phenyl]-1-([2-(trimethylsilyl)ethoxy]methyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



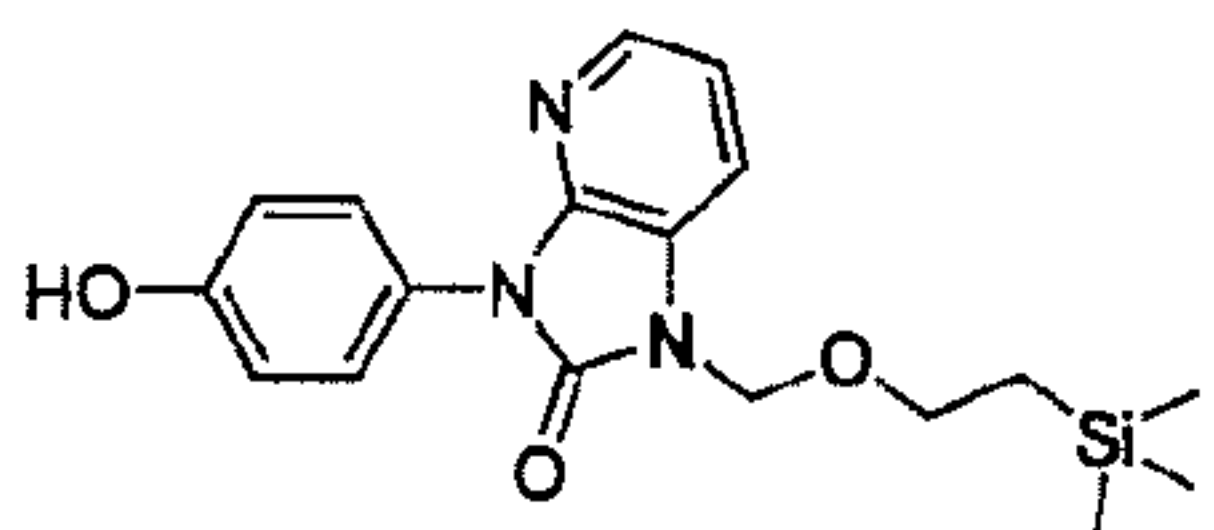
5

[2-(Chloromethoxy)ethyl](trimethyl)silane (1.673 mL) was added to a solution of 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.0 g) and sodium hydride (0.504 g) (60% in mineral oil) in DMF (5.0 mL) at 0°C. The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube) for 1h. After the reaction, the reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 100% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1-([2-(trimethylsilyl)ethoxy]methyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.75 g) as a white solid.

MS (ESI⁺): [M+H]⁺ 448.1

[0279]

10b) 3-(4-hydroxyphenyl)-1-([2-(trimethylsilyl)ethoxy]methyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

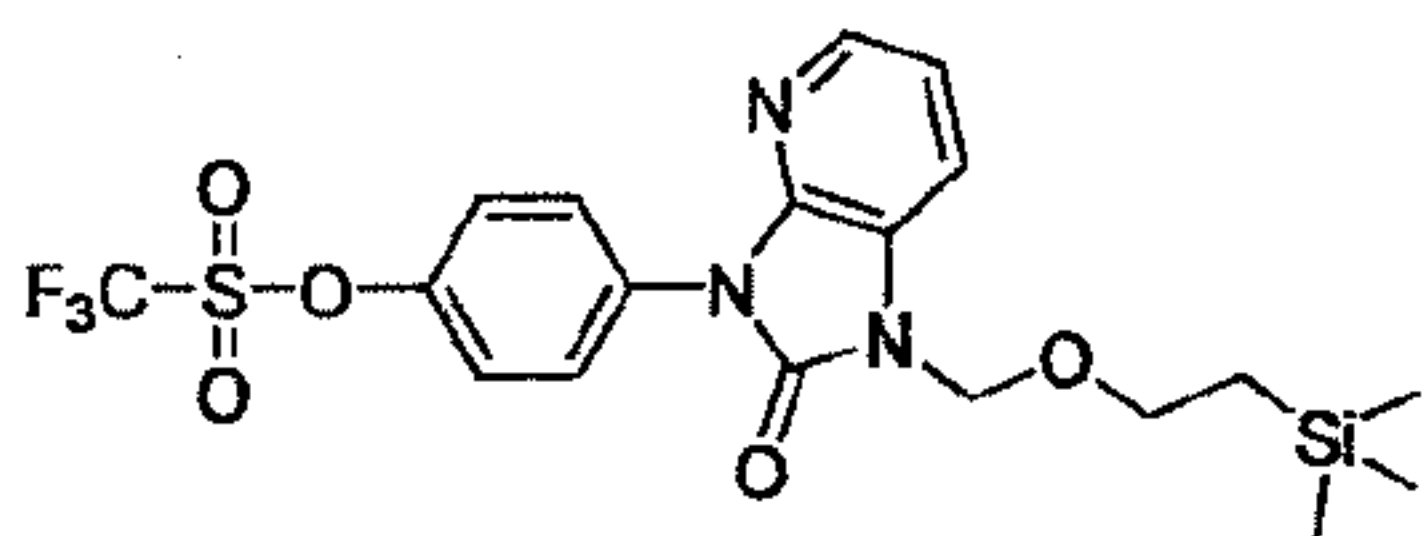


Same procedure of example 7d) with 3-[4-(benzyloxy)phenyl]-1-([2-(trimethylsilyl)ethoxy]methyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.82 g) gave 3-(4-hydroxyphenyl)-1-([2-(trimethylsilyl)ethoxy]methyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.23 g) as a white solid.

MS (ESI⁺): [M+H]⁺ 358.4.

[0280]

10c) 4-(2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl trifluoromethanesulfonate



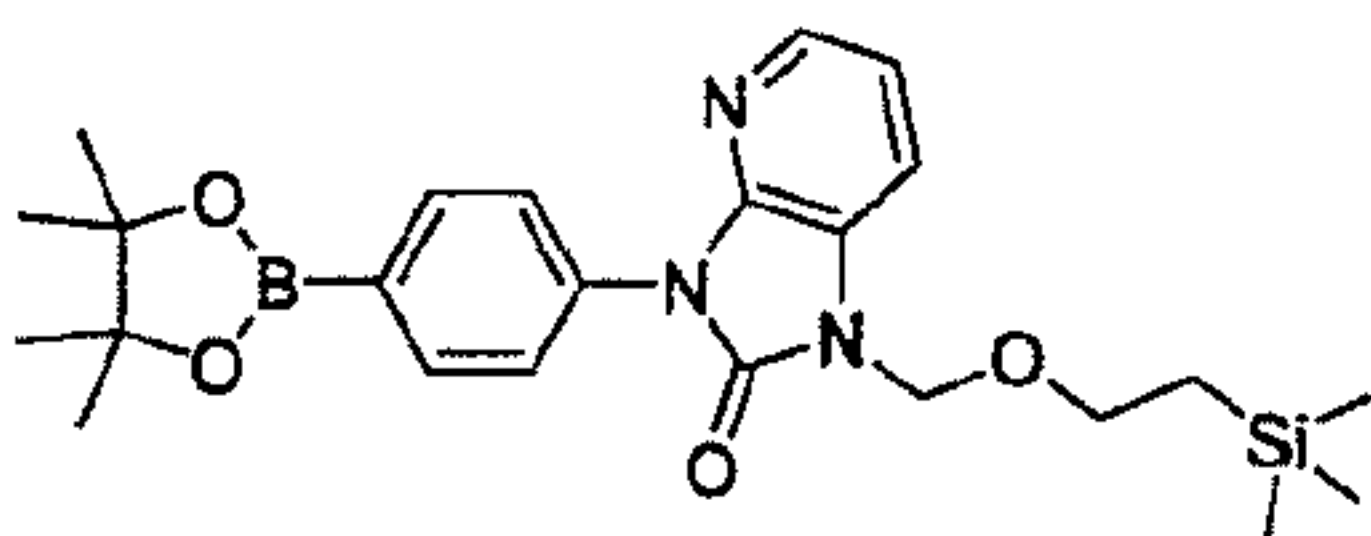
5

N-Phenylbis(trifluoromethanesulfonimide) (4.46 g) was added to a solution of 3-(4-hydroxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.23g) and triethylamine (8.69 mL) in THF (20 mL) at room temperature. The mixture was stirred at 70°C under a dry atmosphere (CaCl₂ tube) for 3h. The mixture was neutralized with sat. NaHCO₃ aq. at 0°C and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 30% EtOAc in hexane) to give 4-(2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl trifluoromethanesulfonate (2.90 g) as tan oil.

20 MS (ESI⁺): [M+H]⁺ 490.3.

[0281]

10d) 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



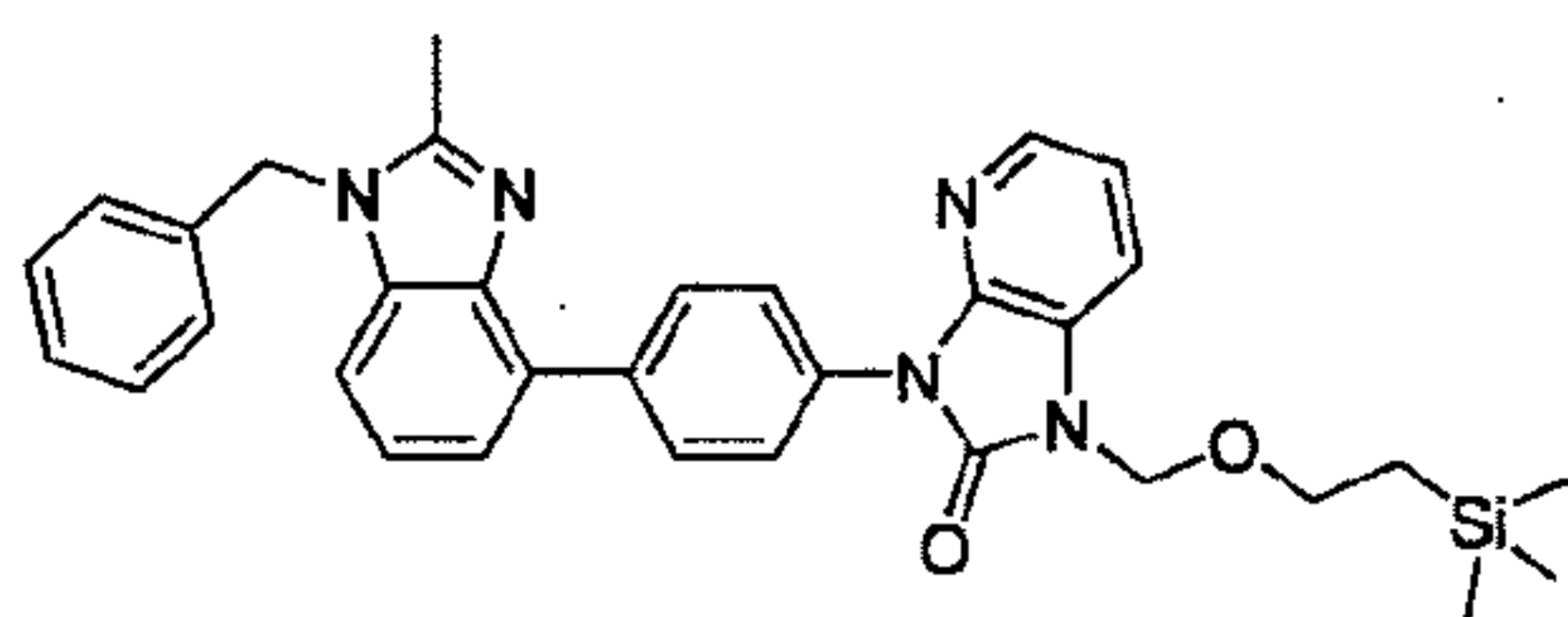
25

The mixture of 4-(2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl trifluoromethanesulfonate (2.6 g), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.77 mL), triethylamine (2.23 mL), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

dichloromethane adduct (0.218 g) and THF (21.2 mL) was heated at 100°C for 3h under microwave irradiation. The mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 30% EtOAc in hexane) to give 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-{{2-(trimethylsilyl)ethoxy}methyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.5 g) as dark yellow oil. MS (ESI+): [M+H]⁺ 468.2.

[0282]

10 10e) 3-[4-(1-benzyl-2-methyl-1H-benzimidazol-4-yl)phenyl]-1-{{2-(trimethylsilyl)ethoxy}methyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



Benzyl chloride (1.527 mL) was added to a solution of 4-bromo-2-methyl-1H-benzimidazole (1.40g) and sodium hydride (0.531 g) in DMF (10 mL) at 0°C. The mixture was stirred at room temperature under a dry atmosphere for 1 h. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 5% - 50% EtOAc in hexane) to give 1-benzyl-4-bromo-2-methyl-1H-benzo[d]imidazole (1.88 g) as tan oil. The mixture of 1-benzyl-4-bromo-2-methyl-1H-benzo[d]imidazole (496 mg), 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-{{2-(trimethylsilyl)ethoxy}methyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (700 mg), Pd(Ph₃P)₄ (87 mg), sodium carbonate (476 mg) and THF (18 mL)-water (0.90 mL) was heated at 100°C for 1h under microwave irradiation. The mixture was poured into water at room temperature and extracted with EtOAc. The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 10% - 50% EtOAc in hexane) to give 3-[4-(1-benzyl-2-methyl-1H-

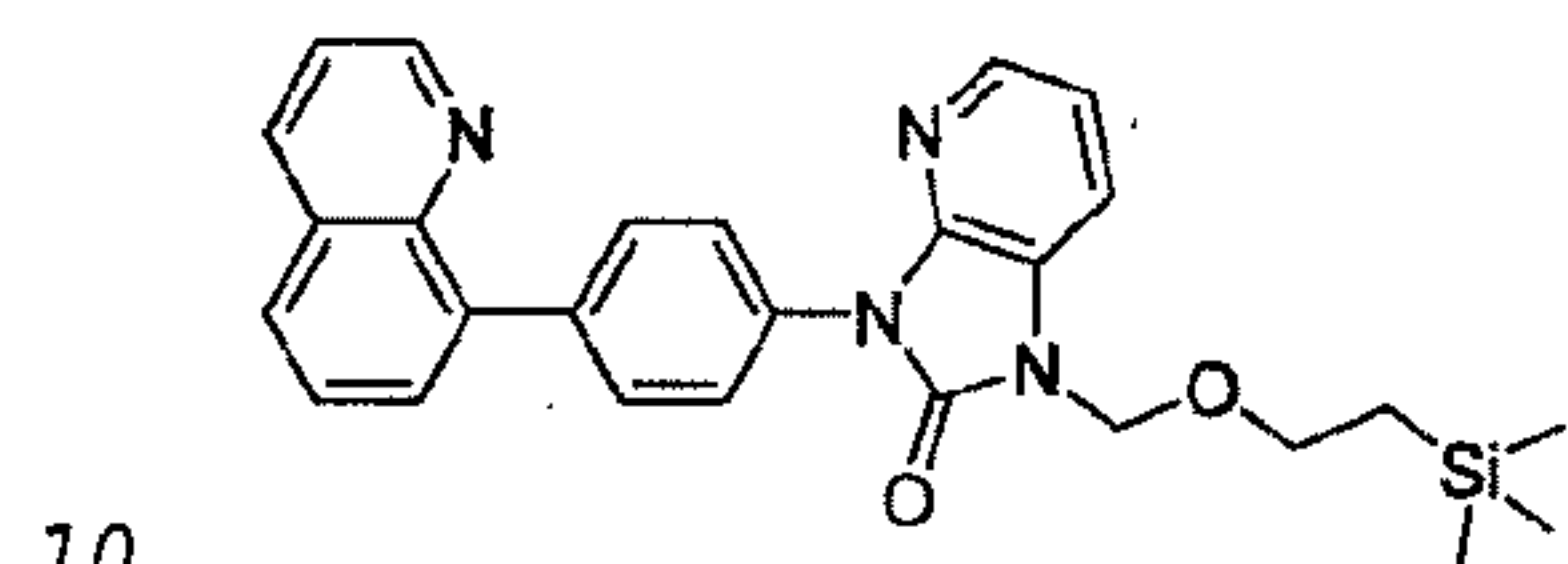
benzimidazol-4-yl)phenyl]-1-{[2-(trimethylsilyl)ethoxy)methyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (450 mg) as white crystals.

MS (ESI⁺): [M+H]⁺ 562.4.

5 [0283]

Example 11

3-(4-quinolin-8-ylphenyl)-1-{[2-(trimethylsilyl)ethoxy)methyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



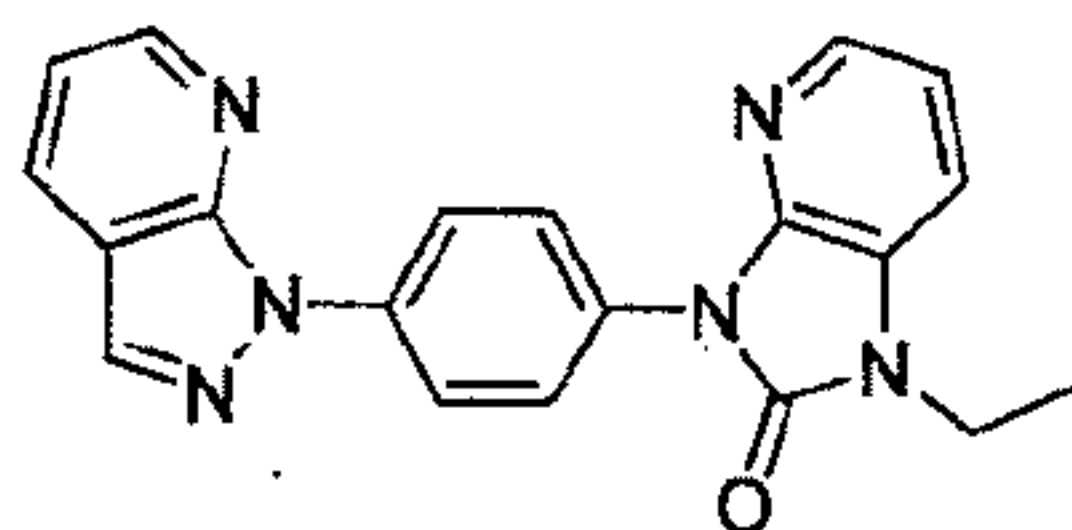
The mixture of 4-(2-oxo-1-{[2-(trimethylsilyl)ethoxy)methyl]-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl trifluoromethanesulfonate (500 mg), 8-quinolineboronic acid (265 mg), Pd(Ph₃P)₄ (35.4 mg), 2 M Na₂CO₃ (1.02 mL) and CH₃CN (10 mL) was heated at 150°C for 20 min under microwave irradiation. The mixture was diluted with sat. NaHCO₃aq. at 0°C and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 50% EtOAc in hexane) to give 3-(4-quinolin-8-ylphenyl)-1-{[2-(trimethylsilyl)ethoxy)methyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (410 mg) as white crystals.

MS (ESI⁺): [M+H]⁺ 469.1.

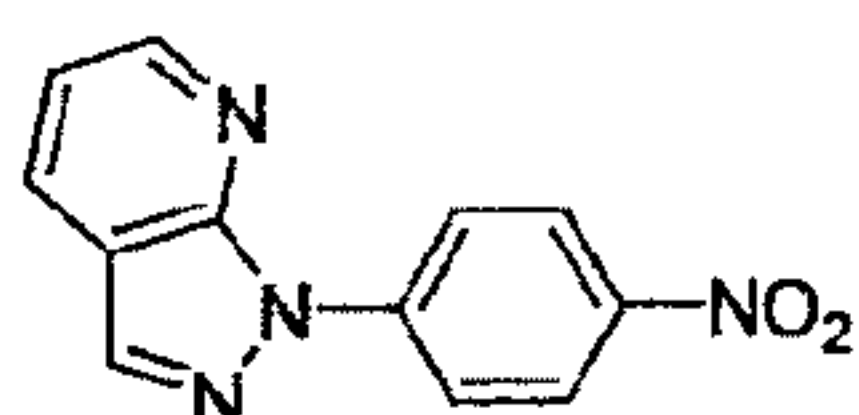
25 [0284]

Example 12

1-Ethyl-3-[4-(1H-pyrazolo[3,4-b]pyridin-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



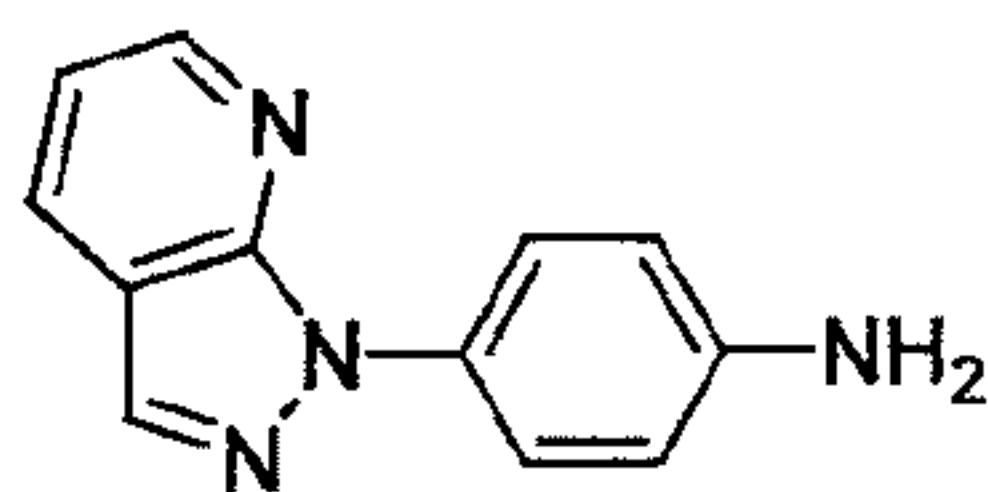
12a) 1-(4-nitrophenyl)-1H-pyrazolo[3,4-b]pyridine



To a stirred solution of 1H-pyrazolo[3,4-b]pyridine (300 mg) in DMF (3.0 mL) was added sodium hydride (101 mg) (60% in mineral oil) with ice-cooling. The mixture was stirred at room temperature for 30 min, and then 1-fluoro-4-nitrobenzene (355 mg) was added. After stirring at room temperature for 2h, the mixture was warmed up to 50°C. The mixture was stirred at 50°C for 12 h. Cesium carbonate (821 mg) was added and the mixture was stirred at 100°C for 12h, and treated with water and AcOEt. The insoluble material was filtered off. The organic layer was separated and the aqueous layer was extracted with AcOEt. The organic layer was combined, dried over MgSO₄ and concentrated in vacuo. The residue was used for the next reaction.

[0285]

12b) 4-(1H-pyrazolo[3,4-b]pyridin-1-yl)aniline

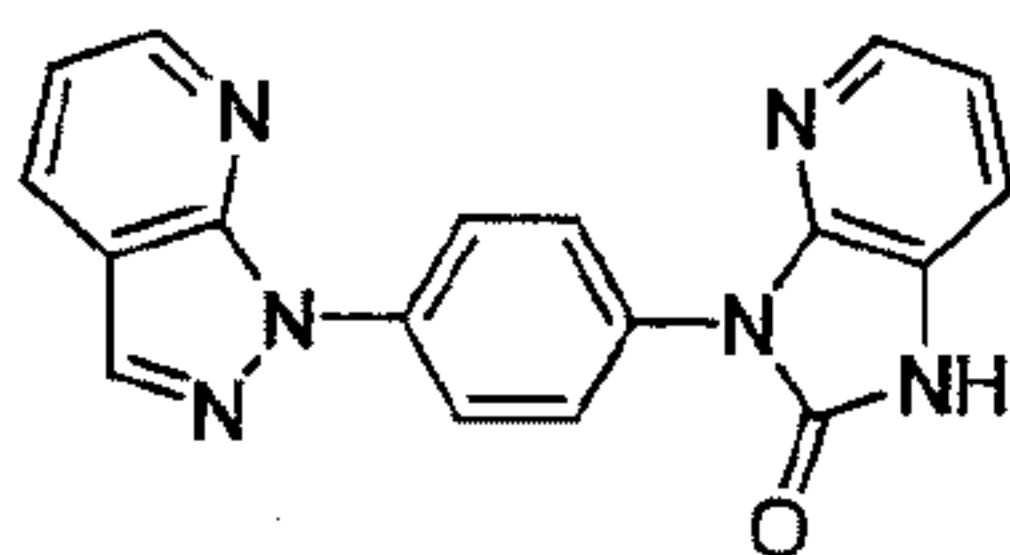


Same procedure of example 1c) with 1-(4-nitrophenyl)-1H-pyrazolo[3,4-b]pyridine obtained from example 12a) gave 4-(1H-pyrazolo[3,4-b]pyridin-1-yl)aniline (50 mg).

MS (ESI+): [M+H]⁺ 211.1.

[0286]

12c) 3-[4-(1H-pyrazolo[3,4-b]pyridin-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of tert-butyl 2-chloropyridin-3-ylcarbamate (120 mg), Pd₂(dba)₃ (21.8 mg), Xantphos (27.5 mg), and sodium tert-butoxide (34.3 mg) in 2-propanol (8.0 mL) and toluene (2.0 mL) was stirred at 90°C for 16h, treated with water and extracted with EtOAc. The organic layer was separated, dried over MgSO₄ and concentrated in vacuo. The residue was suspended

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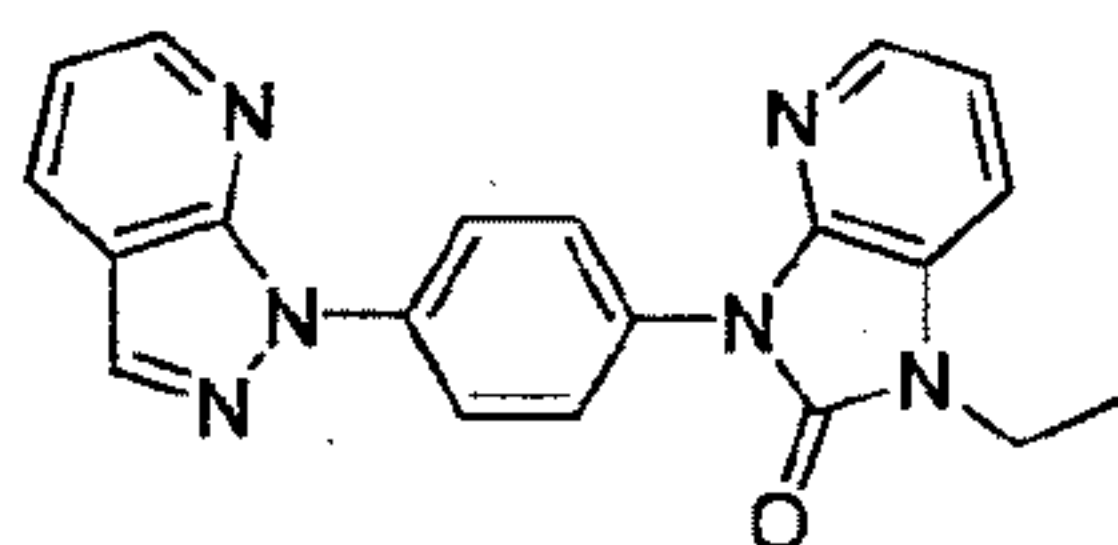
PCT/US2011/041443

in DMSO/ CH₃CN and the insoluble material was collected by filtration to give 3-[4-(1H-pyrazolo[3,4-b]pyridin-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (40 mg). The filtrate was concentrated and chromatographed on silica
 5 gel eluting with AcOEt/Hexane=2/1. Removal of solvent gave second crop (10 mg).

MS (ESI⁺): [M+H]⁺ 329.0.

[0287]

12d) 1-Ethyl-3-[4-(1H-pyrazolo[3,4-b]pyridin-1-yl)phenyl]-1,3-
 10 dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-[4-(1H-pyrazolo[3,4-b]pyridin-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (50 mg) and iodoethane (10.5 μ l) was stirred at 50°C for 30 min,
 15 treated with water and extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel eluting with Hexane/AcOEt=2/1 - 1/2. The product was crystallized from AcOEt/hexane to give 1-ethyl-3-[4-(1H-pyrazolo[3,4-b]pyridin-1-yl)phenyl]-1,3-
 20 dihydro-2H-imidazo[4,5-b]pyridin-2-one (13 mg).

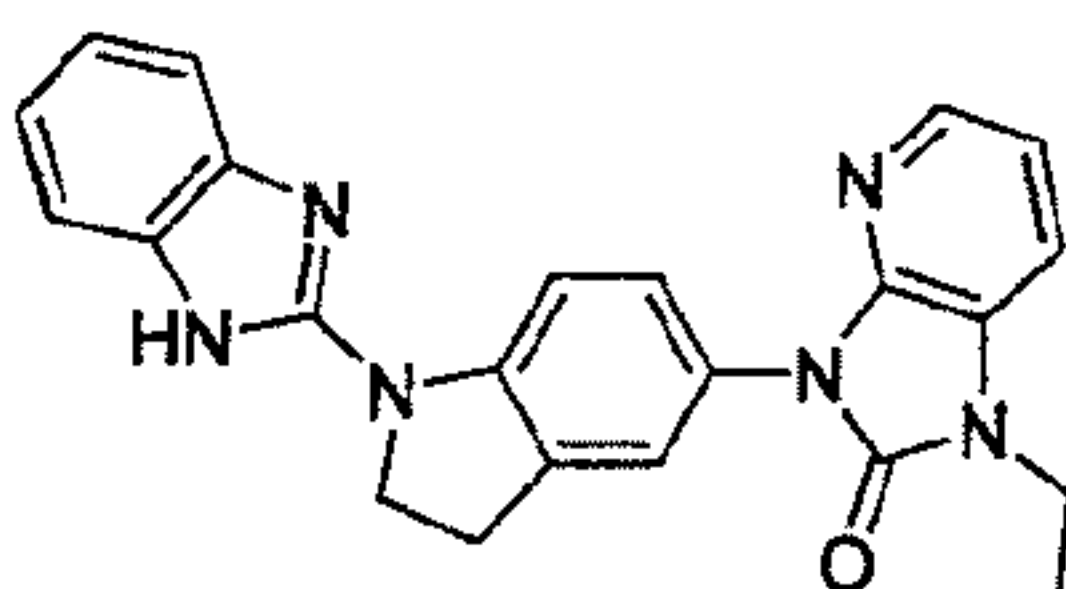
MS (ESI⁺): [M+H]⁺ 357.4.

¹H NMR (300 MHz, DMSO-d₆) δ 1.31 (3H, t, J = 7.2 Hz), 4.00 (2H, q, J = 7.2 Hz), 7.20 (1H, dd, J = 7.7, 5.1 Hz), 7.35-7.48 (1H, m), 7.64-7.77 (1H, m), 7.83-7.97 (2H, m), 7.97-8.07 (1H, m),
 25 8.39-8.50 (3H, m), 8.53 (1H, s), 8.73 (1H, dd, J = 4.5, 1.5 Hz).

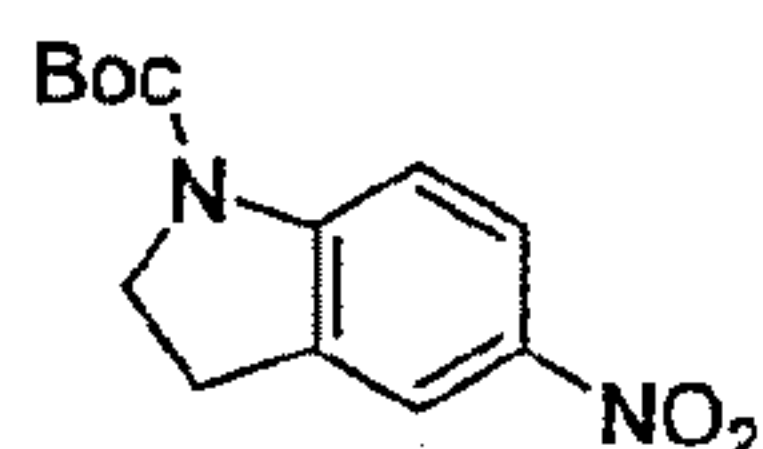
[0288]

Example 13

3-[1-(1H-benzimidazol-2-yl)-2,3-dihydro-1H-indol-5-yl]-1-
 30 ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



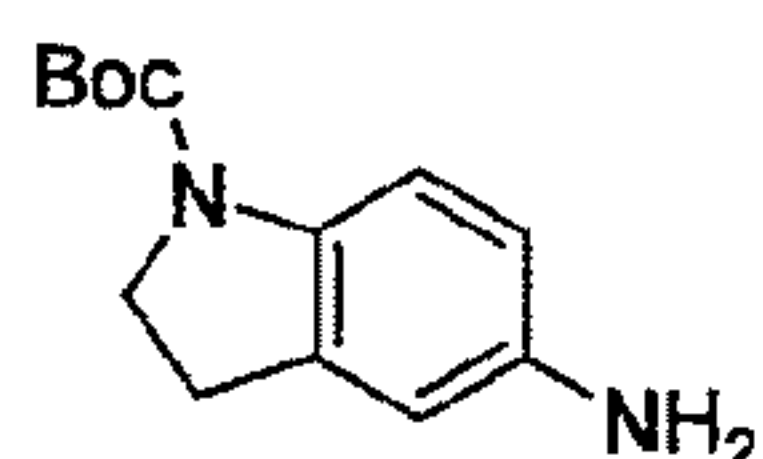
13a) tert-butyl 5-nitro-2,3-dihydro-1H-indole-1-carboxylate



To a stirred mixture of 5-nitroindoline (5.0 g) and Boc₂O (7.07 mL) in THF (100 mL) was added DMAP (0.5 g) at room temperature. The mixture was stirred at 60°C for 3h. The mixture was quenched with water, treated with sat. NaHCO₃aq. and extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was used for the next reaction without further purification.

10 [0289]

13b) tert-butyl 5-amino-2,3-dihydro-1H-indole-1-carboxylate

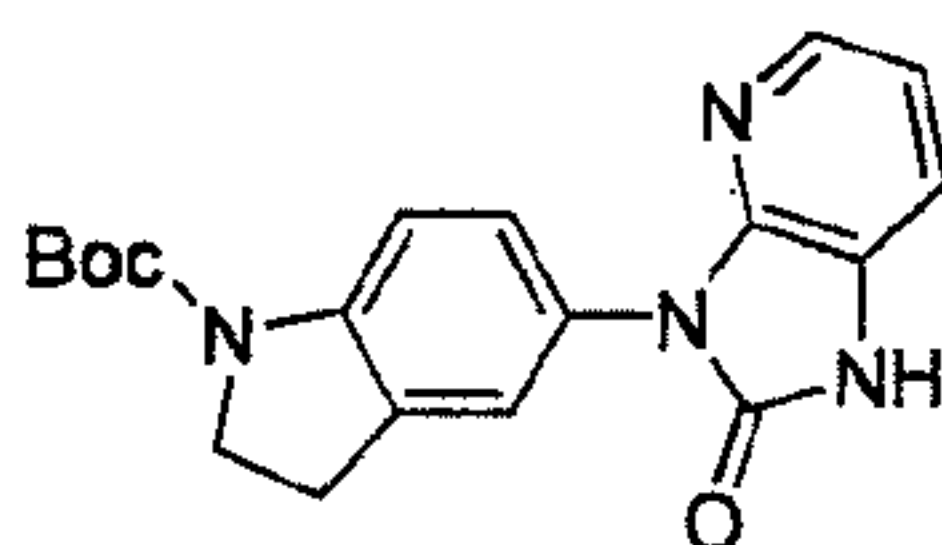


Under H₂ atmosphere, a mixture of tert-butyl 5-nitro-2,3-dihydro-1H-indole-1-carboxylate, obtained from example 13a), and 10% Pd-C (5 g) in EtOH (100 mL) was stirred at room temperature for 12h, filtered and concentrated in vacuo to give tert-butyl 5-amino-2,3-dihydro-1H-indole-1-carboxylate (6.80 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.47 (9H, s), 2.91 (2H, t, J = 8.5 Hz), 3.79 (2H, t, J = 8.5 Hz), 4.73 (2H, brs), 6.33 (1H, dd, J = 8.7, 2.3 Hz), 6.43 (1H, s), 6.95-7.53 (1H, m).

[0290]

13c) tert-butyl 5-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2,3-dihydro-1H-indole-1-carboxylate



25

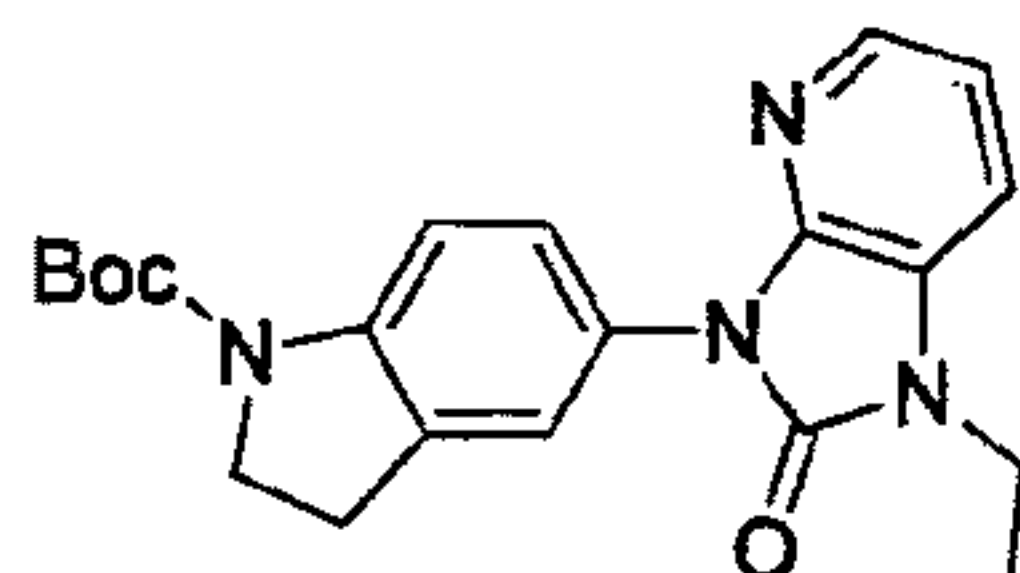
A mixture of tert-butyl 5-amino-2,3-dihydro-1H-indole-1-carboxylate (4.10 g), tert-butyl 2-chloropyridin-3-ylcarbamate (4.20 g), Pd₂(dba)₃ (0.48 g), Xantphos (0.608 g), sodium tert-butoxide (2.52 g) in 2-propanol (64 mL) and toluene (12 mL)

was stirred at 90°C for 40 h, and treated with water and extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was suspended in CH₃CN and the precipitate was collected by filtration to give tert-butyl 5-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2,3-dihydro-1H-indole-1-carboxylate (1.64 g). The filtrate was evaporated and then the residue was chromatographed on silica gel eluting with AcOEt/ Hexane = 2/1 to afford second crop (1.4 g).

10 MS (ESI⁺): [M+H]⁺ 353.3.

[0291]

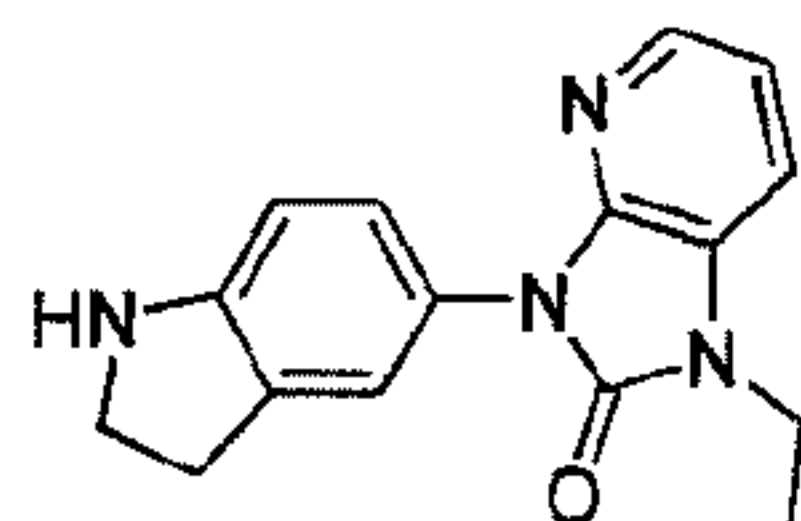
13d) tert-butyl 5-(1-ethyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2,3-dihydro-1H-indole-1-carboxylate



15 A mixture of tert-butyl 5-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2,3-dihydro-1H-indole-1-carboxylate (900 mg), ethyl iodide (418 mg) and cesium carbonate (1.25 g) in DMF (10 mL) was stirred at 50°C for 12 h, treated with water and extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel eluting with AcOEt/ Hexane to give tert-butyl 5-(1-ethyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2,3-dihydro-1H-indole-1-carboxylate (830 mg) as an amorphous solid. MS (ESI⁺): [M+H]⁺ 381.2.

25 [0292]

13e) 3-(2,3-dihydro-1H-indol-5-yl)-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



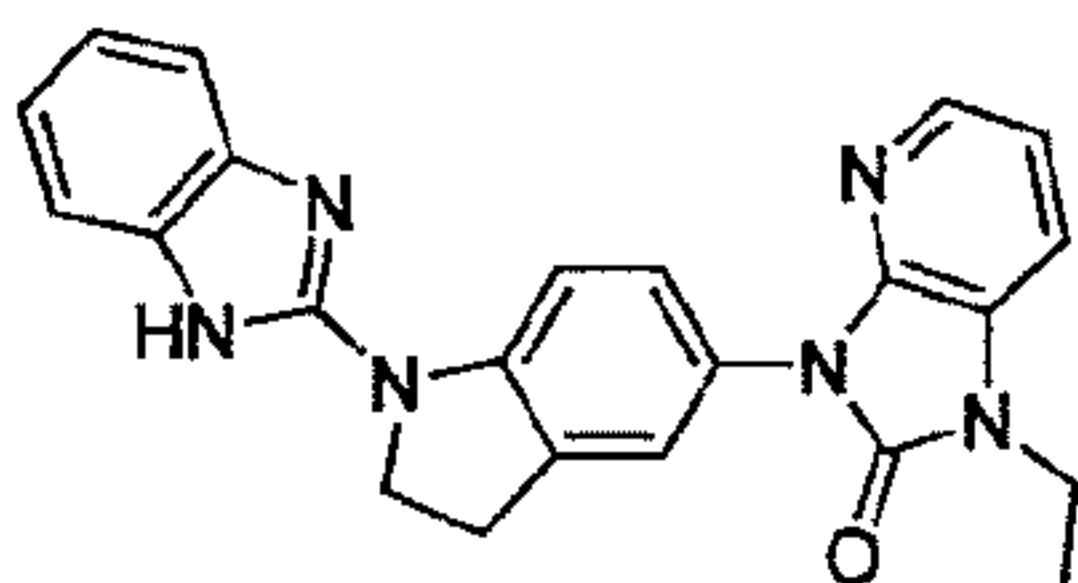
To a stirred solution of tert-butyl 5-(1-ethyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2,3-dihydro-1H-indole-1-carboxylate (100 mg) in EtOAc (2 mL) was added 4N HCl in

AcOEt solution (2.0 mL). The mixture was stirred at 50°C for 2h and evaporated. The residue was treated with sat.NaHCO₃aq. and extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated in vacuo to give 3-(2,3-dihydro-1H-indol-5-yl)-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one. This residue was used for the next reaction.

MS (ESI⁺): [M+H]⁺ 281.2.

[0293]

13f) 3-[1-(1H-benzimidazol-2-yl)-2,3-dihydro-1H-indol-5-yl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-(2,3-dihydro-1H-indol-5-yl)-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one obtained from example 13e) and 2-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazole (108 mg) in NMP (2.0 mL) was stirred at 120°C for 12 h, treated with sat.NaHCO₃aq. and extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by preparative HPLC and crystallized from AcOEt/ Hexane to give 3-[1-(1H-benzimidazol-2-yl)-2,3-dihydro-1H-indol-5-yl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (12 mg).

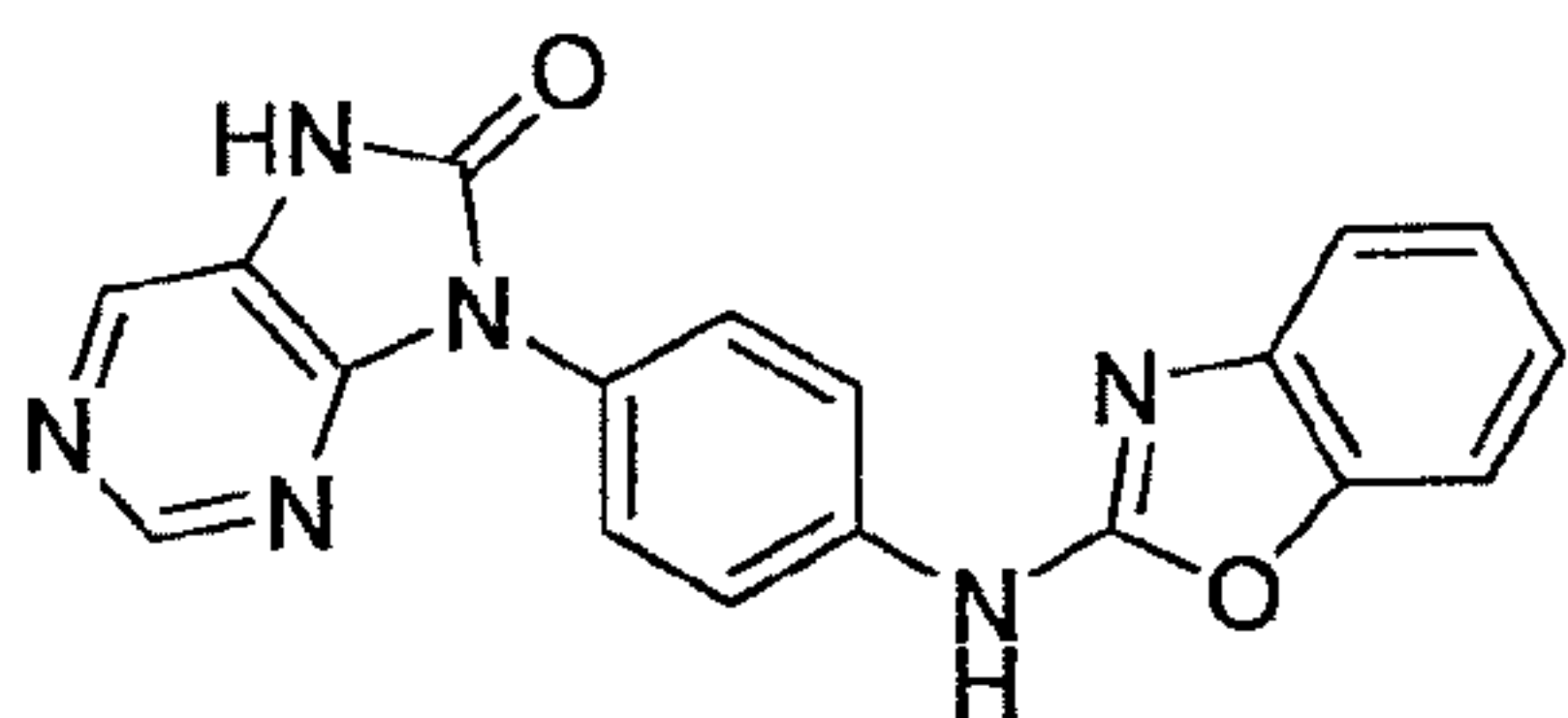
MS (ESI⁺): [M+H]⁺ 397.4.

¹H NMR (300 MHz, DMSO-d₆) δ 1.29 (3H, t, J = 7.2 Hz), 3.33-3.39 (2H, m), 3.92-4.03 (2H, m), 4.24 (2H, t, J = 8.7 Hz), 6.96-7.20 (3H, m), 7.30-7.36 (1H, m), 7.38-7.48 (3H, m), 7.56-7.70 (1H, m), 7.91-8.03 (1H, m), 8.36 (1H, d, J = 8.7 Hz), 11.72 (1H, s).

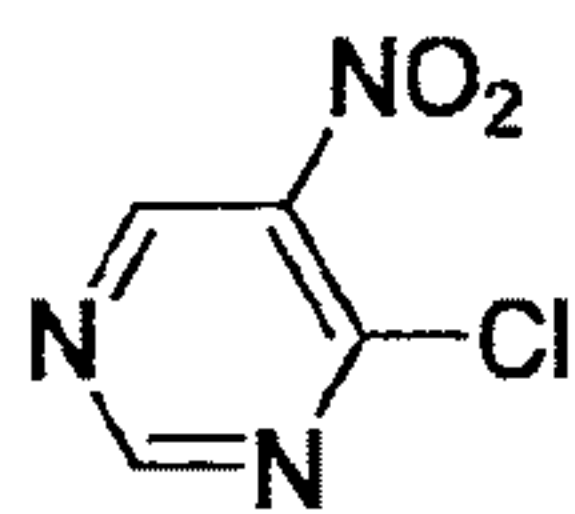
[0294]

Example 14

9-[4-(1,3-benzoxazol-2-ylamino)phenyl]-7,9-dihydro-8H-purin-8-one



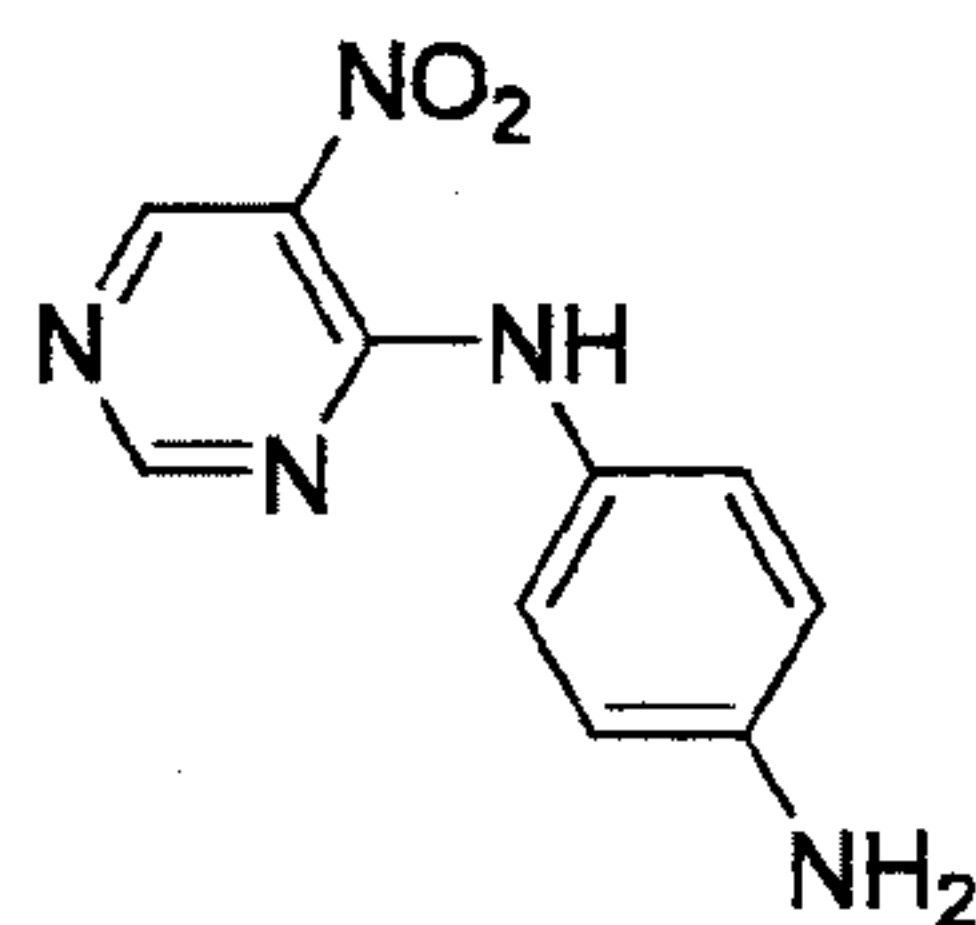
14a) 4-chloro-5-nitropyrimidine



The mixture of 5-nitropyrimidin-4-ol (1.04 g) and
 5 phosphorus oxychloride (5.66 g) in acetonitrile (10 mL) was
 stirred at reflux for 2 h. After this time, the reaction
 mixture was cooled to ambient temperature, diluted with ethyl
 acetate (50 mL), and filtered and the filtrate was
 concentrated under reduced pressure. The residue obtained was
 10 diluted with ethyl acetate (100 mL), washed with saturated
 aqueous sodium bicarbonate (50 mL) then brine (50 mL), and
 filtered and the filtrate was concentrated under reduced
 pressure. The residue obtained was purified by chromatography
 (silica, heptane to 1:3 ethyl acetate/heptane) to afford 4-
 15 chloro-5-nitropyrimidine (383 mg, 33%) as a colorless oil.
¹H NMR (300 MHz, CDCl₃) δ 9.19 (s, 1H), 9.25 (s, 1H).

[0295]

14b) N-(5-nitropyrimidin-4-yl)benzene-1,4-diamine



20 A mixture of 4-chloro-5-nitropyrimidine (380 mg) and
 benzene-1,4-diamine (257 mg) in N-methylpyrrolidone (5 mL) was
 stirred overnight at ambient temperature. After this time, the
 reaction mixture was diluted with water (50 mL) and extracted
 with ethyl acetate (3 × 50 mL). The combined organic layers
 25 were washed with saturated sodium bicarbonate (50 mL) then
 brine (50 mL), dried over sodium sulfate, and filtered and the

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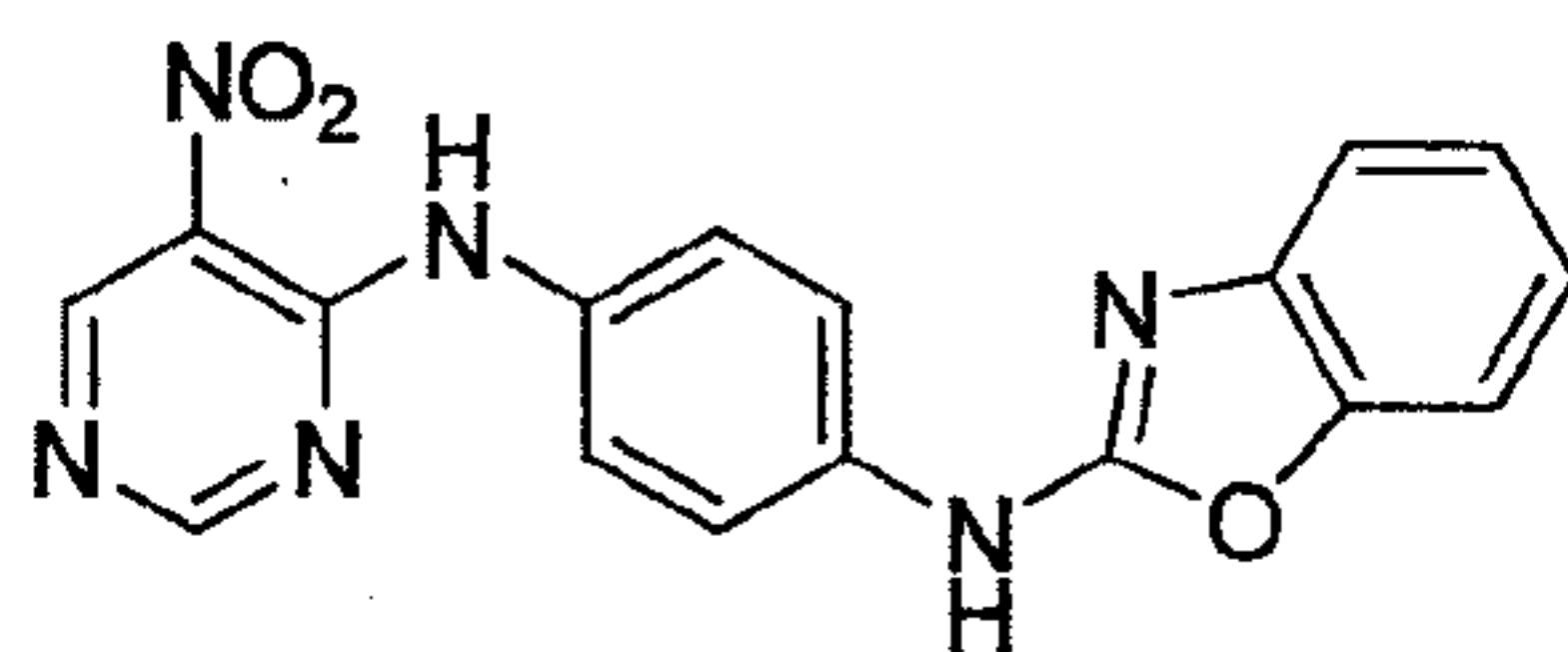
filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 3:97 methanol/methylene chloride) to afford N-(5-nitropyrimidin-4-yl)benzene-1,4-diamine (260 mg) as a brown oil.

MS (ESI⁺): [M+H]⁺ 232.

¹H NMR (300 MHz, CDCl₃) δ 3.79 (br s, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 8.74 (s, 1H), 9.28 (s, 1H), 9.92 (br s, 1H).

[0296]

14c) N-1,3-benzoxazol-2-yl-N'-(5-nitropyrimidin-4-yl)benzene-1,4-diamine

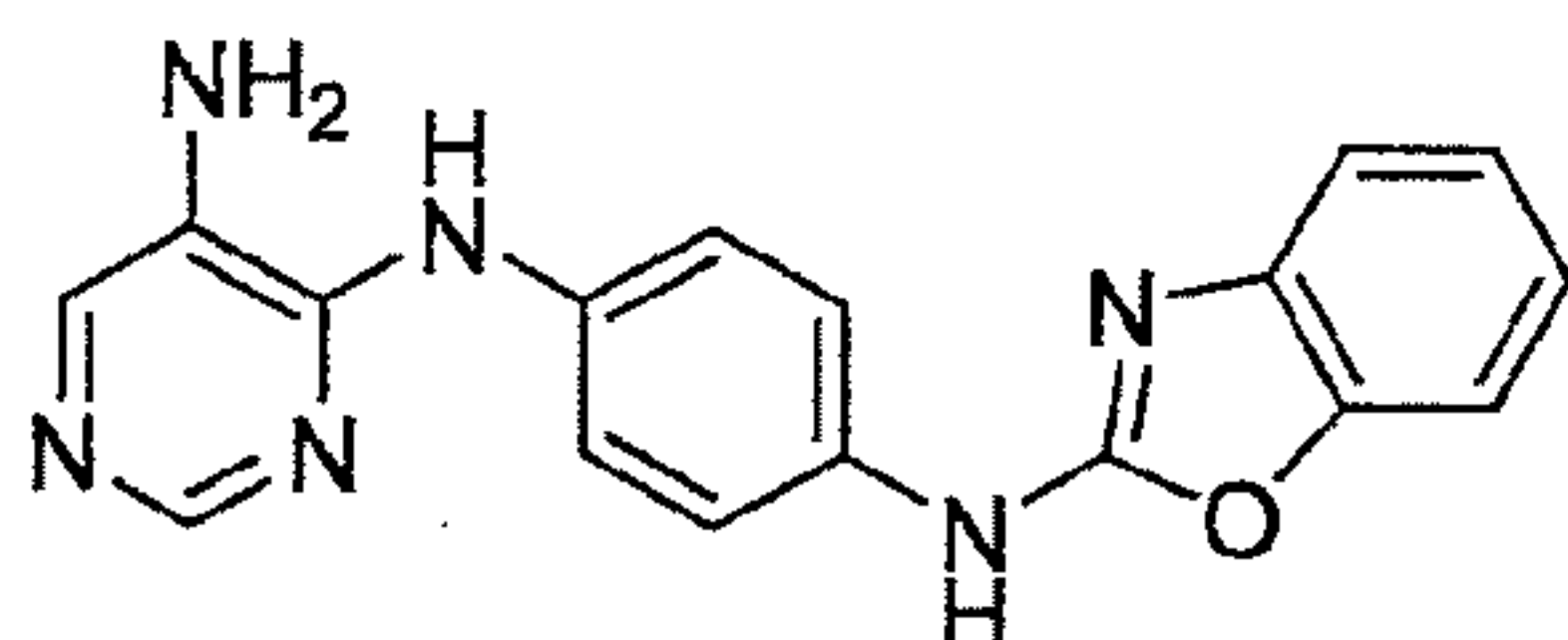


A mixture of N-(5-nitropyrimidin-4-yl)benzene-1,4-diamine (256 mg), 2-chloro-1,3-benzoxazole (110 mg) in N-methylpyrrolidone (3 mL) was stirred at 120°C for 45 min. After this time, the reaction mixture was cooled to ambient temperature, diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL) then brine (50 mL), dried over sodium sulfate, and filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 1:3 ethyl acetate/methylene chloride) to afford N-1,3-benzoxazol-2-yl-N'-(5-nitropyrimidin-4-yl)benzene-1,4-diamine (107 mg) as a red solid.

MS (ESI⁺): [M+H]⁺ 349.

[0297]

14d) N⁴-[4-(1,3-benzoxazol-2-ylamino)phenyl]pyrimidine-4,5-diamine



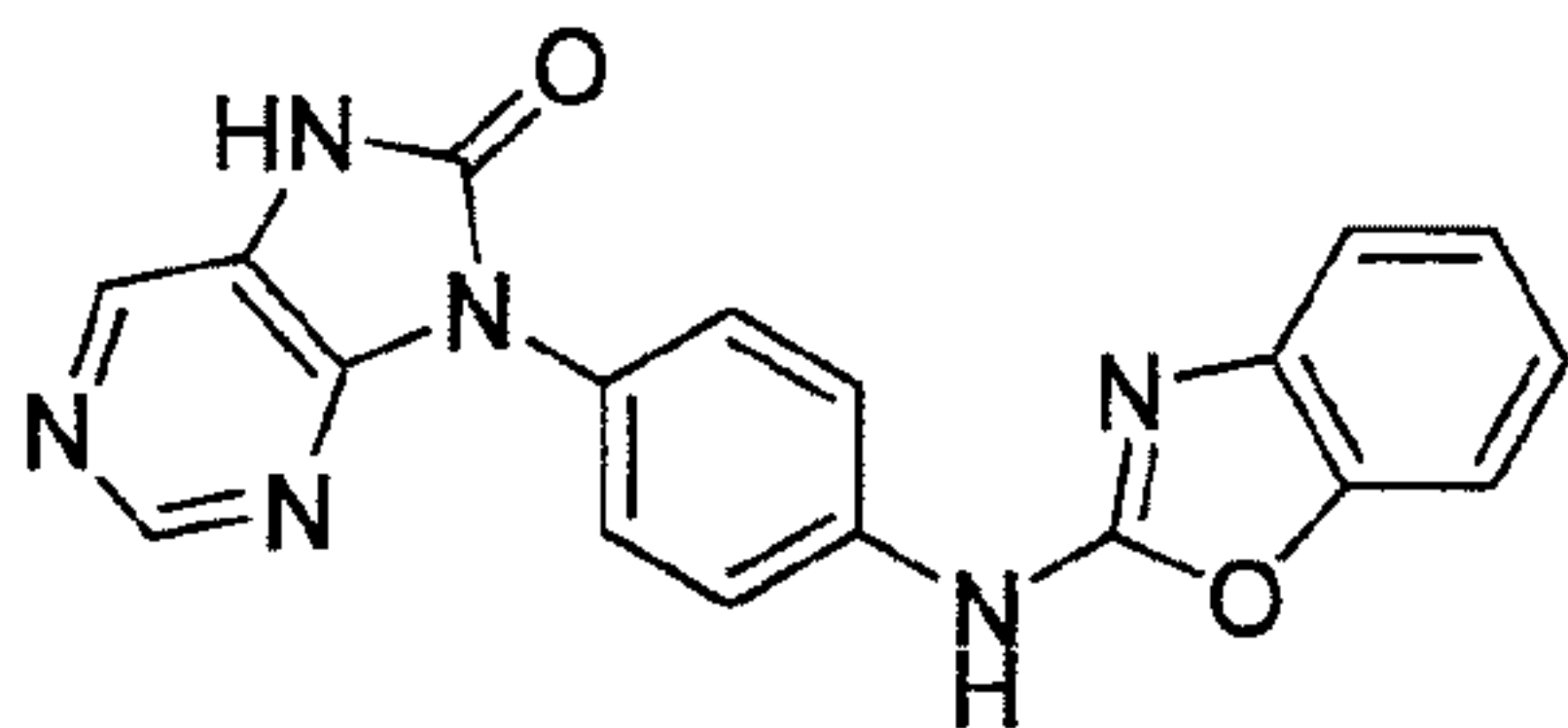
A mixture of N-1,3-benzoxazol-2-yl-N'-(5-nitropyrimidin-4-yl)benzene-1,4-diamine (54 mg) and 5% palladium on carbon (22 mg, 50% water by weight) in methanol (5 mL) was stirred under an atmosphere of hydrogen (balloon) for 1 h. After this time, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford N⁴-[4-(1,3-benzoxazol-2-ylamino)phenyl]pyrimidine-4,5-diamine (49 mg) as a brown solid.

10 MS (ESI⁺): [M+H]⁺ 319.

¹H NMR (300 MHz, DMSO-*d*₆) δ 5.14 (br s, 2H), 7.11 (td, *J* = 7.5, 1.2 Hz, 1H), 7.21 (td, *J* = 7.5, 0.9 Hz, 1H), 7.43 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.70 (s, 4H), 7.76 (s, 1H), 8.02 (s, 1H), 8.28 (br s, 1H), 10.52 (br s, 1H).

15 [0298]

14e) 9-[4-(1,3-benzoxazol-2-ylamino)phenyl]-7,9-dihydro-8H-purin-8-one



A mixture of N⁴-[4-(1,3-benzoxazol-2-ylamino)phenyl]pyrimidine-4,5-diamine (55 mg) and bis(2,5-dioxopyrrolidin-1-yl) carbonate (53 mg) in DMF (5 mL) was stirred overnight at 80°C then at 95°C for 3 h. After this time, the reaction mixture was cooled to ambient temperature, diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL), 5% aqueous lithium chloride (50 mL) then brine (50 mL), dried over sodium sulfate, and filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 1:9

methanol/methylene chloride), solvent exchanged with acetonitrile and freeze dried from acetonitrile/water to afford 9-[4-(1,3-benzoxazol-2-ylamino)phenyl]-7,9-dihydro-8H-purin-8-one (19 mg) as off-white crystals.

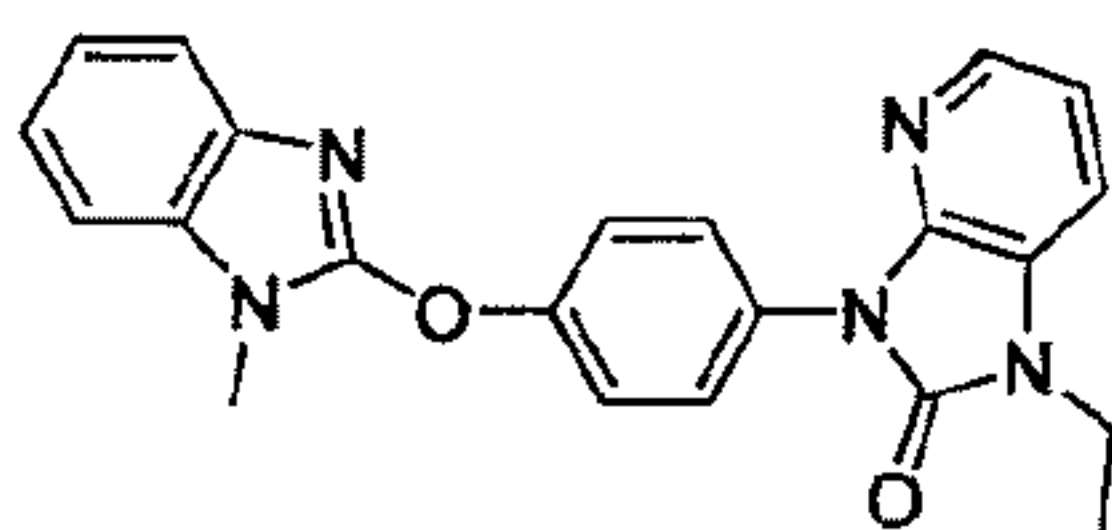
5 MS (ESI⁺): [M+H]⁺ 345.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.16 (td, *J* = 7.5, 1.0 Hz, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 2H), 7.91 (d, *J* = 9.0 Hz, 2H), 8.33 (s, 1H), 8.56 (s, 1H), 10.84 (br s, 1H),
10 11.62 (br s, 1H).

[0299]

Example 19

1-ethyl-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-*b*]pyridin-2-one



15

2-Chloro-1-methyl-1H-benzimidazole (500 mg) was added to a solution of 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-*b*]pyridin-2-one (789 mg) and NaH (132 mg) in DMF (10 mL) at room temperature. The mixture was heated at 150°C
20 for 1h under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-ethyl-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-*b*]pyridin-2-one (950 mg) as white crystals.
25

MS (API⁺): [M+H]⁺ 386.2.

¹H NMR (300 MHz, DMSO-*d*₆) δ 1.17-1.45 (3H, m), 3.76 (3H, s), 3.92-4.06 (2H, m), 7.08-7.27 (3H, m), 7.39-7.53 (2H, m), 7.56-7.64 (2H, m), 7.65-7.73 (1H, m), 7.73-7.84 (2H, m), 7.96-8.08
30 (1H, m).

Anal. Calcd for

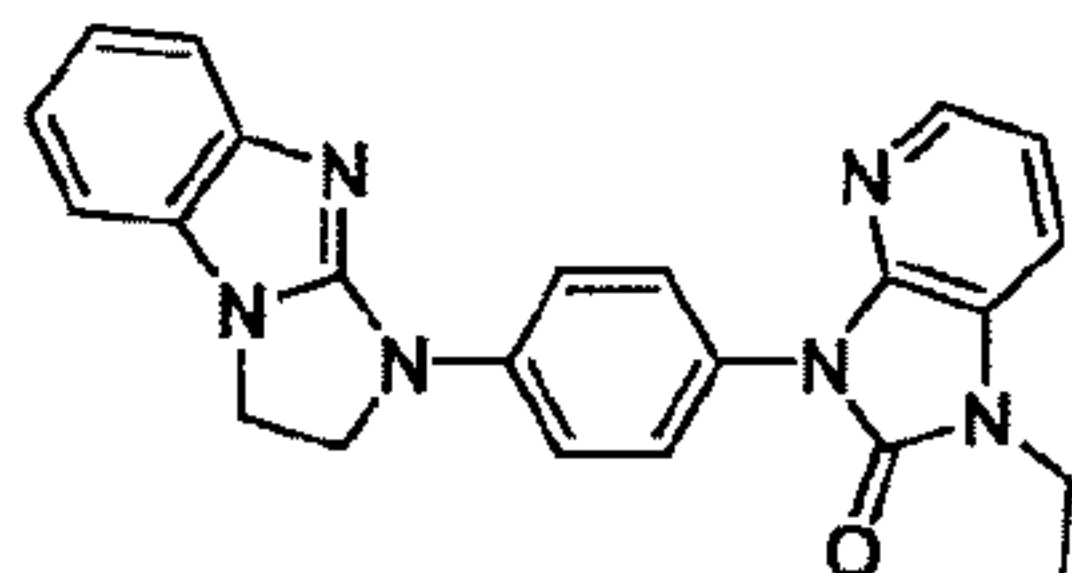
C₂₂H₁₉N₅O₂: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.40; H, 5.00; N, 17.94.

Mp: 184-186°C

[0300]

Example 24

3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



5

To a mixture of 3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (150 mg) and ethyl iodide (0.1 mL) in DMF (4.0 mL) was added sodium hydride (62 mg) (60% in mineral oil) at 10 0°C. The mixture was stirred at 0°C for 1 h, and then H₂O was added. The precipitate was collected and washed with MeOH to give 3-[4-(2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (23 mg) as white powder.

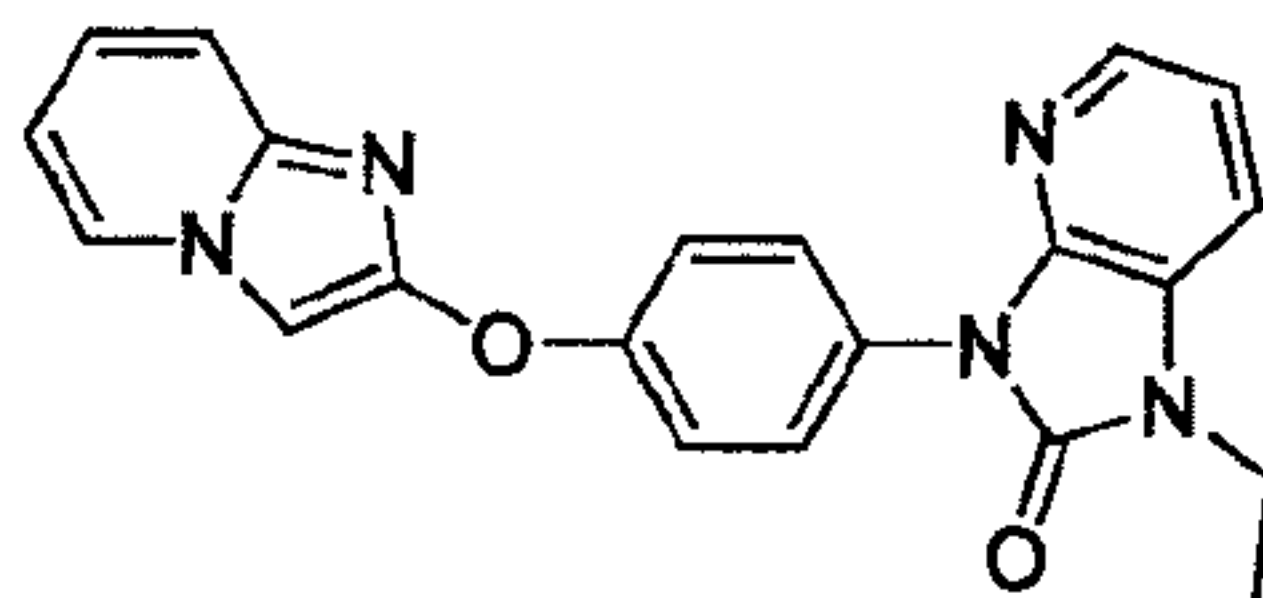
15 MS (API⁺): [M+H]⁺ 397.1.

¹H NMR (300 MHz, DMSO-d₆) δ 1.30 (3H, t, J=7.2Hz), 3.98 (2H, q, J=7.2Hz), 4.34-4.46 (2H, m), 4.55-4.67 (2H, m), 7.03-7.11 (2H, m), 7.13-7.21 (1H, m), 7.27-7.35 (1H, m), 7.40-7.49 (1H, m), 7.62-7.71 (3H, m), 7.90-8.01 (3H, m).

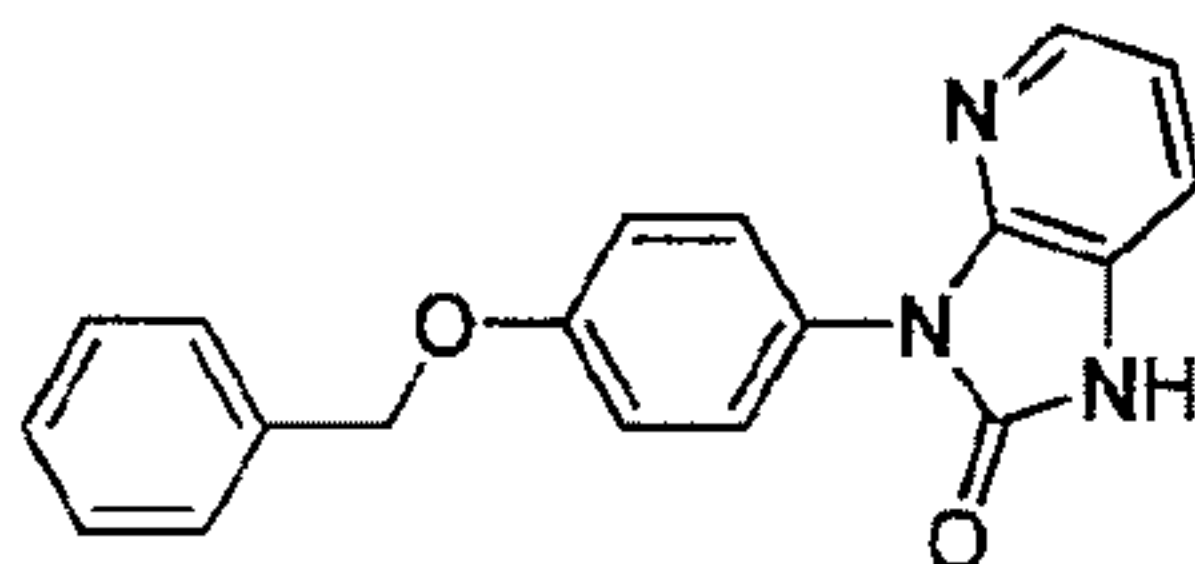
20 [0301]

Example 31

1-ethyl-3-[4-(imidazo[1,2-a]pyridin-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



25 31a) 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



The mixture of tert-butyl 2-chloropyridin-3-ylcarbamate (12.5 g), 4-benzyloxylaniline hydrochloride (19.3 g), 9,9-

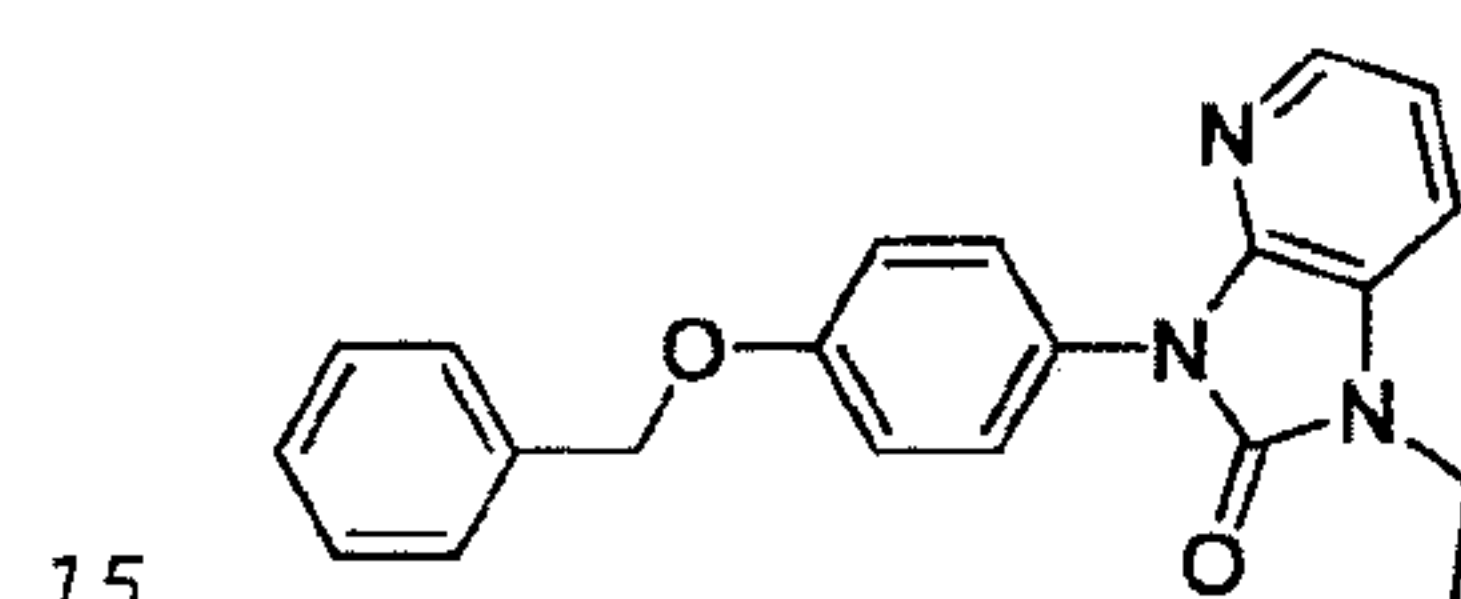
dimethyl-4,5-bis(diphenylphosphino)xanthene (2.53 g), $\text{Pd}_2(\text{dba})_3$ (2.0 g) and sodium tert-butoxide (12.6 g) in toluene (160 mL) - 2-propanol (40.0 mL) was stirred at 100°C under Ar overnight. The reaction mixture was concentrated in vacuo. The residue
 5 was purified by column chromatography (silica gel, eluted with 0% - 100% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (12 g) as a light brown solid.

MS (API+): $[\text{M}+\text{H}]^+$ 318.1.

10 ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 5.18 (2H, s), 7.02-7.22 (3H, m), 7.29-7.59 (8H, m), 7.86-7.94 (1H, m), 11.11-11.64 (1H, m).

[0302]

31b) 3-[4-(benzyloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



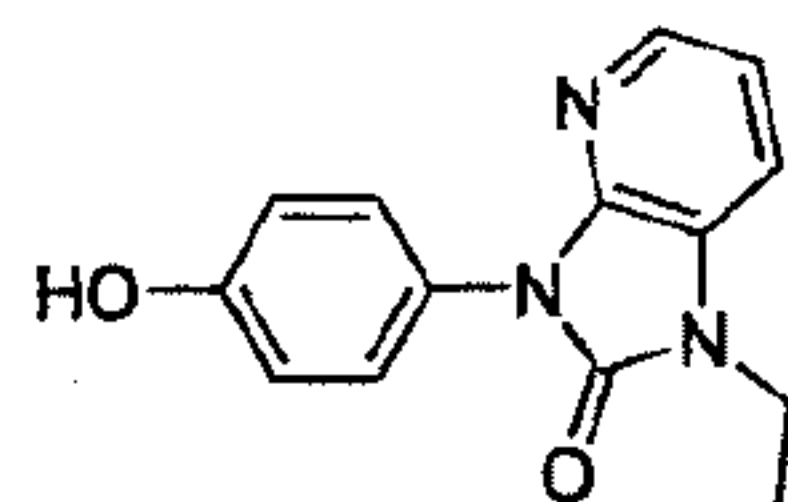
The mixture of 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.50 g), sodium hydride (380 mg) and iodoethane (1.60 mL) in DMF (40 mL) was stirred at 20°C under a dry atmosphere (CaCl_2 tube) for 1h. The mixture was
 20 concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 30% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.70 g) as a colorless solid.

25 MS (API+): $[\text{M}+\text{H}]^+$ 346.4.

^1H NMR (300 MHz, CDCl_3) δ 1.40 (3H, t, $J = 7.2$ Hz), 4.02 (2H, q, $J = 7.2$ Hz), 5.11 (2H, s), 7.01-7.17 (3H, m), 7.22-7.29 (1H, m), 7.29-7.49 (5H, m), 7.53-7.61 (2H, m), 8.00-8.09 (1H, m).

[0303]

30 31c) 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



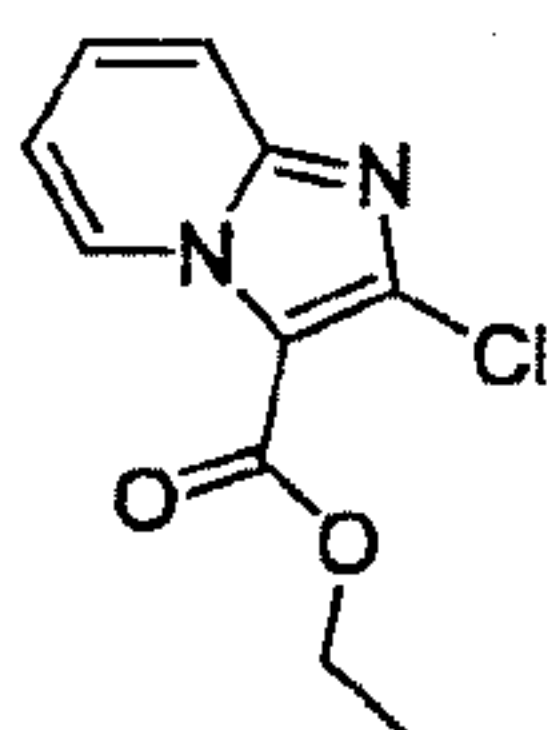
A mixture of 3-[4-(benzyloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.70 g) and 10% palladium-carbon (0.83 g) in EtOH (250 mL) was hydrogenated under
 5 balloon pressure at room temperature for 3h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.42 g) as a white solid.

MS (API+): $[M+H]^+$ 256.1.

10 ^1H NMR (300 MHz, DMSO- d_6) δ 1.27 (3H, t, $J = 7.2$ Hz), 3.95 (2H, q, $J = 7.2$ Hz), 6.84-6.95 (2H, m), 7.08-7.18 (1H, m), 7.32-7.40 (2H, m), 7.57-7.67 (1H, m), 7.89-7.99 (1H, m), 9.67-9.79 (1H, m).

[0304]

15 31d) ethyl 2-chloroimidazo[1,2-a]pyridine-3-carboxylate



n-Butyllithium (1.6M in hexane, 45.1 mL) was added to a solution of 2-chloroimidazo[1,2-a]pyridine (10 g) in THF (120 mL) at -78°C . After stirring for 30 min, ethyl chlorocarbonate
 20 (7.82 g) in THF (10 mL) was added to the mixture at the same temperature and stirred for 1 h and then 10 h at room temperature. The mixture was quenched with water, and extracted with ethyl acetate, and the extract was washed with brine, and dried over magnesium sulfate. The residue was
 25 purified by column chromatography (silica gel, eluted with 10% - 50% EtOAc in hexane) to give ethyl 2-chloroimidazo[1,2-a]pyridine-3-carboxylate (13.20 g) as an off-white solid.

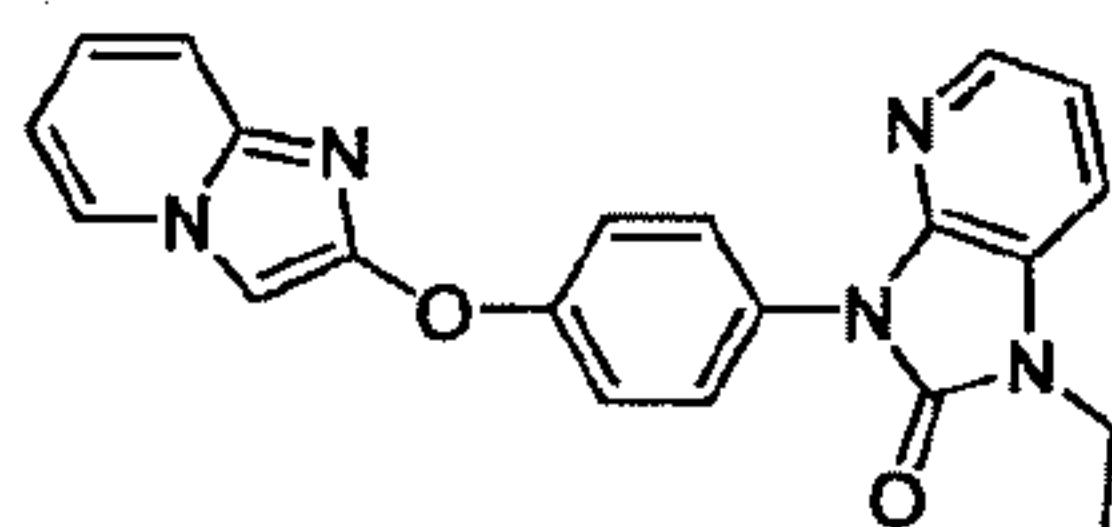
MS (API+): $[M+H]^+$ 225.0.

^1H NMR (300 MHz, DMSO- d_6) δ 1.37 (3 H, m), 4.40 (2 H, m), 7.31
 30 (1 H, s), 7.66 (1 H, s), 7.72 - 7.86 (1 H, m), 9.17 - 9.32 (1

H, m).

[0305]

31e) 1-ethyl-3-[4-(imidazo[1,2-a]pyridin-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



5

The mixture of ethyl 2-chloroimidazo[1,2-a]pyridine-3-carboxylate (220 mg), NaH (70 mg) and 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (255 mg) in DMF (2 mL) was stirred at 100°C under a dry atmosphere (CaCl₂ tube) for 1h. The mixture was diluted with MeOH and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 30% EtOAc in hexane) to give 1-ethyl-3-[4-(imidazo[1,2-a]pyridin-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (40 mg) as white crystals.

MS (API+): [M+H]⁺ 372.4.

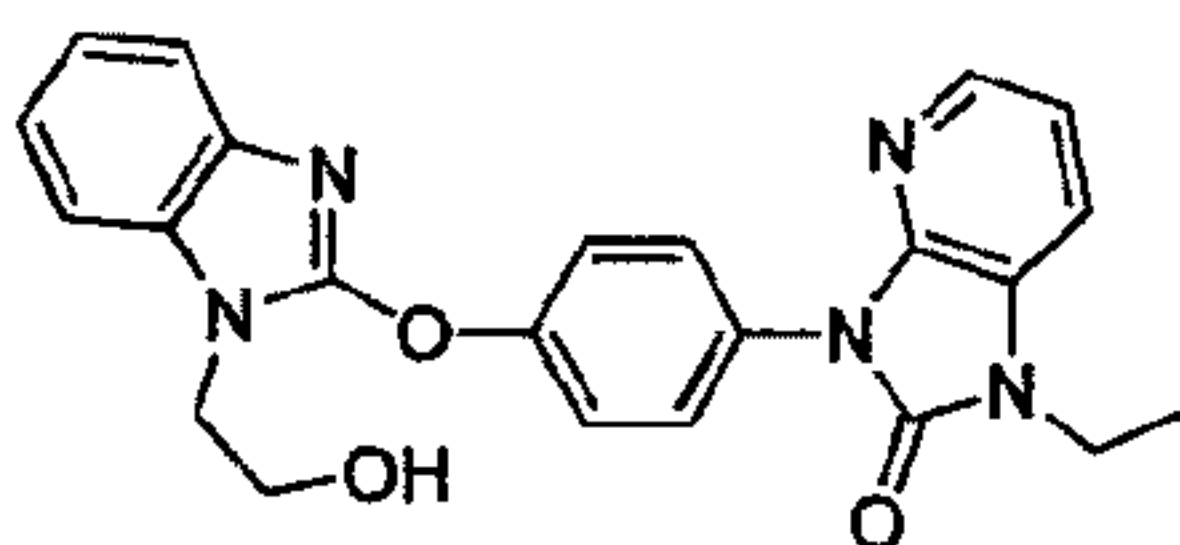
¹H NMR (300 MHz, DMSO-d₆) δ 1.23-1.36 (3H, m), 3.92-4.06 (2H, m), 6.90-7.00 (1H, m), 7.11-7.23 (1H, m), 7.23-7.41 (3H, m), 7.44-7.54 (1H, m), 7.60-7.75 (4H, m), 7.94-8.10 (1H, m), 8.47-8.60 (1H, m).

20

[0306]

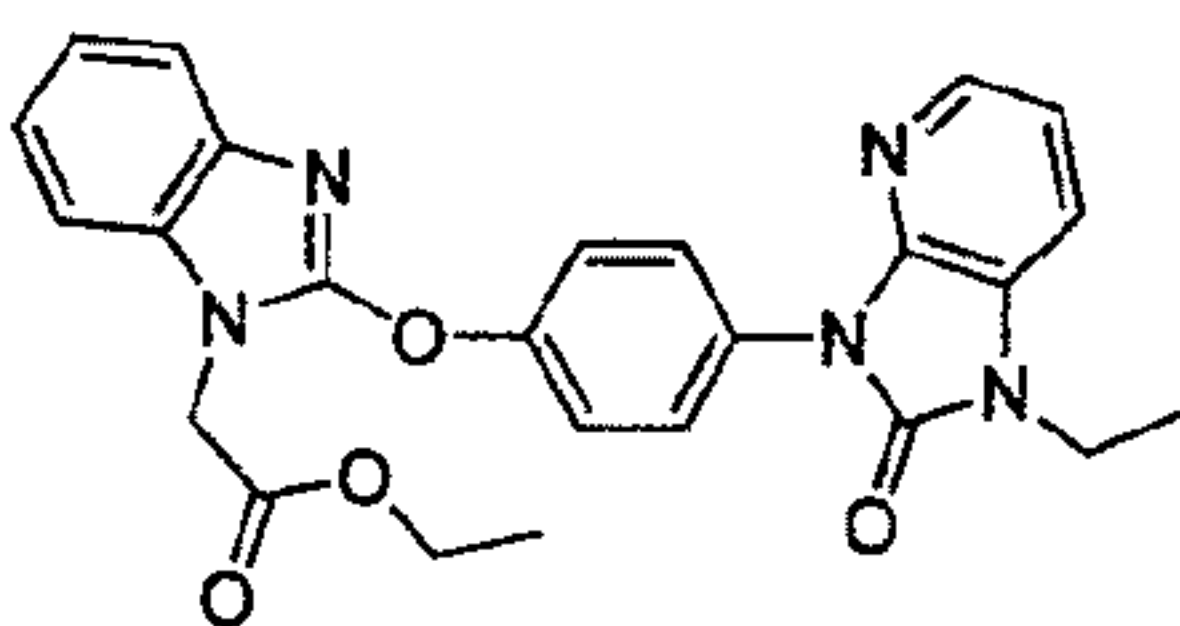
Example 39

1-ethyl-3-(4-{[1-(2-hydroxyethyl)-1H-benzimidazol-2-yl]oxy}phenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



25

39a) ethyl {2-[4-(1-ethyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenoxy]-1H-benzimidazol-1-yl}acetate



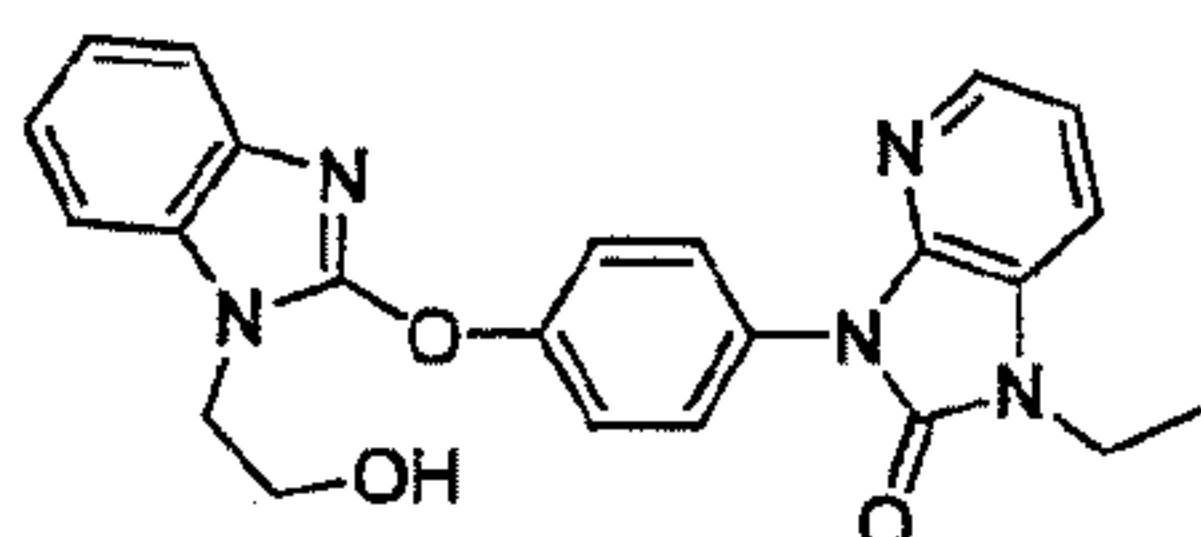
Ethyl bromoacetate (0.240 mL) was added to a solution of

3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (400 mg) and sodium hydride (86 mg) in DMF (2 mL) at room temperature. The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube) for 2h.
 5 The reaction mixture was diluted with MeOH (5 mL), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluted with 0% - 50% EtOAc in hexane) to give ethyl {2-[4-(1-ethyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenoxy]-1H-benzimidazol-1-yl}acetate (480 mg) as off-white crystals.
 10 MS (API+): [M+H]⁺ 458.2.

¹H NMR (300 MHz, DMSO-d₆) δ 1.24 (3H, t, J = 7.0 Hz), 1.30 (3H, t, J = 7.2 Hz), 3.99 (2H, q, J = 7.2 Hz), 4.22 (2H, q, J = 7.0 Hz), 5.18-5.28 (2H, m), 7.11-7.25 (3H, m), 7.42-7.60 (4H, m),
 15 7.65-7.72 (1H, m), 7.74-7.83 (2H, m), 7.96-8.05 (1H, m).

[0307]

39b) 1-ethyl-3-(4-{[1-(2-hydroxyethyl)-1H-benzimidazol-2-yl]oxy}phenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



20 Lithium aluminum hydride (33.2 mg) was added to a solution of ethyl {2-[4-(1-ethyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenoxy]-1H-benzimidazol-1-yl}acetate (200 mg) in THF (4 mL) at 0°C. The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube)
 25 for 30 min. The mixture was quenched with EtOAc and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 10% - 50% EtOAc in hexane) to give 1-ethyl-3-(4-{[1-(2-hydroxyethyl)-1H-benzimidazol-2-yl]oxy}phenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (100 mg) as colorless crystals.
 30

MS (API+): [M+H]⁺ 416.5.

¹H NMR (300 MHz, DMSO-d₆) δ 1.31 (3H, t, J = 7.0 Hz), 3.75-3.88 (2H, m), 3.99 (2H, q, J = 7.0 Hz), 4.23-4.37 (2H, m), 4.98-

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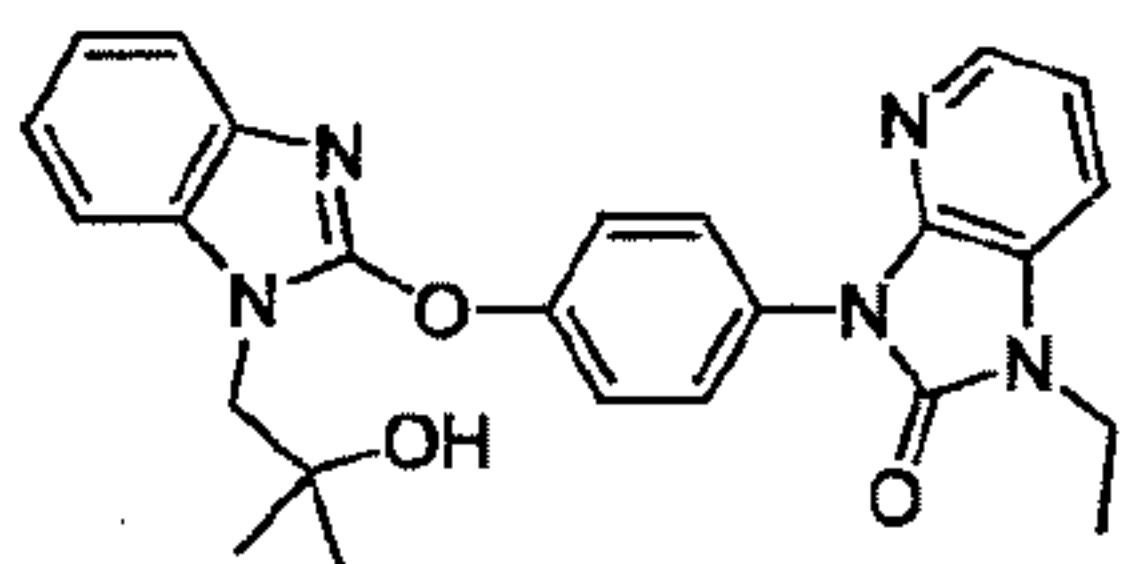
PCT/US2011/041443

5.07 (1H, m), 7.09-7.28 (3H, m), 7.39-7.65 (4H, m), 7.65-7.87 (3H, m), 7.95-8.08 (1H, m).

[0308]

Example 40

5 1-ethyl-3-(4-{[1-(2-hydroxy-2-methylpropyl)-1H-benzimidazol-2-yl]oxy}phenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



Bromomethylmagnesium (3M in ether, 1.924 mL) was added to a solution of ethyl {2-[4-(1-ethyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)phenoxy]-1H-benzimidazol-1-yl}acetate (220 mg) in THF (40 mL) at 0°C. The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube) for 3h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-ethyl-3-(4-{[1-(2-hydroxy-2-methylpropyl)-1H-benzimidazol-2-yl]oxy}phenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (130 mg) as white crystals.

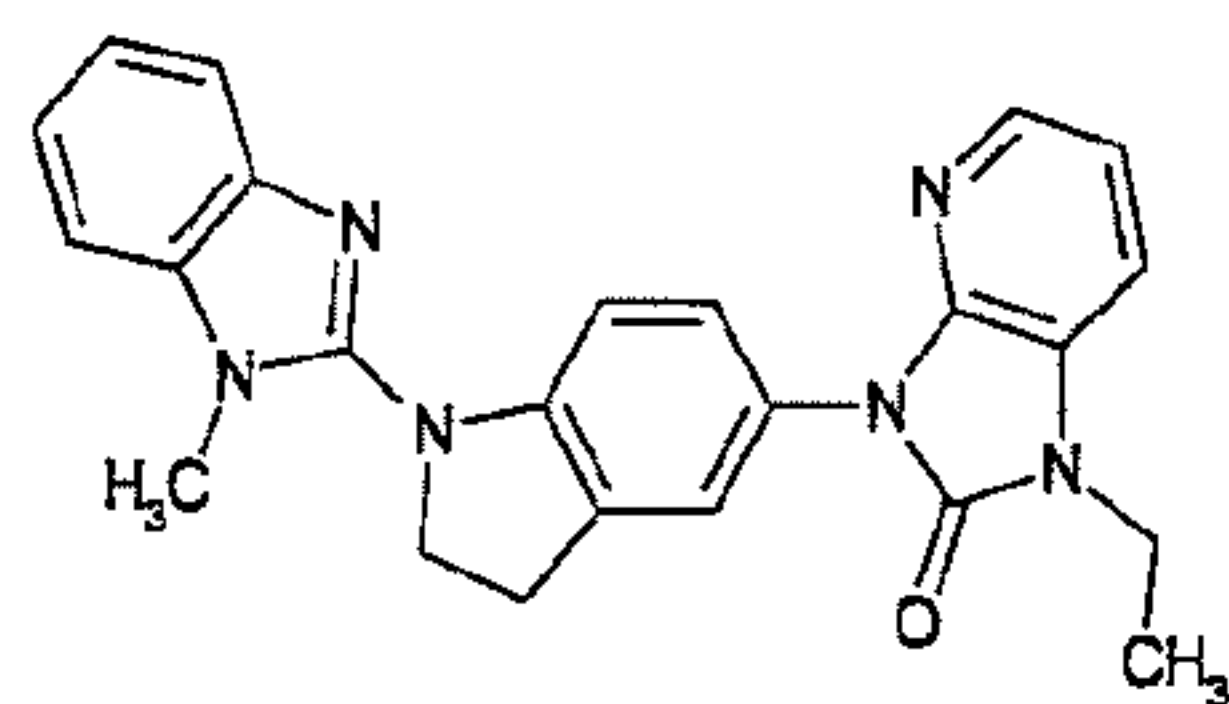
MS (API+): [M+H]⁺ 444.4.

20 ¹H NMR (300 MHz, DMSO-d₆) δ 1.24 (6H, s), 1.31 (3H, t, J = 7.2 Hz), 3.99 (2H, q, J = 7.2 Hz), 4.11 (2H, s), 4.79 (1H, s), 7.07-7.26 (3H, m), 7.37-7.46 (1H, m), 7.50-7.64 (3H, m), 7.65-7.81 (3H, m), 7.96-8.05 (1H, m).

[0309]

25 Example 48

1-ethyl-3-[1-(1-methyl-1H-benzimidazol-2-yl)-2,3-dihydro-1H-indol-5-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-(2,3-dihydro-1H-indol-5-yl)-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (100 mg) and 2-chloro-

1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazole (101 mg) in NMP (2 mL) was stirred at 120°C for 10h, treated with saturated NaHCO₃ solution and extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in DMF (2 mL), and then iodomethane (0.022 mL) and Cs₂CO₃ (0.176 g) were added. The mixture was stirred at room temperature for 3h, treated with water and extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was suspended in CH₃CN and the precipitate was filtered off. The residue was purified by prep. HPLC, and then chromatographed on silica gel eluting with AcOEt/Hexane. Crystallization from AcOEt/ Hexane gave the title compound (12 mg).

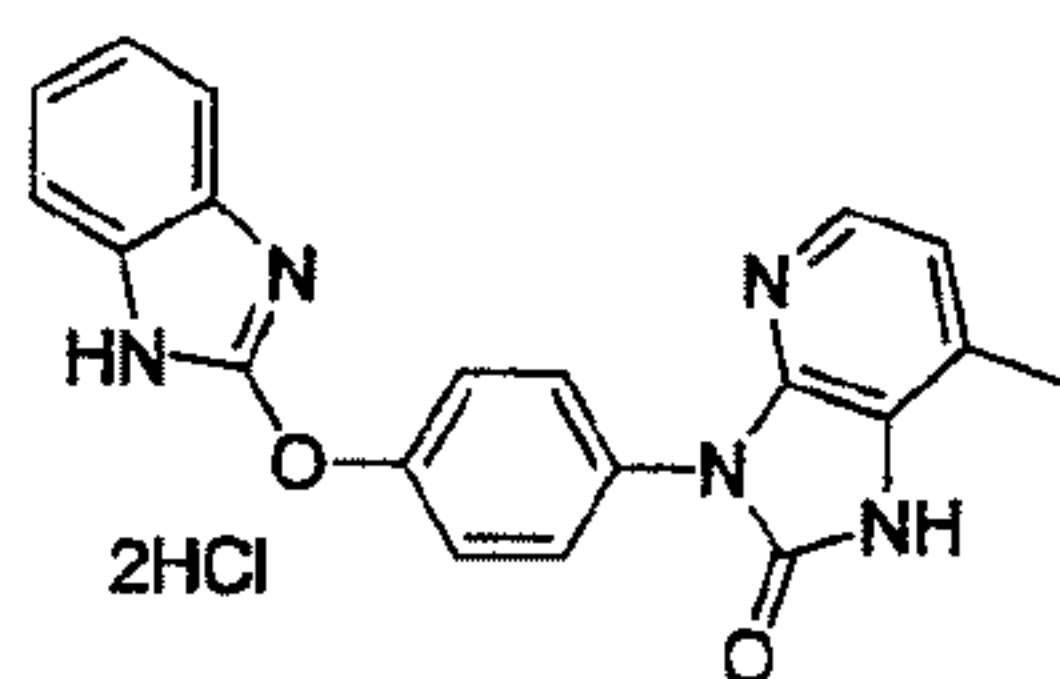
MS (API+): [M+H]⁺ 411.4.

¹H NMR (300 MHz, DMSO-d₆) δ 1.29 (3H, t, J = 7.0 Hz), 3.26 (2H, t, J = 8.1 Hz), 3.77 (3H, s), 3.96 (2H, q, J = 6.8 Hz), 4.20 (2H, t, J = 8.5 Hz), 7.06-7.25 (4H, m), 7.27-7.36 (1H, m), 7.43-7.54 (3H, m), 7.59-7.71 (1H, m), 7.87-8.05 (1H, m).

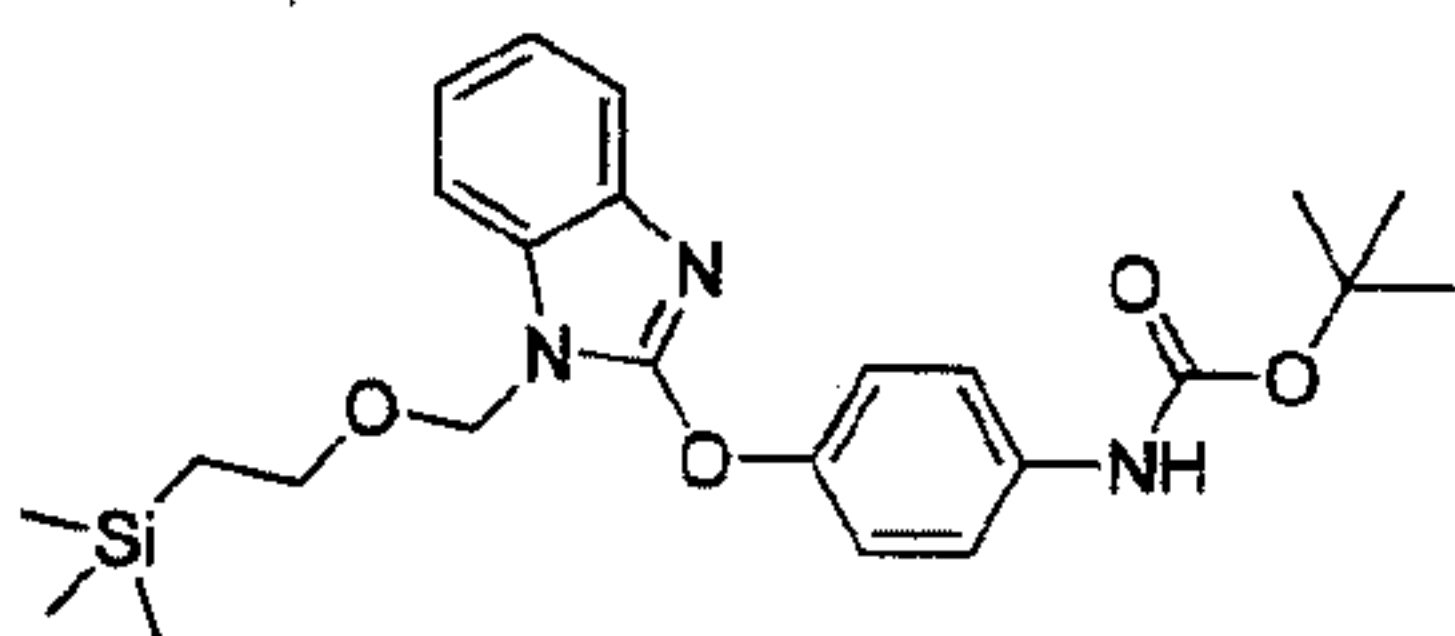
[0310]

Example 62

3-[4-(1H-benzimidazol-2-yloxy)phenyl]-7-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride



62a) tert-butyl {4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}carbamate



A mixture of 2-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazole (8.7 g), tert-butyl 4-hydroxyphenylcarbamate (6.4 g) and cesium carbonate (20 g) in DMF (60 mL) was stirred at 60°C for 24 h. After

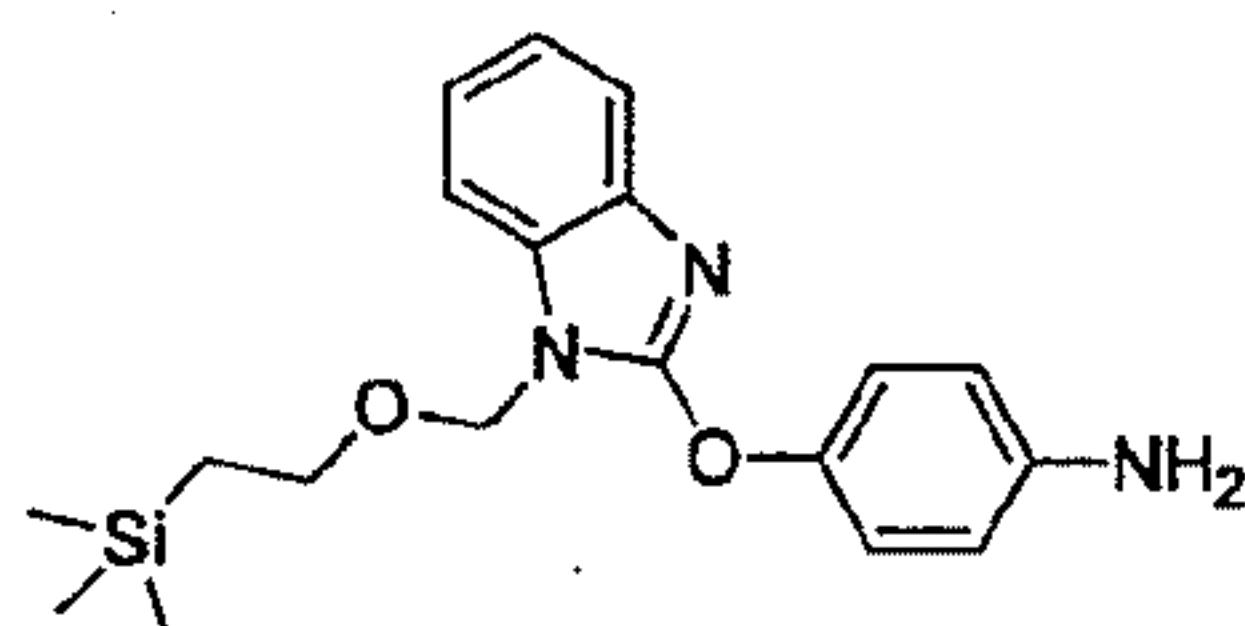
cooling to room temperature, to the mixture was added SiO₂, the mixture was evaporated, and then the residue was purified by column chromatography (silica gel, eluted with 0% - 50% EtOAc in hexane) to give tert-butyl {4-[(1-{[2-

5 (trimethylsilyl)ethoxy)methyl]-1H-benzimidazol-2-yl)oxy]phenyl}carbamate (14 g) as brown oil.

MS (API+): [M+H]⁺ 456.2.

[0311]

62b) 4-[(1-{[2-(trimethylsilyl)ethoxy)methyl]-1H-benzimidazol-2-yl)oxy]aniline

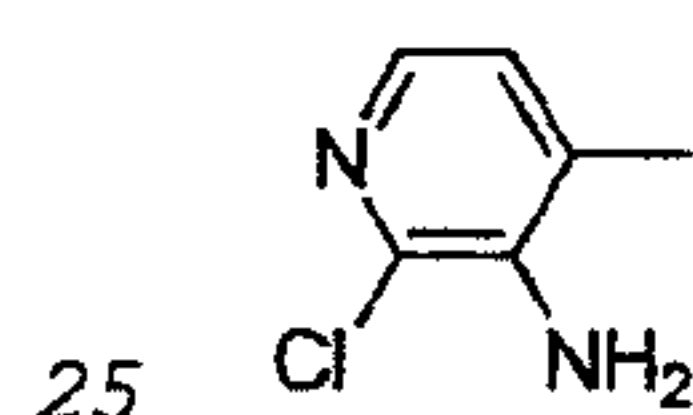


A mixture of tert-butyl {4-[(1-{[2-(trimethylsilyl)ethoxy)methyl]-1H-benzimidazol-2-yl)oxy]phenyl}carbamate (14 g) and 4N HCl/AcOEt (30 mL) in
 15 EtOAc (30 mL) was stirred at room temperature overnight. The mixture was neutralized with 1N NaOHaq., and extracted with AcOEt. The organic layer was dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 100% EtOAc in hexane) to give 4-
 20 [(1-{[2-(trimethylsilyl)ethoxy)methyl]-1H-benzimidazol-2-yl)oxy]aniline (5.4 g) as an orange solid.

MS (API+): [M+H]⁺ 356.2.

[0312]

62c) 2-chloro-4-methylpyridin-3-amine

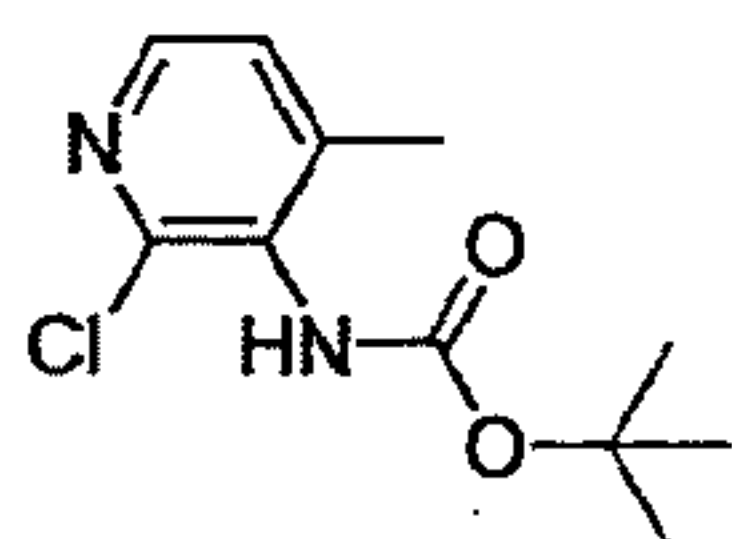


A mixture of 4-methylpyridin-3-amine (0.62 g), 12N hydrogen chloride (3.8 mL) and 30% hydrogen peroxide (0.75 mL) was stirred at 0°C to room temperature for 1 h. The mixture was neutralized with K₂CO₃, and the mixture was extracted with
 30 AcOEt. The organic layer was dried over MgSO₄, and concentrated in vacuo to give 2-chloro-4-methylpyridin-3-amine (0.75 g) as an orange solid.

MS (API+): $[M+H]^+$ 143.1.

[0313]

62d) tert-butyl (2-chloro-4-methylpyridin-3-yl)carbamate

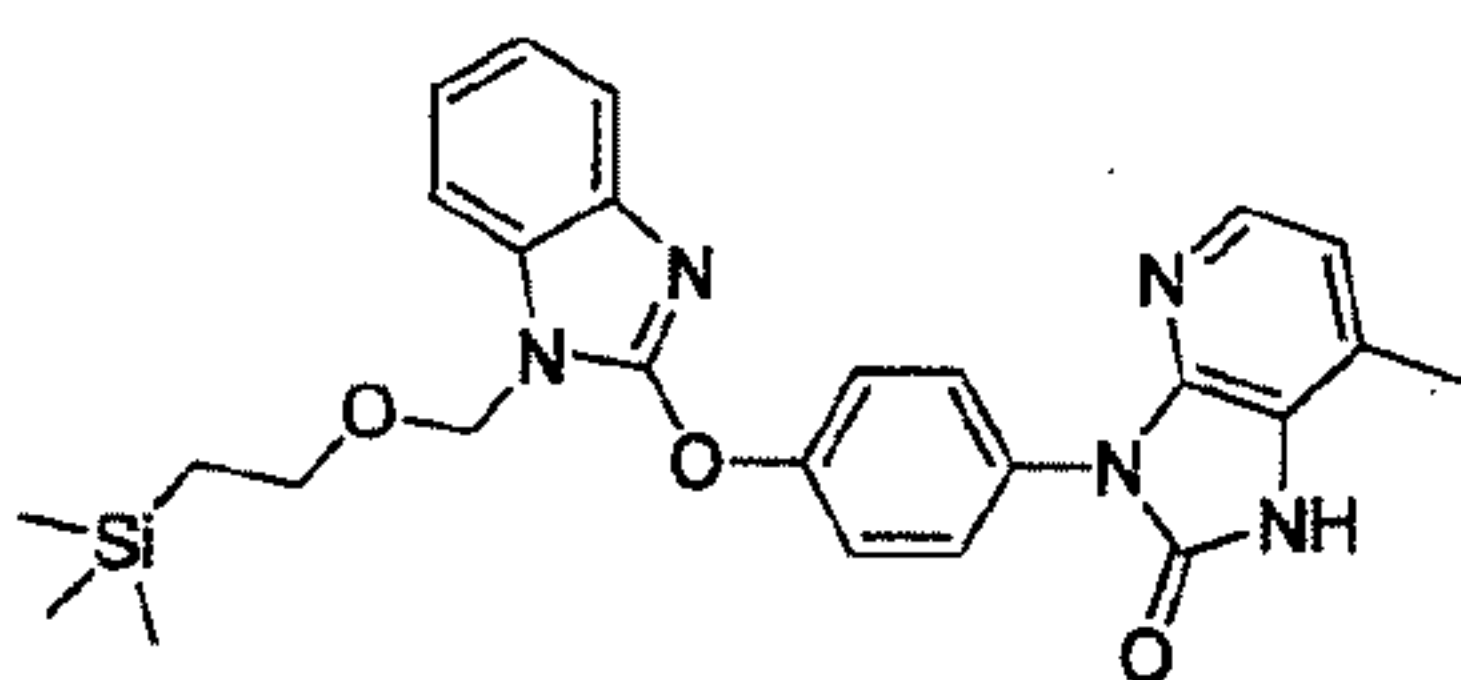


5 To a mixture of 2-chloro-4-methylpyridin-3-amine (0.75 g) and di-tert-butyl dicarbonate (1.3 mL) in THF (10 mL) was added dropwise hexamethyldisilazane sodium salt (2M in THF, 6.1 mL) at 0°C. The mixture was stirred at 0°C to room temperature overnight. The mixture was neutralized with 1N HCl aq., and the mixture was extracted with AcOEt. The organic layer was dried over MgSO₄, and concentrated in vacuo to give tert-butyl (2-chloro-4-methylpyridin-3-yl)carbamate (1.2 g) as an orange solid.

¹H NMR (300 MHz, DMSO-d₆) δ 1.34 (9H, brs), 2.15 (3H, s), 7.23 (1H, d, J = 4.9 Hz), 8.05 (1H, d, J = 4.9 Hz), 8.79 (1H, brs).

[0314]

62e) 7-methyl-3-{4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



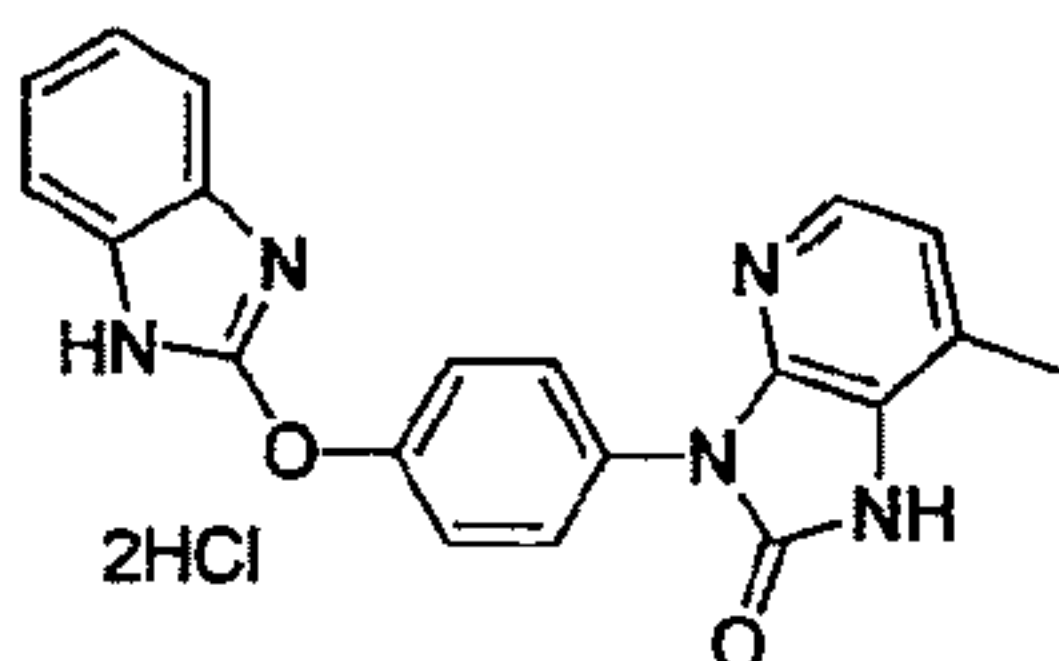
20 The mixture of sodium 2-methylpropan-2-olate (0.16 g), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (0.054 g), tert-butyl (2-chloro-4-methylpyridin-3-yl)carbamate (0.28 g), 4-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]aniline (0.41 g) and Pd₂(dba)₃ (0.043 g) in toluene (40 mL) and 2-propanol (10 mL) was stirred at 100°C under N₂ overnight. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 100% EtOAc in hexane) to give 7-methyl-3-{4-[(1-{[2-

(trimethylsilyl)ethoxy)methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (0.21 g) as white crystals.

MS (API+): $[M+H]^+$ 488.3.

5 [0315]

62f) 3-[4-(1H-benzimidazol-2-yloxy)phenyl]-7-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride



A mixture of 7-methyl-3-{4-[(1-{[2-

10 (trimethylsilyl)ethoxy)methyl}-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (0.053 g) and 2N HCl in EtOH (5.0 mL) was stirred at 60°C for 10 h. After cooling to room temperature, the solvent was removed. The residue was recrystallized from EtOH-AcOEt to
15 give 3-[4-(1H-benzimidazol-2-yloxy)phenyl]-7-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride (0.030 g).

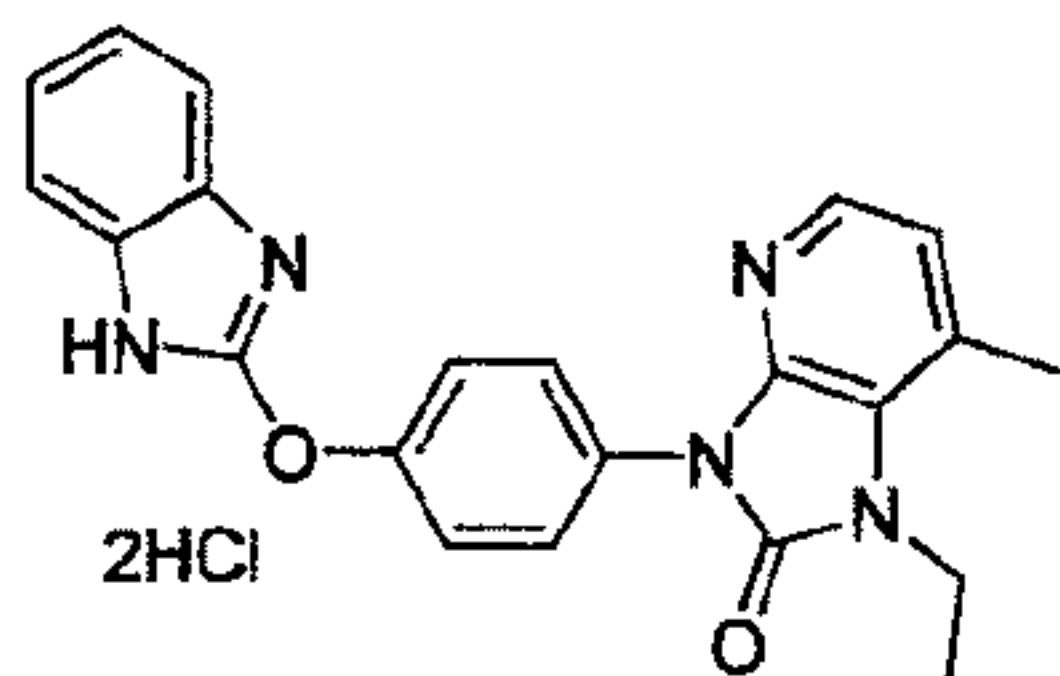
MS (API+): $[M+H]^+$ 358.1.

^1H NMR (300 MHz, DMSO- d_6) δ 2.37 (3H, s), 4.57 (3H, brs), 6.97
20 (1H, d, J = 5.3 Hz), 7.15 (2H, dd, J = 6.1, 3.4 Hz), 7.40 (2H, dd, J = 5.9, 3.2 Hz), 7.52-7.62 (2H, m), 7.71-7.80 (2H, m), 7.85 (1H, d, J = 5.3 Hz), 11.54 (1H, s).

[0316]

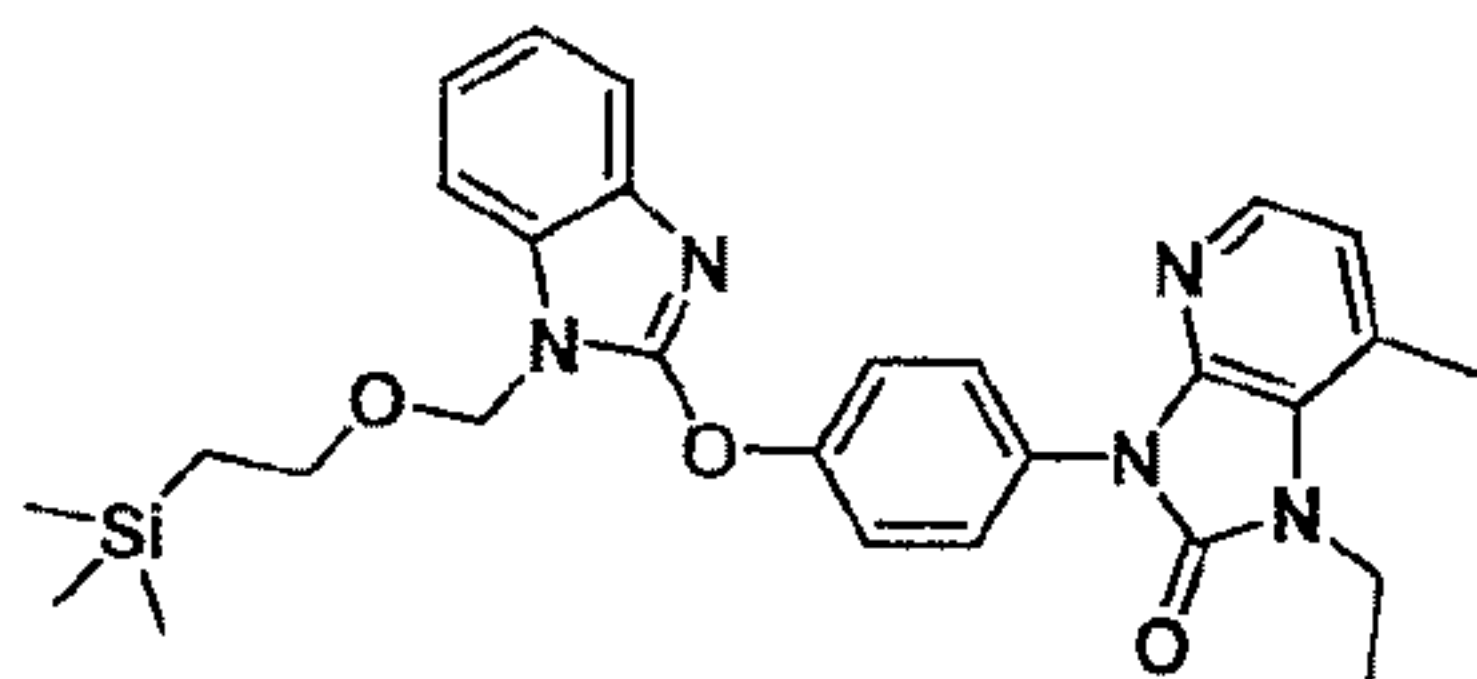
Example 64

25 3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1-ethyl-7-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride



64a) 1-ethyl-7-methyl-3-{4-[(1-{[2-(trimethylsilyl)ethoxy)methyl}-1H-benzimidazol-2-

yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

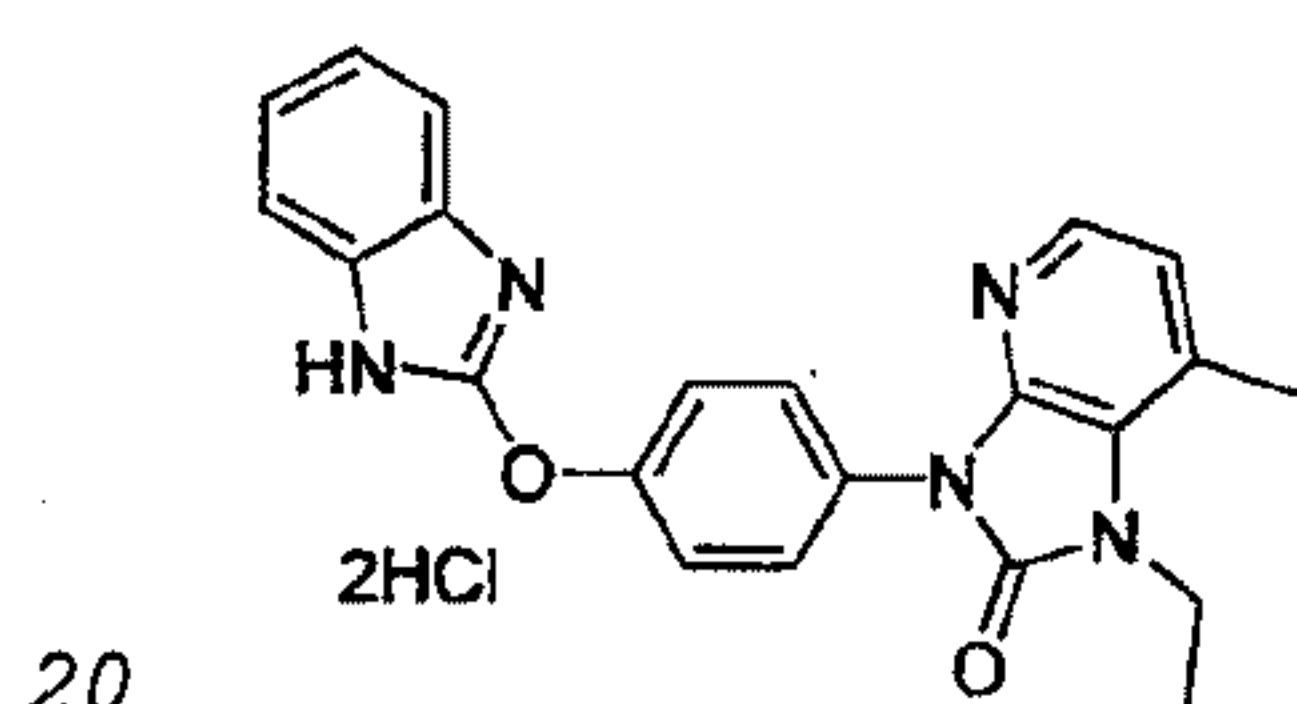


A mixture of 7-methyl-3-{4-[(1-{[2-(
(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-
5 yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
(0.15 g), iodoethane (0.027 mL) and sodium hydride (0.015 g)
(60% in oil) in DMF (4.0 mL) was stirred at room temperature
for 4 h. To the mixture was added H₂O, and the mixture was
extracted with AcOEt. The organic layer was dried (MgSO₄) and
10 concentrated in vacuo. The residue was purified by column
chromatography (silica gel, eluted with 0% - 50% EtOAc in
hexane) to give 1-ethyl-7-methyl-3-{4-[(1-{[2-
(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-
yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (90
15 mg) as pale yellow crystals.

MS (API⁺): [M+H]⁺ 516.3.

[0317]

64b) 3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1-ethyl-7-methyl-
1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride



20

A mixture of 1-ethyl-7-methyl-3-{4-[(1-{[2-
(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-
yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
(0.090 g) and 2N HCl in EtOH (5.0 mL) was stirred at 60°C for
25 10 h. After cooling to room temperature, the solvent was
removed. The residue was recrystallized from EtOH-AcOEt to
give 3-[4-(1H-benzimidazol-2-yloxy)phenyl]-1-ethyl-7-methyl-
1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride
(0.040 g).

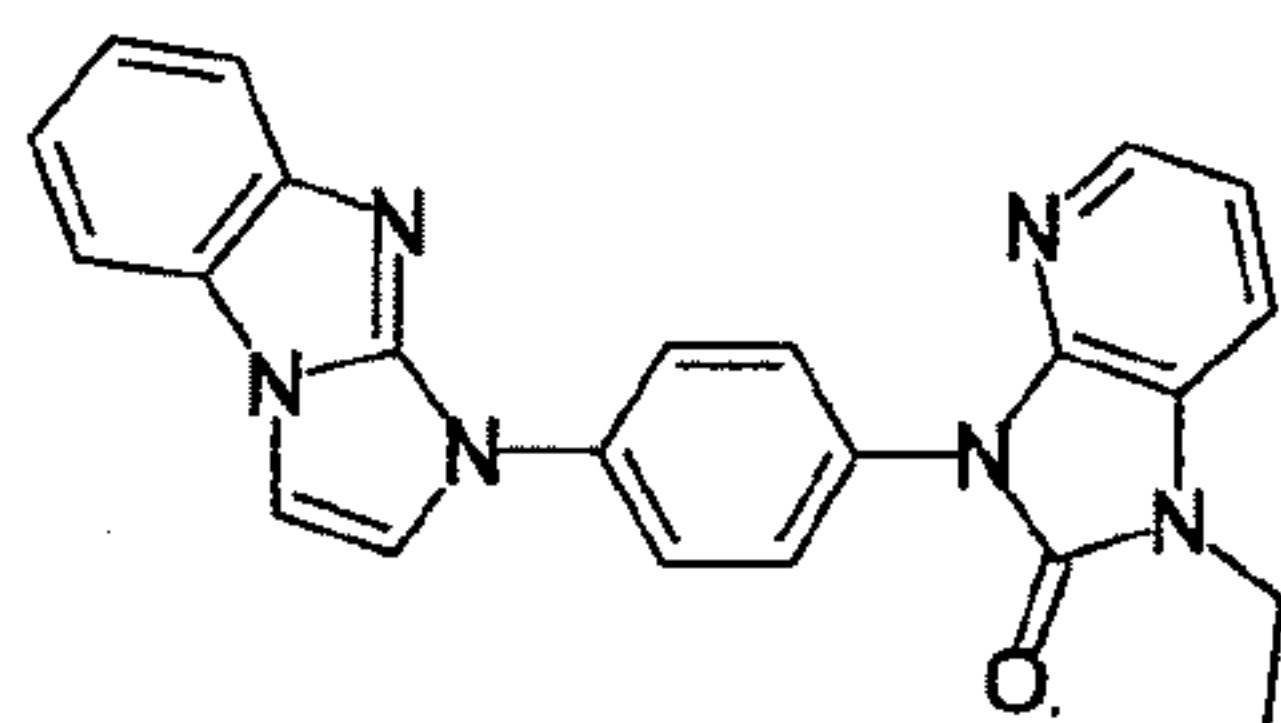
MS (API+): $[M+H]^+$ 386.2.

^1H NMR (300 MHz, DMSO- d_6) δ 1.32 (3H, t, J = 7.2 Hz), 2.61 (3H, s), 4.12 (2H, q, J = 7.2 Hz), 7.01 (1H, d, J = 5.3 Hz), 7.20 (2H, dd, J = 5.9, 3.2 Hz), 7.40-7.49 (2H, m), 7.58-7.66 (2H, m), 7.72-7.81 (2H, m), 7.87 (1H, d, J = 4.9 Hz), 8.12 (3H, brs).

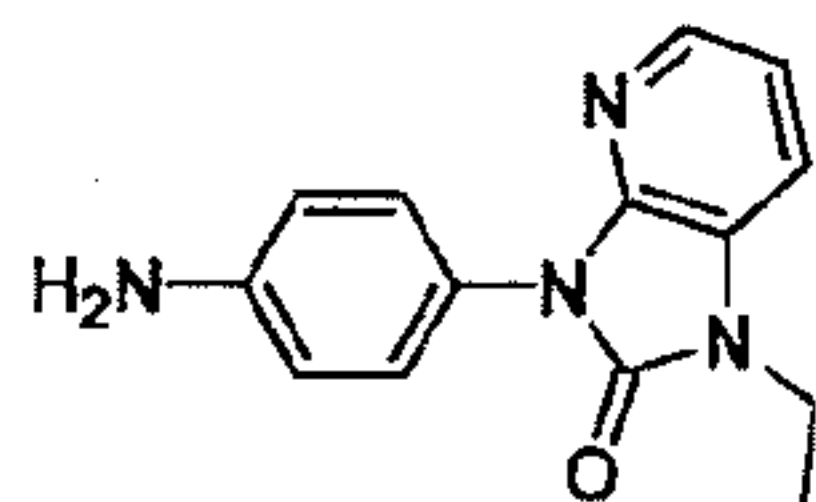
[0318]

Example 65

1-Ethyl-3-[4-(1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



65a) 3-(4-aminophenyl)-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

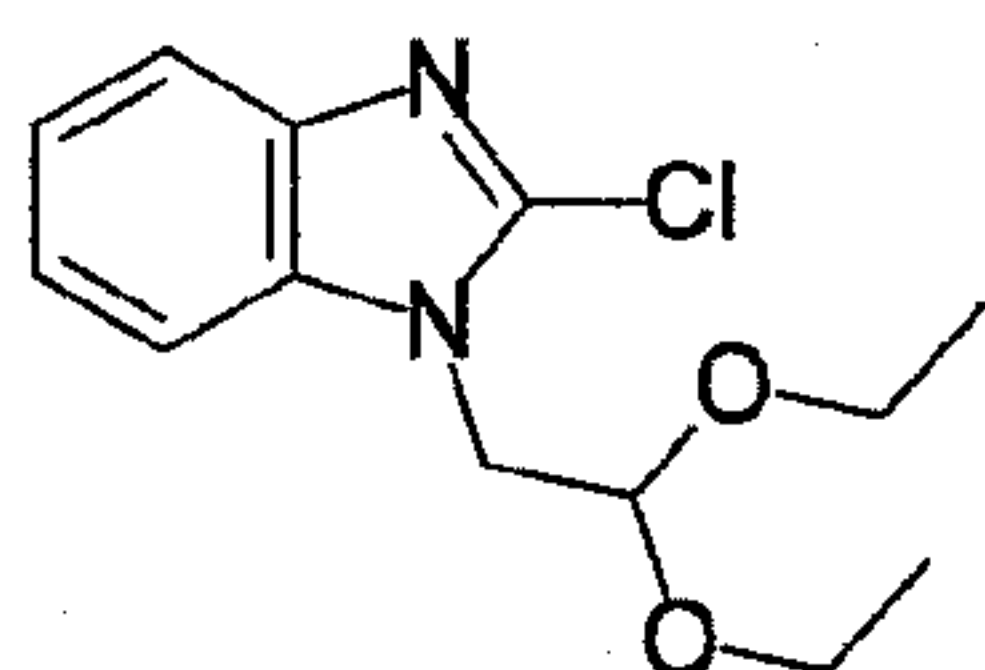


The mixture of tert-butyl 2-chloropyridin-3-ylcarbamate (10.0 g), 4-nitroaniline (8.0 g), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (2.53 g), $\text{Pd}_2(\text{dba})_3$ (2 g) and sodium tert-butoxide (12.5 g) in toluene (160 mL) - 2-propanol (40.0 mL) was stirred at 100°C under Ar overnight. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 100% EtOAc in hexane) to give 3-(4-nitrophenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (4.0 g) as a light brown solid. A mixture of 3-(4-nitrophenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (3.50 g), sodium hydride (0.400 g) and iodoethane (2.0 mL) in DMF (40 mL) was stirred at 20°C under a dry atmosphere (CaCl_2 tube) for 1h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 30% EtOAc in hexane) to give 1-ethyl-3-(4-nitrophenyl)-1,3-

dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.70 g) as a brown solid. A mixture of 1-ethyl-3-(4-nitrophenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.70 g) and 10% palladium-carbon (0.832 g) in EtOH (250 mL) was hydrogenated under balloon
5 pressure at room temperature for 3h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 3-(4-aminophenyl)-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.00 g) as a brown solid.
MS (API+): [M+H]⁺ 255.1.

10 [0319]

65b) 2-chloro-1-(2,2-diethoxyethyl)-1H-benzimidazole



A mixture of 2-chloro-1H-benzimidazole (6.10 g), bromoacetaldehyde diethyl acetal (7.22 mL), EtOH (70 mL), and
15 8 M NaOH aqueous solution (10 mL) was refluxed for 3 d. The reaction mixture was poured into water and the mixture was extracted with AcOEt. The extract was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography
20 eluting with hexane/AcOEt (10/1) to give 2-chloro-1-(2,2-diethoxyethyl)-1H-benzimidazole (5.50 g).

MS (API+): [M+H]⁺ 269.1.

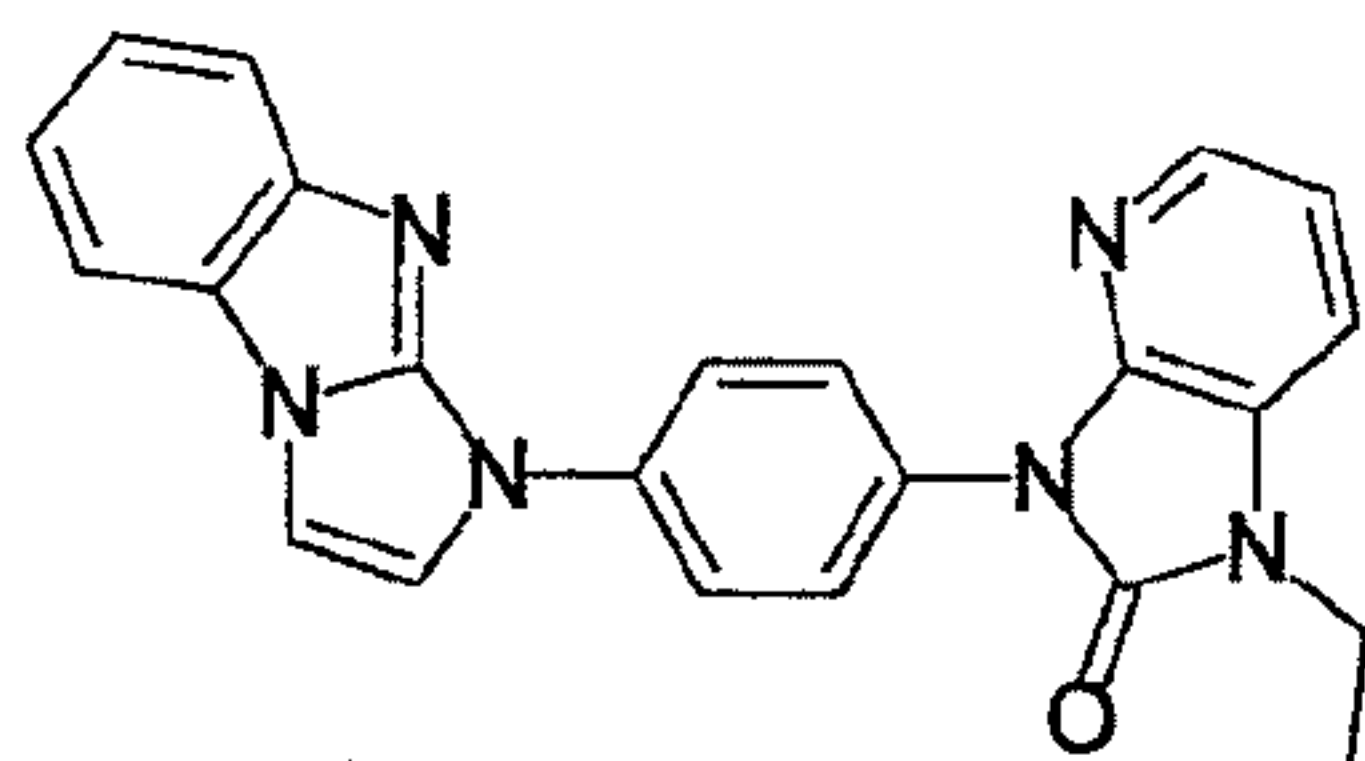
¹H NMR (300 MHz, CDCl₃) δ 1.10 (6H, t, J = 7.2 Hz), 3.39 (2H, dq, J = 9.1, 7.2 Hz), 3.72 (2H, dq, J = 9.1, 7.2 Hz), 4.29 (2H,
25 d, J = 5.7 Hz), 4.72 (1H, t, J = 5.7 Hz), 7.23-7.32 (2H, m), 7.39-7.47 (1H, m), 7.64-7.72 (1H, m).

mp 29-31°C.

Anal. Calcd for C₁₃H₁₇ClN₂O₂: C, 58.10; H, 6.38; N, 10.42. Found: C, 57.80; H, 6.31; N, 10.47.

30 [0320]

65c) 1-ethyl-3-[4-(1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 2-chloro-1-(2,2-diethoxyethyl)-1H-benzimidazole (860 mg) and 3-(4-aminophenyl)-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (636 mg) was heated at
 5 150°C for 50 min. The reaction mixture was partitioned between AcOEt/THF (1/1) and 1 M NaOH aqueous solution. The organic layer was separated, washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography eluting with THF and
 10 recrystallized from THF to give 1-ethyl-3-[4-(1H-imidazo[1,2-a]benzimidazol-1-yl)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (311 mg).

MS (API⁺): [M+H]⁺ 395.3.

¹H NMR (300 MHz, CDCl₃) δ 1.43 (3H, t, J = 7.2 Hz), 4.05 (2H, q, J = 7.2 Hz), 7.10 (1H, dd, J = 7.9, 5.3 Hz), 7.17-7.22 (1H, m),
 15 7.29 (1H, dd, J = 7.9, 1.5 Hz), 7.32-7.37 (2H, m), 7.44 (1H, d, J = 2.6 Hz), 7.62 (1H, d, J = 7.6 Hz), 7.80 (1H, d, J = 8.3 Hz), 7.91-7.96 (2H, m), 8.08 (1H, dd, J = 5.3, 1.5 Hz), 8.15-8.20 (2H, m).

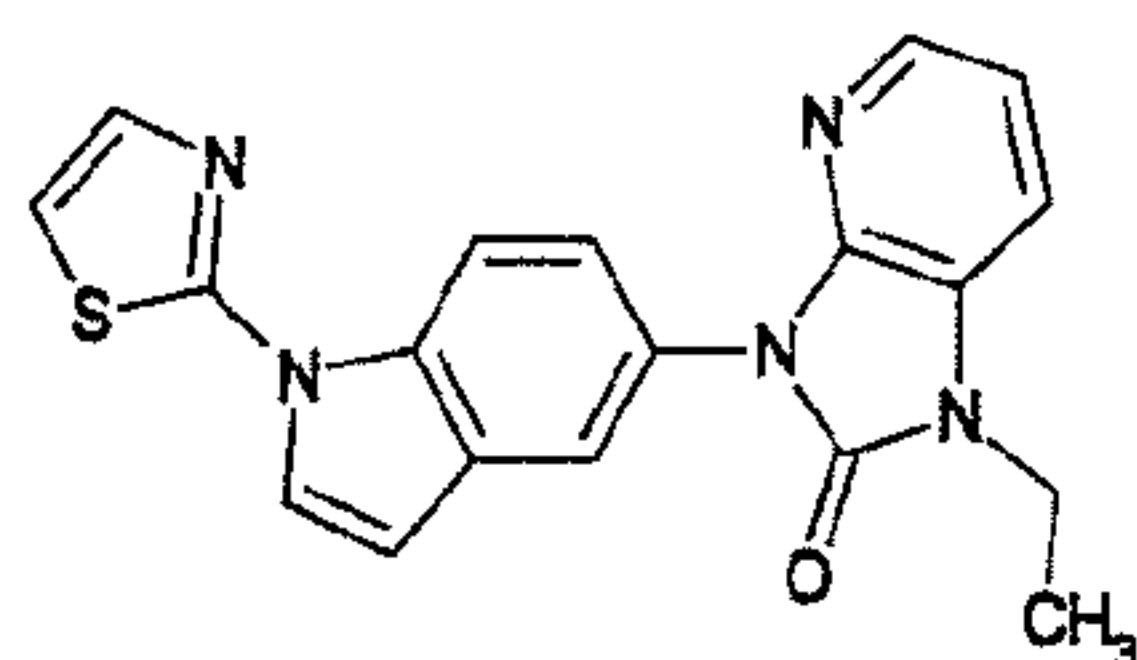
20 mp 220-221°C.

Anal. Calcd for C₂₃H₁₈N₆O: C, 70.04; H, 4.60; N, 21.31. Found: C, 70.12; H, 4.63; N, 21.39.

[0321]

Example 66

25 1-ethyl-3-[1-(1,3-thiazol-2-yl)-1H-indol-5-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-(2,3-dihydro-1H-indol-5-yl)-1-ethyl-1,3-

dihydro-2H-imidazo[4,5-b]pyridin-2-one (75 mg), 2-chlorothiazole (48.0 mg) and Cs_2CO_3 (174 mg) in DMF (3 mL) was stirred at 100°C for 3 days, treated with saturated NaHCO_3 solution, and extracted with AcOEt. The organic layer was
 5 separated, dried over MgSO_4 and concentrated in vacuo. The residue was purified by prep. HPLC and crystallized from AcOEt/Hexane to give the title compound as white crystals (27.0 mg).

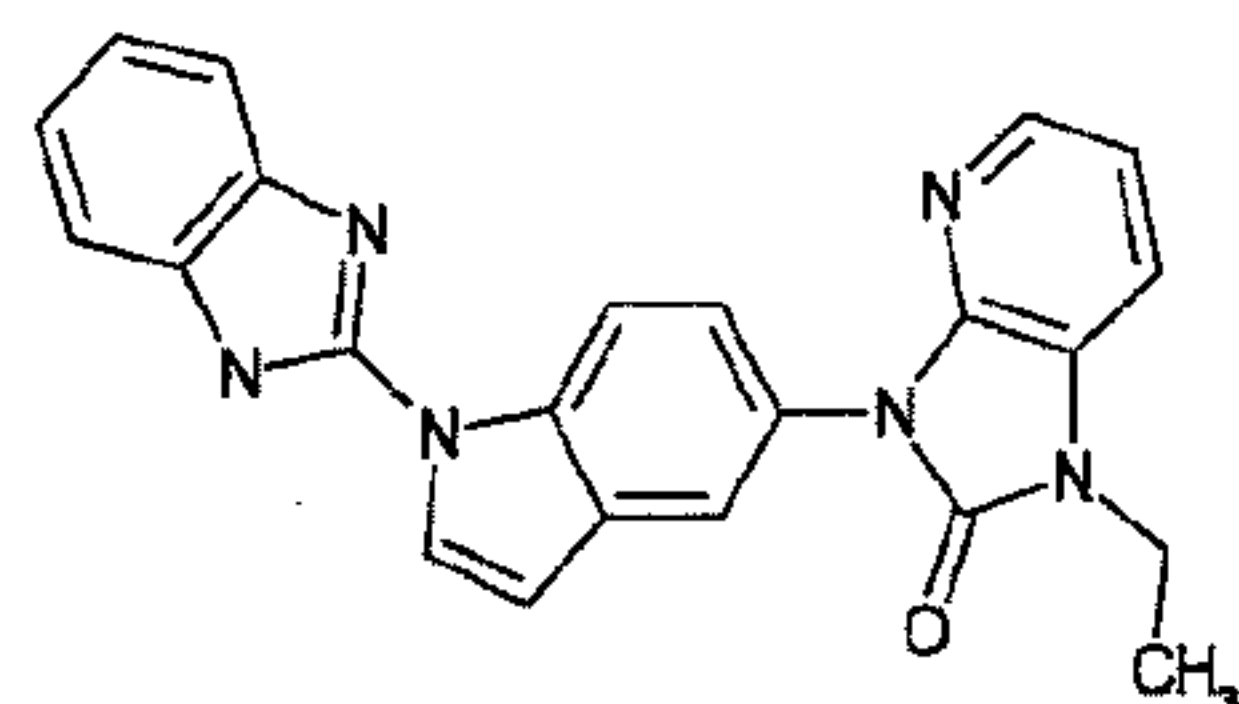
MS (API+): $[\text{M}+\text{H}]^+$ 362.0.

10 ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 7.2$ Hz), 4.00 (2H, q, $J = 7.2$ Hz), 6.93 (1H, d, $J = 3.4$ Hz), 7.08-7.22 (1H, m), 7.54-7.64 (2H, m), 7.65-7.78 (2H, m), 7.88-8.08 (3H, m), 8.41-8.52 (1H, m).

[0322]

15 Example 69

3-[1-(1H-benzimidazol-2-yl)-1H-indol-5-yl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



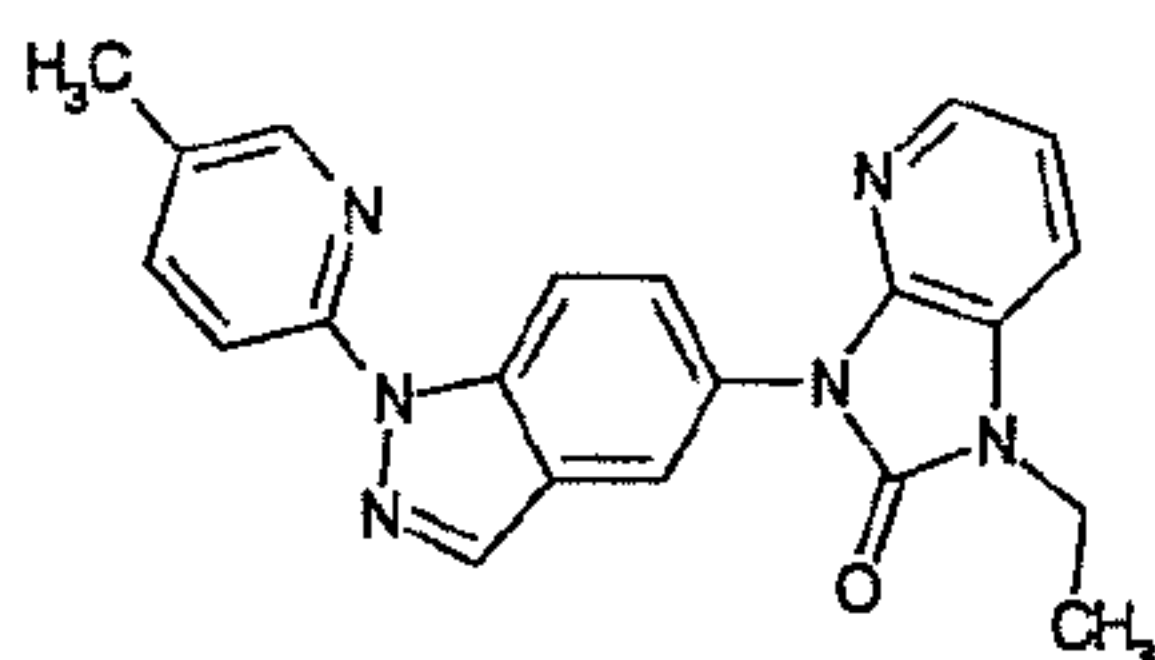
A mixture of 3-[1-(1H-benzimidazol-2-yl)-2,3-dihydro-1H-indol-5-yl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
 20 (100 mg) and manganese dioxide (439 mg) in toluene (8 mL) was stirred at 100°C for 5h, filtered, treated with water and extracted with AcOEt. The organic layer was dried over MgSO_4 and concentrated in vacuo. The residue was chromatographed on
 25 silica gel eluting with AcOEt/Hexane. Crystallization from AcOEt/ Hexane gave the title compound (28.0 mg).

MS (API+): $[\text{M}+\text{H}]^+$ 395.2.

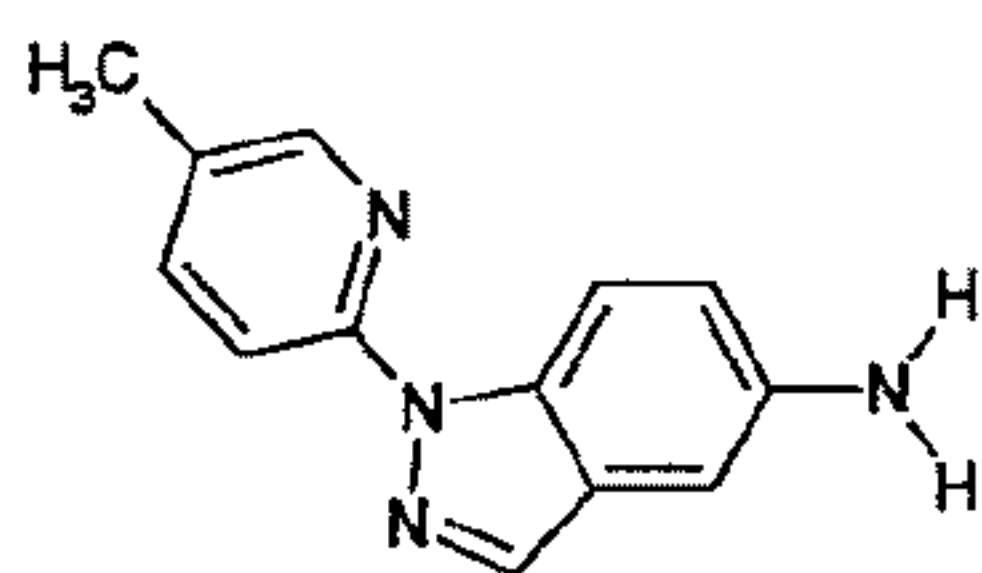
[0323]

Example 70

30 1-ethyl-3-[1-(5-methylpyridin-2-yl)-1H-indazol-5-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



70a) 1-(5-methylpyridin-2-yl)-1H-indazol-5-amine



To a stirred solution of 5-nitro-1H-indazole (500 mg) in
 5 DMF (10 mL) was added 60% sodium hydride (129 mg) at room
 temperature. The mixture was stirred for 30min, and 5-bromo-2-
 chloropyridine (649 mg) was added. The mixture was exposed to
 microwave irradiation at 230°C for 1h, treated with sat.
 ammonium chloride solution, and extracted with AcOEt. The
 10 organic layer was dried over MgSO₄ and concentrated in vacuo.
 The residue was chromatographed on silica gel eluting with
 AcOEt/Hexane to give a mixture of 1-(5-bromopyridin-2-yl)-5-
 nitro-1H-indazole and 2-(5-bromopyridin-2-yl)-5-nitro-2H-
 indazole.

15 To the mixture of 1-(5-bromopyridin-2-yl)-5-nitro-1H-
 indazole and 2-(5-bromopyridin-2-yl)-5-nitro-2H-indazole were
 added methylboronic acid (141 mg), Pd(Ph₃P)₄ (91 mg), DME (3
 mL) and a solution of Cs₂CO₃ (766 mg) in H₂O (1 mL),
 successively. The mixture was exposed to microwave irradiation
 20 at 140°C for 1h, treated with water, and extracted with AcOEt.
 The organic layer was dried over MgSO₄ and concentrated in
 vacuo to give a mixture of 1-(5-methylpyridin-2-yl)-5-nitro-
 1H-indazole and 2-(5-methylpyridin-2-yl)-5-nitro-2H-indazole.

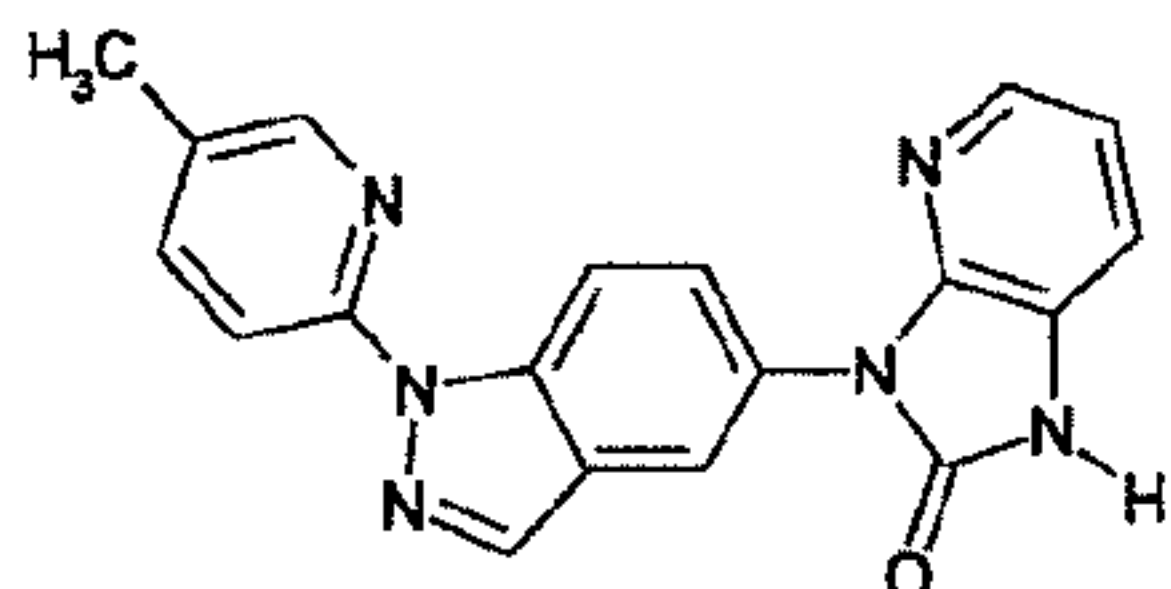
The mixture of 1-(5-methylpyridin-2-yl)-5-nitro-1H-
 25 indazole and 2-(5-methylpyridin-2-yl)-5-nitro-2H-indazole was
 dissolved in EtOH (20 mL), and 10% Pd/C (250 mg) was added.
 Under H₂ atmosphere, the mixture was stirred at room
 temperature for 12h, filtered and concentrated in vacuo. The
 residue was chromatographed on silica gel eluting with
 30 AcOEt/Hexane to give the title compound as white crystals (76

mg).

^1H NMR (300 MHz, DMSO- d_6) δ 2.33 (3H, s), 5.06 (2H, s), 6.84 (1H, d, $J = 1.5$ Hz), 6.91 (1H, dd, $J = 8.9, 2.1$ Hz), 7.71-7.87 (2H, m), 8.09 (1H, s), 8.33 (1H, d, $J = 2.3$ Hz), 8.38-8.46 (1H, m).

[0324]

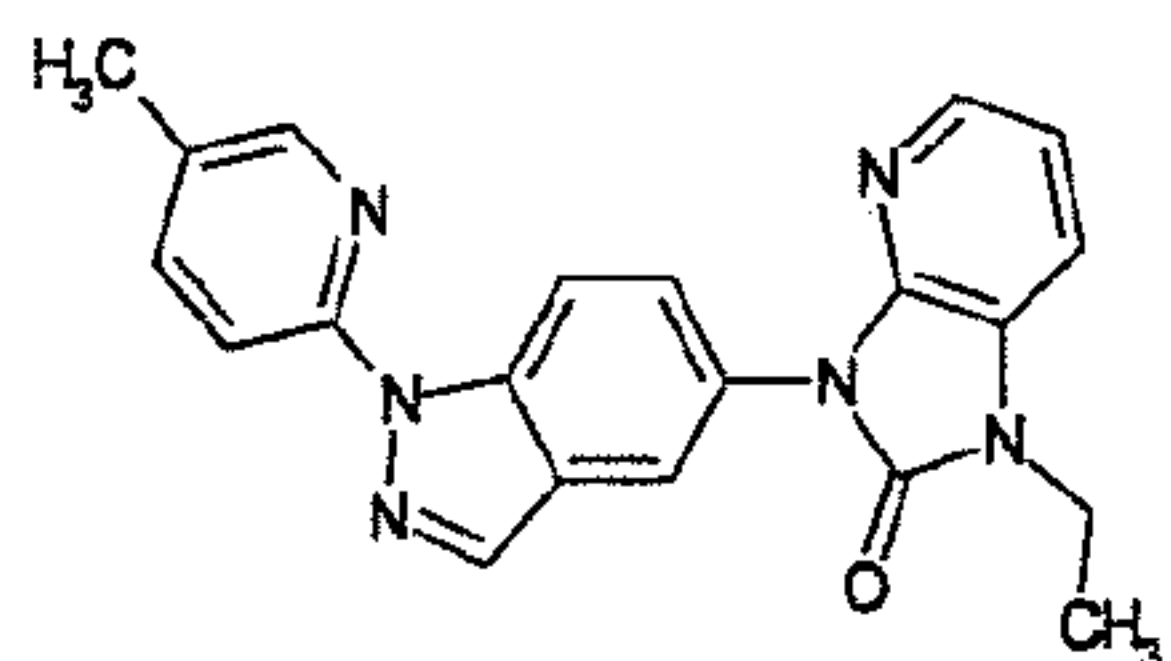
70b) 3-[1-(5-methylpyridin-2-yl)-1H-indazol-5-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



Under argon atmosphere, a mixture of 1-(5-methylpyridin-2-yl)-1H-indazol-5-amine (71 mg), tert-butyl 2-chloropyridin-3-ylcarbamate (80 mg), $\text{Pd}_2(\text{dba})_3$ (29.0 mg), Xantphos (36.6 mg) and sodium tert-butoxide (33.5 mg) in 2-propanol (2 mL) and toluene (0.5 mL) was stirred at 90°C for 24h, treated with water and extracted with EtOAc. The organic layer was separated, dried over MgSO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with AcOEt/Hexane to give the title compound as white crystals (70.0 mg). MS (API+): $[\text{M}+\text{H}]^+$ 343.3.

[0325]

70c) 1-ethyl-3-[1-(5-methylpyridin-2-yl)-1H-indazol-5-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-[1-(5-methylpyridin-2-yl)-1H-indazol-5-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (70 mg) and iodoethane (35.1 mg) in DMF (2 mL) was stirred at 50°C for 3h, treated with water, and extracted with AcOEt. The organic layer was dried over MgSO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with AcOEt/Hexane. The product was crystallized from AcOEt/Hexane

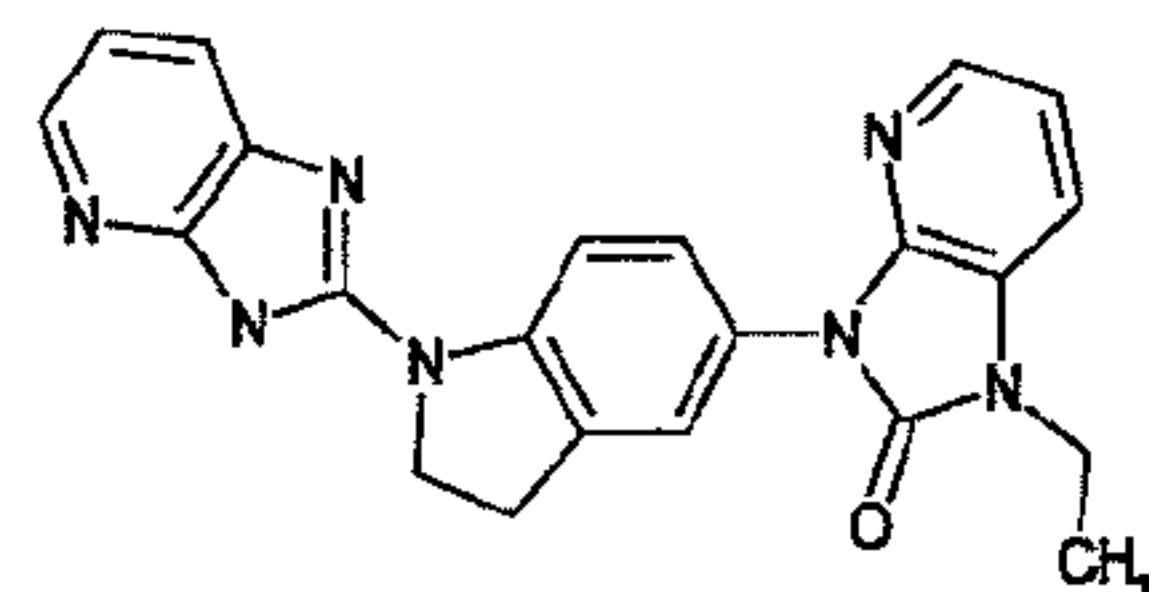
to give the title compound as white crystals (25.0 mg).

MS (API+): [M+H]⁺ 371.0.

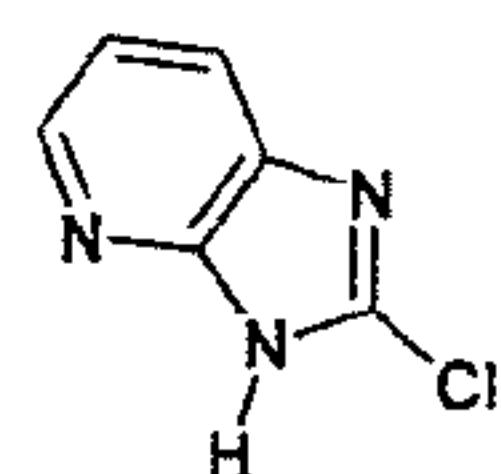
[0326]

Example 71

- 5 1-ethyl-3-[1-(3H-imidazo[4,5-b]pyridin-2-yl)-2,3-dihydro-1H-indol-5-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



71a) 2-Chloro-3H-imidazo[4,5-b]pyridine

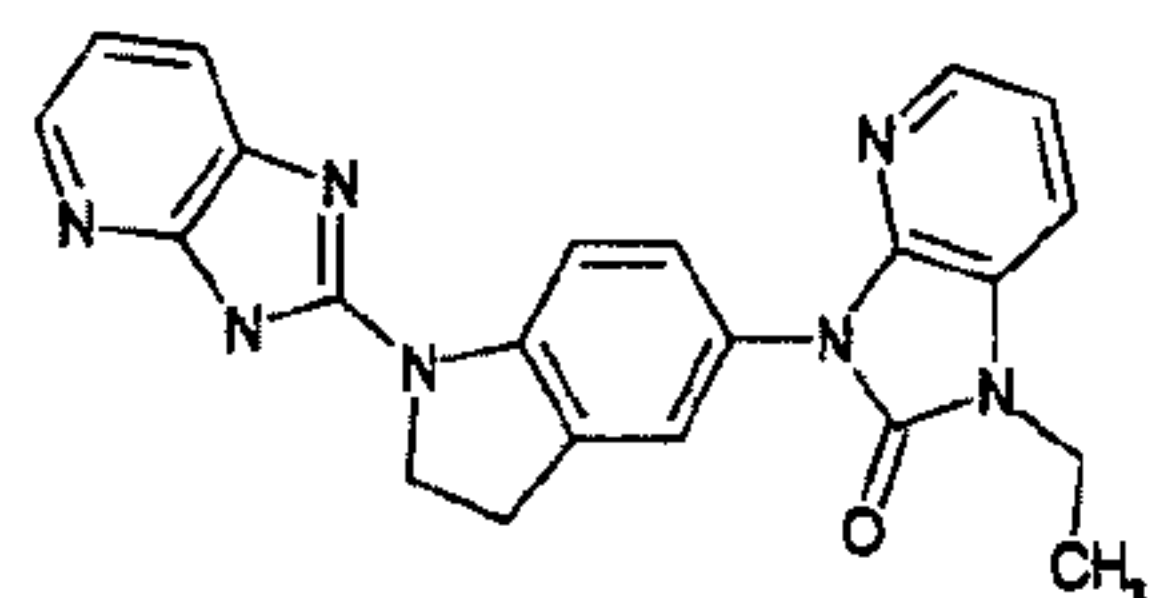


- 10 2-(Methylthio)-3H-imidazo[4,5-b]pyridine (3.5 g) was dissolved in conc. HCl (10 mL), and then the mixture was cooled to 0°C. Chlorine gas was bubbled through the mixture for 2h in iced bath. The mixture was poured onto ice, and neutralized to pH 7 with aqueous ammonium solution. The
15 precipitate was collected by filtration to give the title compound as white crystals (1.0 g).

MS (API+): [M+H]⁺ 154.0.

[0327]

- 71b) 1-ethyl-3-[1-(3H-imidazo[4,5-b]pyridin-2-yl)-2,3-dihydro-
20 1H-indol-5-yl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



- Under nitrogen atmosphere, a mixture of 3-(2,3-dihydro-1H-indol-5-yl)-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (100 mg) and 2-chloro-3H-imidazo[4,5-b]pyridine (60.3 mg)
25 in NMP (4 mL) was stirred at 150°C for 2h, treated with water, and extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by

prep. HPLC. Crystallization from EtOH/ H₂O to give the title compound (18.0 mg).

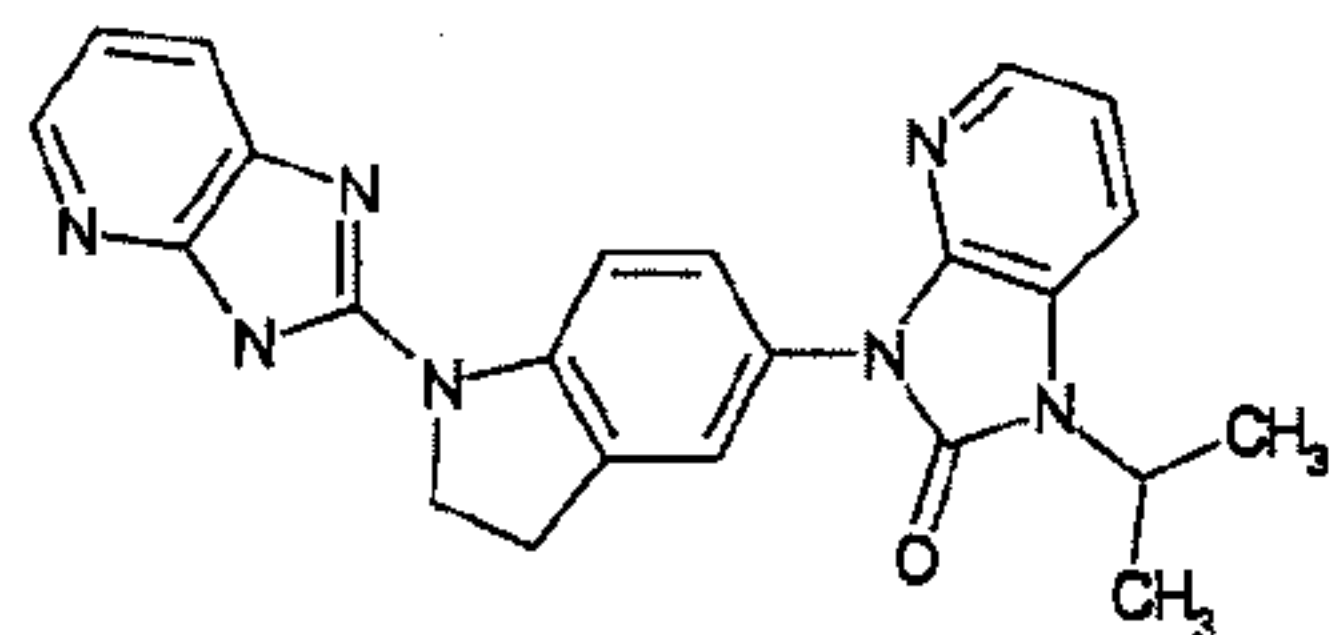
MS (API+): [M+H]⁺ 398.2.

¹H NMR (300 MHz, DMSO-d₆) δ 1.29 (3H, t, J = 7.0 Hz), 3.36-3.41 (2H, m), 3.97 (2H, q, J = 7.1 Hz), 4.19-4.34 (2H, m), 6.98-7.10 (1H, m), 7.12-7.20 (1H, m), 7.39-7.49 (2H, m), 7.62-7.72 (2H, m), 7.93-8.01 (1H, m), 8.02-8.17 (1H, m), 8.41 (1H, d, J = 9.1 Hz).

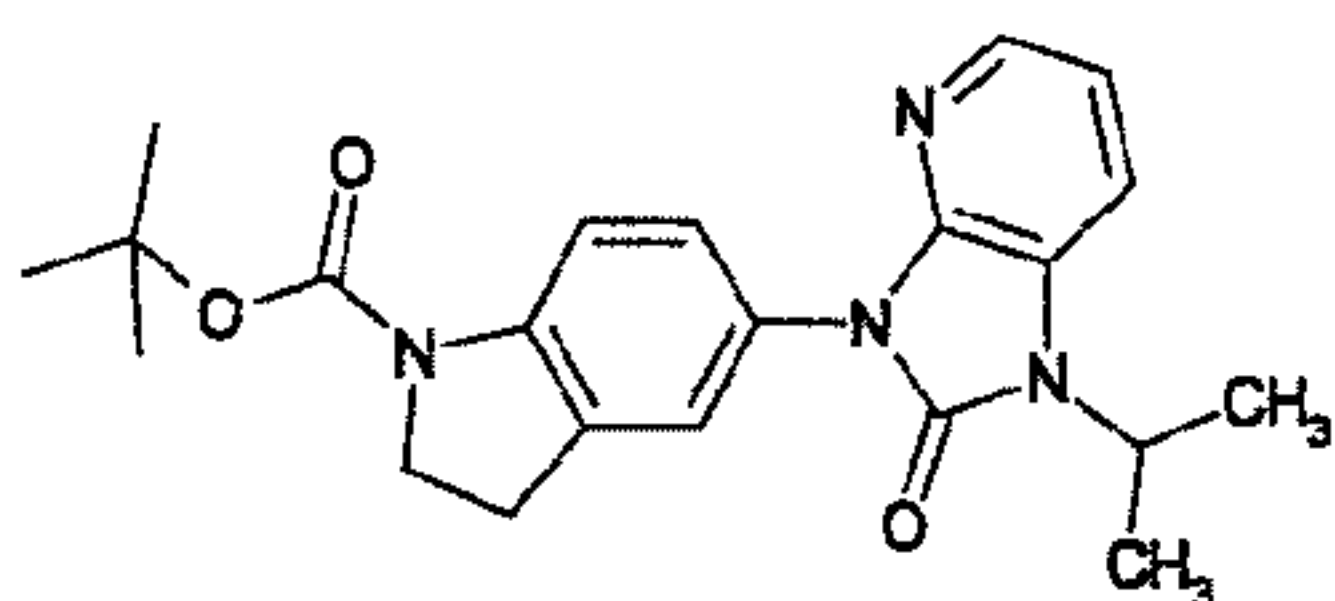
[0328]

10 Example 72

3-[1-(3H-imidazo[4,5-b]pyridin-2-yl)-2,3-dihydro-1H-indol-5-yl]-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



15 72a) tert-Butyl 5-[1-(1-methylethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl]-2,3-dihydro-1H-indole-1-carboxylate

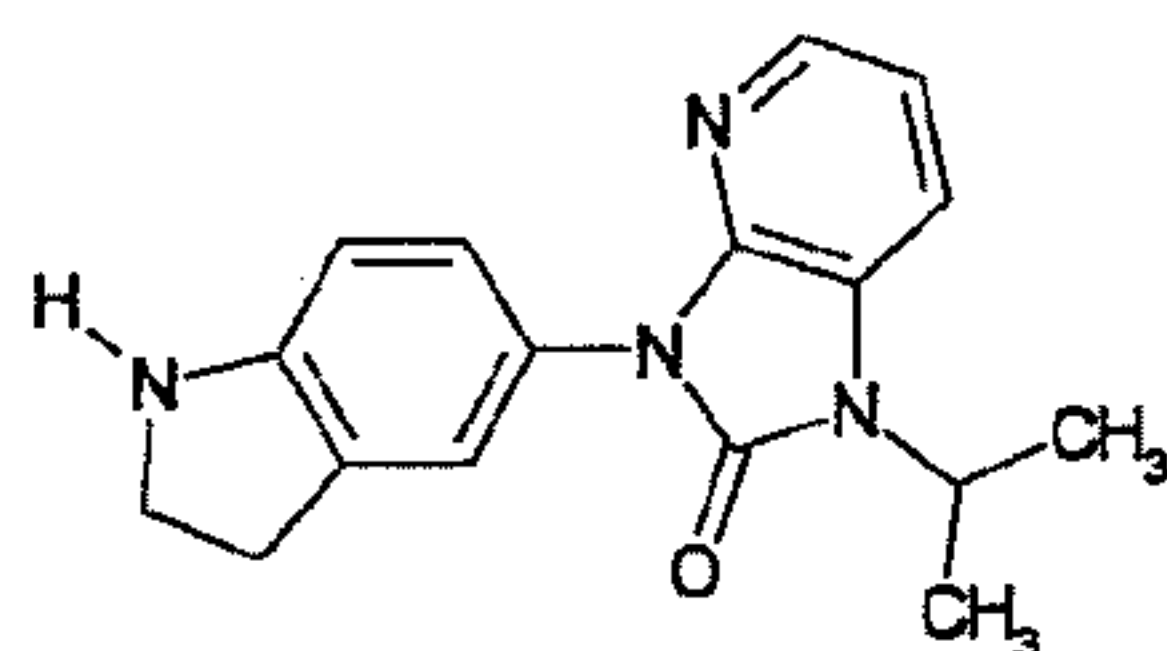


A mixture of tert-butyl 5-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2,3-dihydro-1H-indole-1-carboxylate (1480 mg) and 2-iodopropane (714 mg) in DMF (5 mL) was stirred at 60°C for 4h, treated with water, and extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel eluting with AcOEt/Hexane to give the title compound as white crystals (570 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.44-1.60 (15H, m), 3.12 (2H, t, J = 8.7 Hz), 3.92-4.01 (2H, m), 4.65-4.74 (1H, m), 7.07-7.15 (1H, m), 7.31-7.45 (2H, m), 7.72-7.79 (2H, m), 7.90-7.99 (1H, m).

[0329]

72b) 3-(2,3-dihydro-1H-indol-5-yl)-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

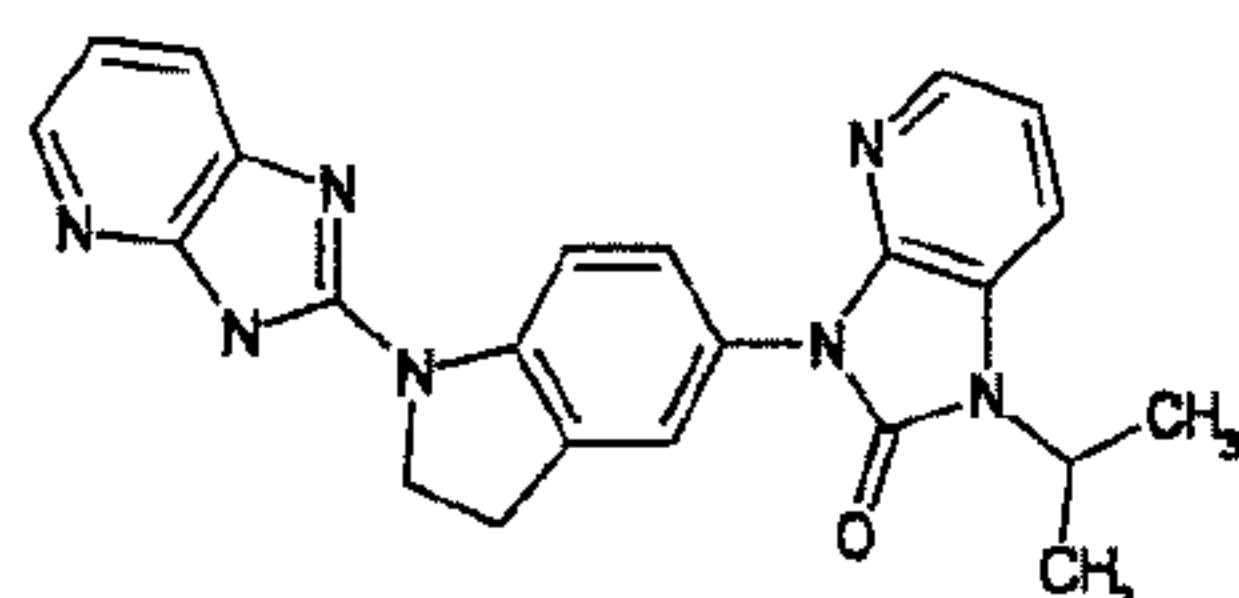


5 To a stirred mixture of tert-butyl 5-[1-(1-methylethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl]-2,3-dihydro-1H-indole-1-carboxylate in AcOEt/ EtOH (1/1, 10 mL) was added 4N HCl in AcOEt (4 mL). The mixture was stirred at 80°C for 2h, evaporated, treated with saturated NaHCO₃, and extracted with
10 AcOEt. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was suspended in IPE and the suspension was collected by filtration to give the title compound as white crystals (313 mg).

MS (API+): [M+H]⁺ 295.1.

15 [0330]

72c) 3-[1-(3H-imidazo[4,5-b]pyridin-2-yl)-2,3-dihydro-1H-indol-5-yl]-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



20 A mixture of 3-(2,3-dihydro-1H-indol-5-yl)-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (200 mg) and 2-chloro-3H-imidazo[4,5-b]pyridine (115 mg) in NMP (4 mL) was stirred at 140°C for 1.5h, treated with saturated NaHCO₃, and extracted with AcOEt. The organic layer was dried
25 over MgSO₄, passed through celite pad covered with activated carbon and concentrated in vacuo. The residue was purified by prep. HPLC. The product was crystallized from EtOH/ hexane to give the title compound (15.0 mg).

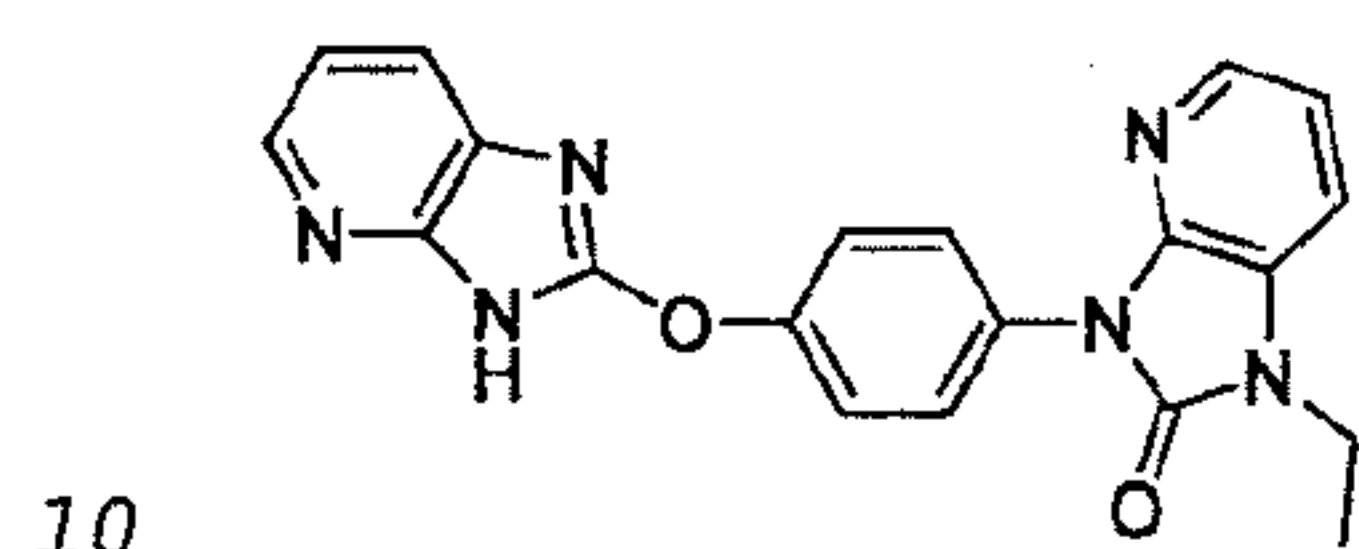
MS (API+): [M+H]⁺ 412.4.

¹H NMR (300 MHz, DMSO-d₆) δ 1.51 (6H, d, J = 7.2 Hz), 3.38-3.45 (2H, m), 4.20-4.35 (2H, m), 4.72 (1H, sep, J = 7.2 Hz), 6.97-7.17 (2H, m), 7.36-7.50 (2H, m), 7.60-7.81 (2H, m), 7.96 (1H, d, J = 5.3 Hz), 8.01-8.18 (1H, m), 8.34-8.47 (1H, m), 12.20 (1H, brs).

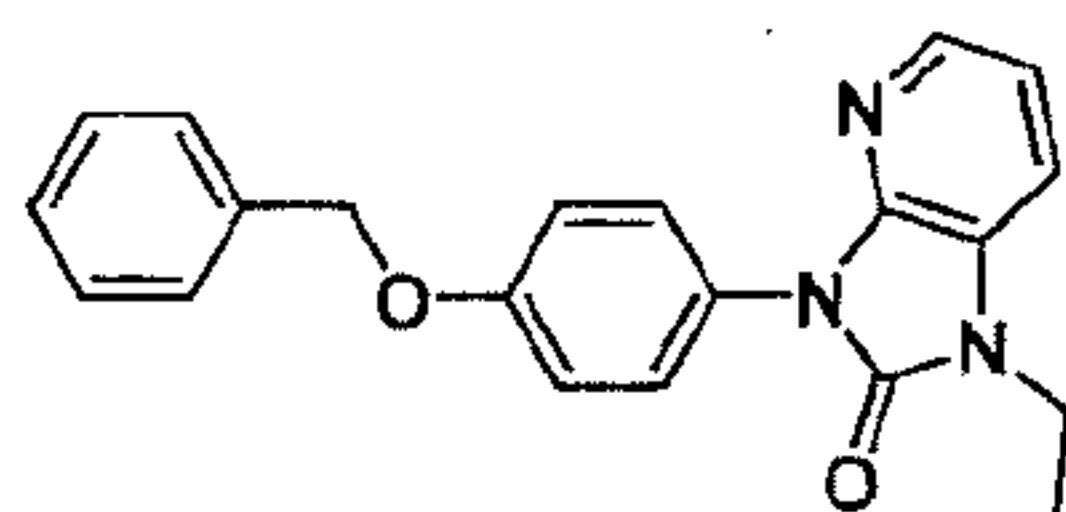
[0331]

Example 75

1-ethyl-3-[4-(3H-imidazo[4,5-b]pyridin-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



75a) 3-[4-(benzyloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

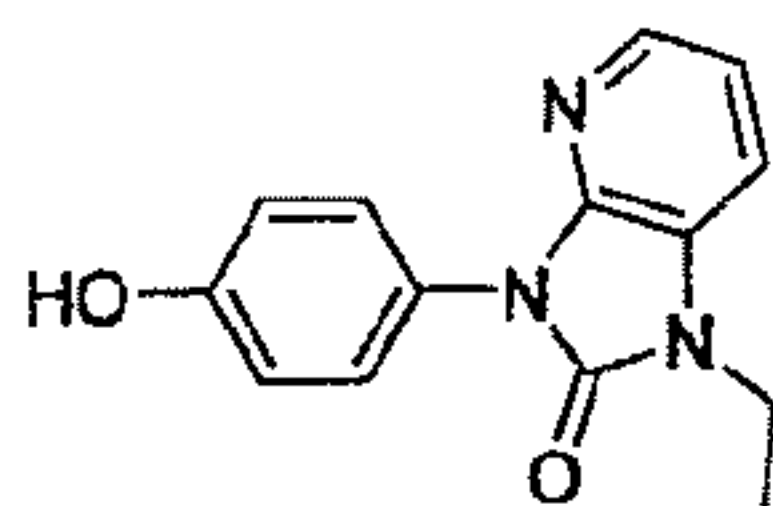


The mixture of 3-[4-(benzyloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.50 g), sodium hydride (0.378 g) and iodoethane (1.60 mL) in DMF (25 mL) was stirred at 20°C under a dry atmosphere (CaCl₂ tube) for 1h. The reaction mixture was diluted with MeOH (10 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 30% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.70g) as a colorless solid. MS (API+): [M+H]⁺ 346.4.

¹H NMR (300 MHz, CDCl₃) δ 1.40 (3H, t, J = 7.2 Hz), 4.02 (2H, q, J = 7.2 Hz), 5.11 (2H, s), 7.01-7.17 (3H, m), 7.22-7.29 (1H, m), 7.29-7.49 (5H, m), 7.53-7.61 (2H, m), 8.00-8.09 (1H, m).

[0332]

75b) 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



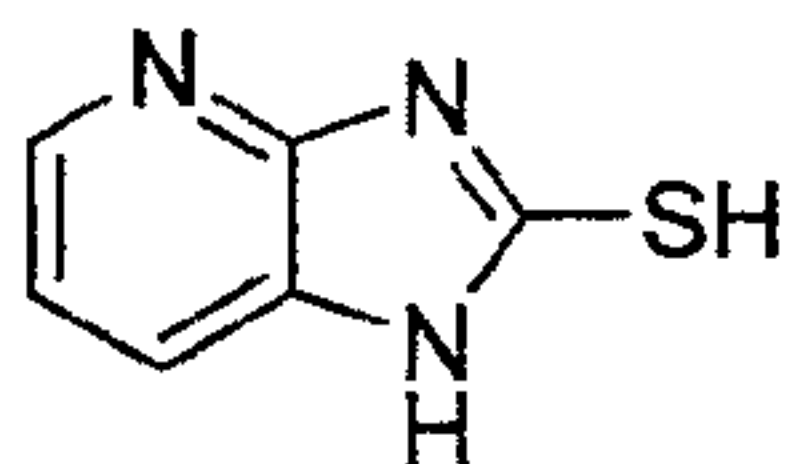
A mixture of 3-[4-(benzyloxy)phenyl]-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2.70 g) and 10% palladium-carbon (0.832 g) in EtOH (250 mL) was hydrogenated under
 5 balloon pressure at room temperature for 3h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.42 g) as a white solid.

MS (API+): $[M+H]^+$ 256.1.

10 ^1H NMR (300 MHz, DMSO- d_6) δ 1.27 (3H, t, $J = 7.2$ Hz), 3.95 (2H, q, $J = 7.2$ Hz), 6.84-6.95 (2H, m), 7.08-7.18 (1H, m), 7.32-7.40 (2H, m), 7.57-7.67 (1H, m), 7.89-7.99 (1H, m), 9.67-9.79 (1H, m).

[0333]

15 75c) 1H-imidazo[4,5-b]pyridine-2-thiol



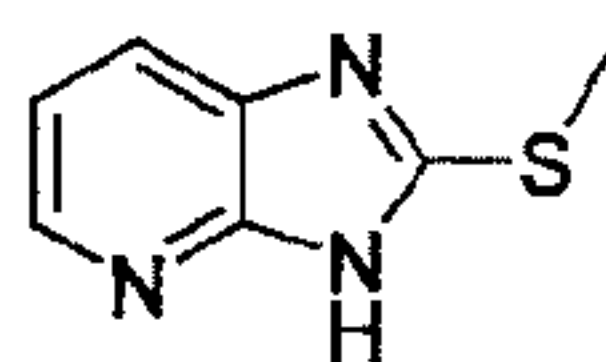
To a solution of pyridine-2,3-diamine (5 g) in EtOH (150 mL) was added carbon disulfide (23 mL) at room temperature. The mixture was stirred at 40°C under Ar for 10 h. The mixture
 20 was cooled to room temperature. The resulting white solid was filtered and washed with ether to give 1H-imidazo[4,5-b]pyridine-2-thiol (5.61 g).

MS (API+): $[M+H]^+$ 152.2.

^1H NMR (300 MHz, DMSO- d_6) δ 7.13 (1 H, m), 7.47 (1 H, d, $J=6.8$ Hz), 7.97 - 8.36 (1 H, m), 12.72 (1 H, br. s.), 13.13 (1 H, br. s.).

[0334]

75d) 2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine



30 To a solution of 1H-imidazo[4,5-b]pyridine-2-thiol (2 g)

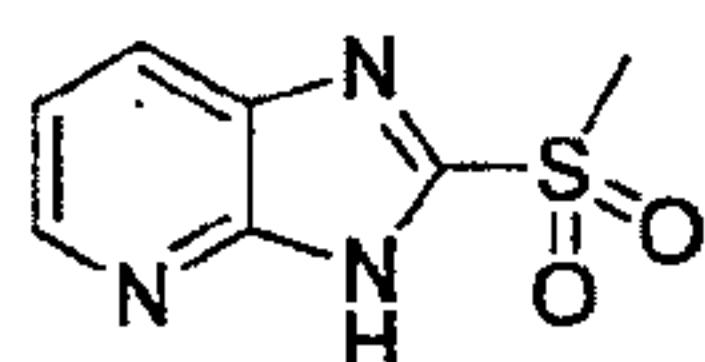
in acetone (30 mL) were added MeI (0.910 mL) and K₂CO₃ (5.48 g) at room temperature. After stirring for 10 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (NH-silica gel, eluted with 10% -
 5 100% EtOAc in hexane) to give 2-(methylsulfanyl)-3H-imidazo[4,5-b]pyridine (1.0 g) as a white solid.

MS (API+): [M+H]⁺ 166.3.

¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.71 (3 H, s), 6.83 - 7.34 (1 H, m), 7.68 - 8.02 (1 H, m), 8.02 - 8.32 (1 H, m), 12.68 - 13.33
 10 (1 H, m).

[0335]

75e) 2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine



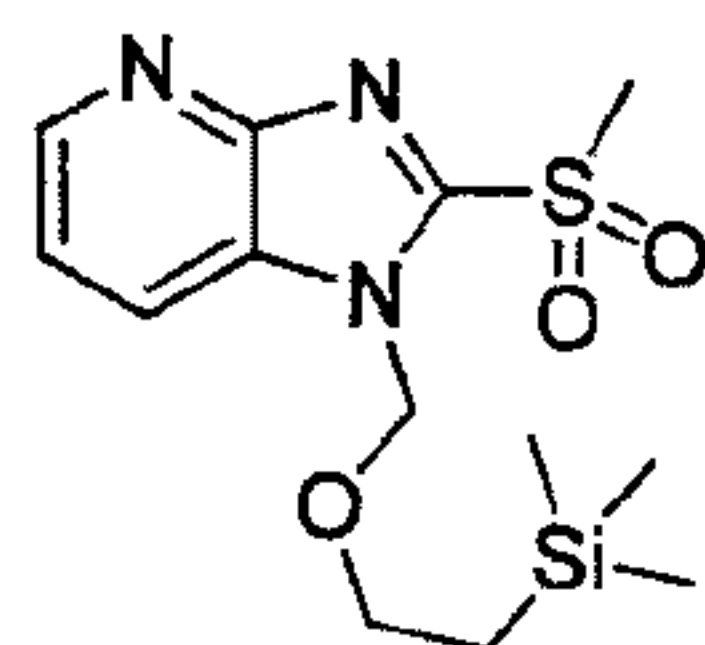
To a solution of 2-(methylsulfanyl)-3H-imidazo[4,5-b]pyridine (500 mg) in EtOAc (10 mL) was added mCPBA (1393 mg) at 0°C. After stirring for 10 h, the mixture was quenched with water, and extracted with ethyl acetate, and the extract was washed with brine, and dried over magnesium sulfate. The crude material was recrystallized from ethyl acetate to give 2-
 15 (methylsulfonyl)-3H-imidazo[4,5-b]pyridine (593 mg).

MS (API+): [M+H]⁺ 198.2.

¹H NMR (300 MHz, DMSO-d₆) δ 3.52 (3H, s), 7.32 - 7.41 (1 H, m), 7.50 - 7.61 (1 H, m), 7.67 - 7.76 (1 H, m), 8.53 - 8.63 (1 H, m).

25 [0336]

75f) 2-(methylsulfonyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazo[4,5-b]pyridine



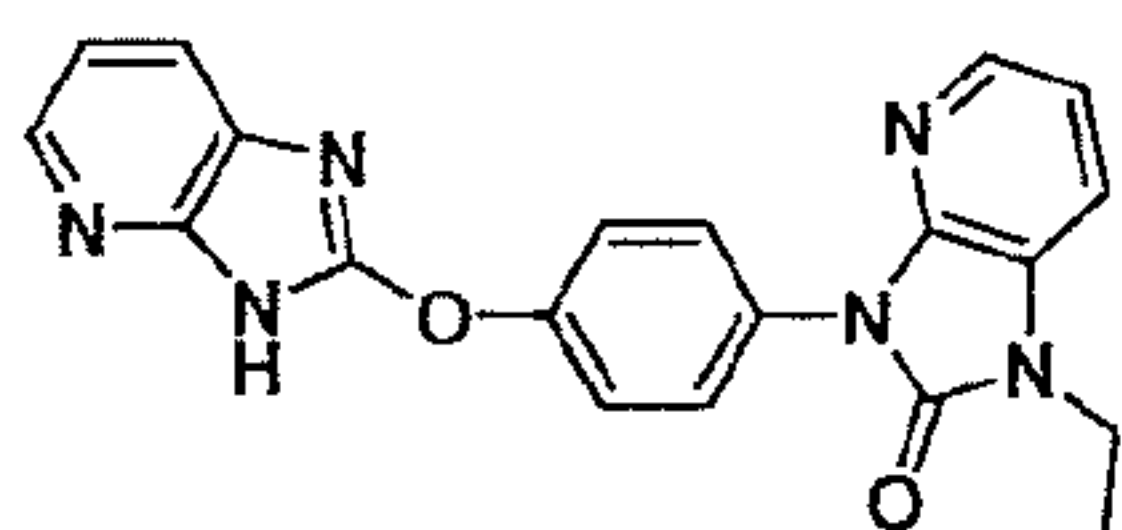
Sodium hydride (146 mg) was added to a solution of 2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine (600 mg) and [2-(chloromethoxy)ethyl]trimethylsilane (609 mg) in DMF (3 mL) at
 30

room temperature. The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube) for 1h. The reaction mixture was diluted with MeOH (2 mL), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 30% EtOAc in hexane) to give 2-(methylsulfonyl)-1-[[2-(trimethylsilyl)ethoxy)methyl]-1H-imidazo[4,5-b]pyridine (250 mg) as light brown oil.

MS (API+): [M+H]⁺ 328.3.

[0337]

10 75g) 1-ethyl-3-[4-(3H-imidazo[4,5-b]pyridin-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



The mixture of 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (281 mg), 2-(methylsulfonyl)-1-[[2-(trimethylsilyl)ethoxy)methyl]-1H-imidazo[4,5-b]pyridine (240 mg) and NaH (35.2 mg) in DMF(dry) (3 mL) was heated at 200°C for 3h under microwave irradiation. The reaction mixture was diluted with MeOH, and concentrated in vacuo. The residue was diluted with 6N HCl. The mixture was neutralized with aq. NaHCO₃ at 0°C and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 100% EtOAc in hexane) to give 1-ethyl-3-[4-(3H-imidazo[4,5-b]pyridin-2-yloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (40 mg) as white crystals.

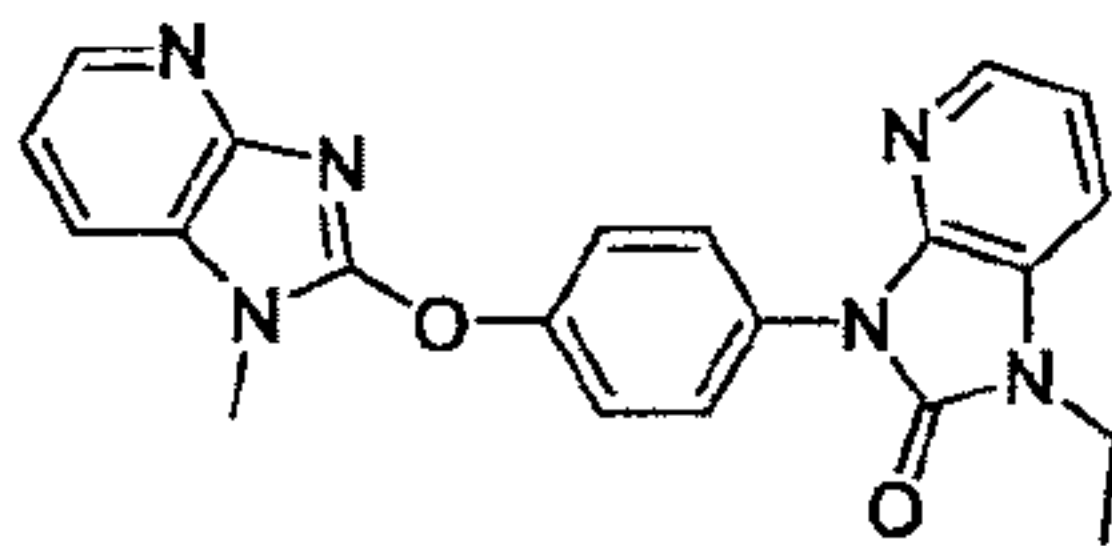
MS (API+): [M+H]⁺ 373.1.

¹H NMR (300 MHz, DMSO-d₆) δ 1.31 (3H, t, J = 7.1 Hz), 3.99 (2H, q, J = 7.1 Hz), 7.10-7.26 (2H, m), 7.55-7.64 (2H, m), 7.66-7.72 (1H, m), 7.73-7.84 (3H, m), 7.97-8.06 (1H, m), 8.11-8.23 (1H, m).

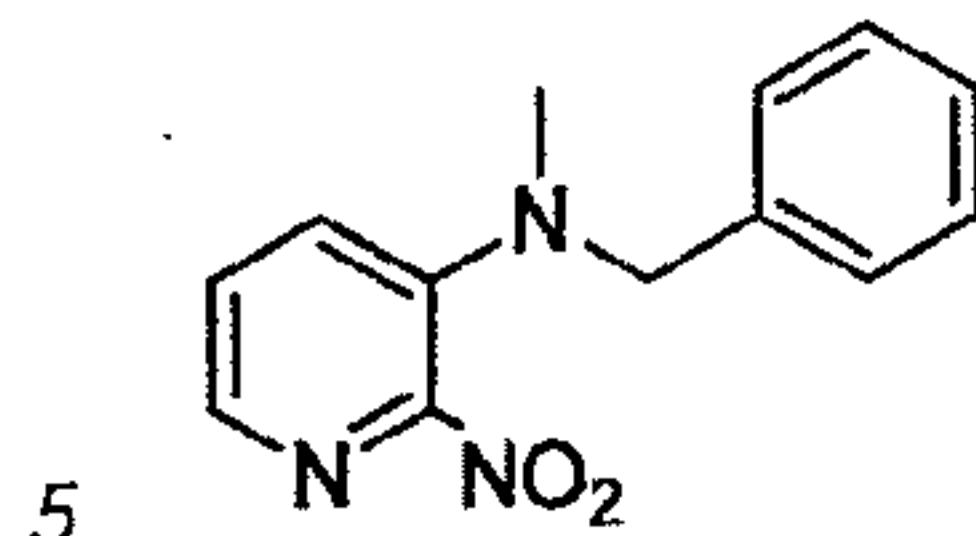
[0338]

Example 85

1-ethyl-3-{4-[(1-methyl-1H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



85a) N-benzyl-N-methyl-2-nitropyridin-3-amine



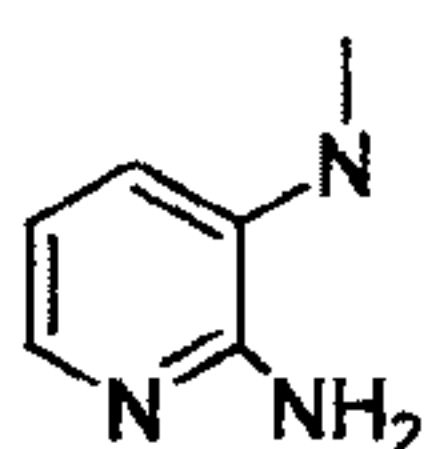
The mixture of N-methylbenzylamine (6.085 mL), TEA (13.19 mL) and 3-chloro-2-nitropyridine (5 g) was stirred at 60°C under N₂ overnight. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 30% EtOAc in hexane) to give N-benzyl-N-methyl-2-nitropyridin-3-amine (2.6 g) as dark yellow oil.

MS (API+): [M+H]⁺ 244.1.

¹H NMR (300 MHz, DMSO-d₆) δ 2.75 (3H, s), 4.44 (2H, s), 7.16-7.47 (5H, m), 7.51-7.62 (1H, m), 7.72-7.82 (1H, m), 7.92-8.02 (1H, m).

[0339]

85b) N³-methylpyridine-2,3-diamine



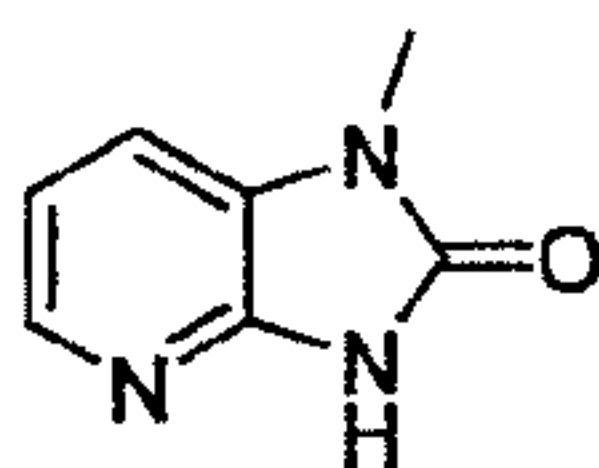
A mixture of N-benzyl-N-methyl-2-nitropyridin-3-amine (2.6 g) and 10% Pd-C (0.569 g) in EtOH (50 mL) was hydrogenated under balloon pressure at room temperature over weekend. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give N³-methylpyridine-2,3-diamine (1.14 g) as pale yellow oil.

MS (API+): [M+H]⁺ not detected.

¹H NMR (300 MHz, DMSO-d₆) δ 2.68 (3H, d, J = 4.9 Hz), 4.85 (1H, q, J = 4.9 Hz), 5.35 (2H, s), 6.41-6.58 (2H, m), 7.21-7.32 (1H, m).

[0340]

85c) 1-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



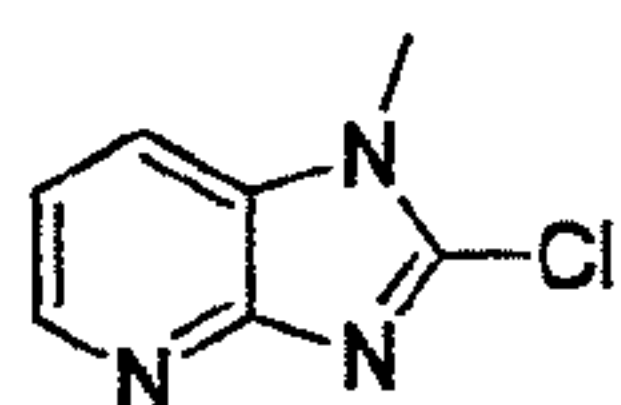
CDI (2.251 g) was added to a solution of N³-
5 methylpyridine-2,3-diamine (1.14 g) in THF(dry) (50 mL) at
room temperature. The mixture was stirred at room temperature
under a dry atmosphere (CaCl₂ tube) over weekend. The reaction
mixture was concentrated in vacuo. The residue was purified by
column chromatography (silica gel, eluted with 0% - 100% EtOAc
10 in hexane) to give 1-methyl-1,3-dihydro-2H-imidazo[4,5-
b]pyridin-2-one (1.1 g) as a white solid.

MS (API+): [M+H]⁺ not detected.

¹H NMR (300 MHz, DMSO-d₆) δ 3.29 (3H, s), 7.02 (1H, dd, J = 7.9,
5.3 Hz), 7.40 (1H, dd, J = 7.9, 1.5 Hz), 7.90 (1H, dd, J = 5.3,
15 1.5 Hz), 11.51 (1H, brs).

[0341]

85d) 2-chloro-1-methyl-1H-imidazo[4,5-b]pyridine



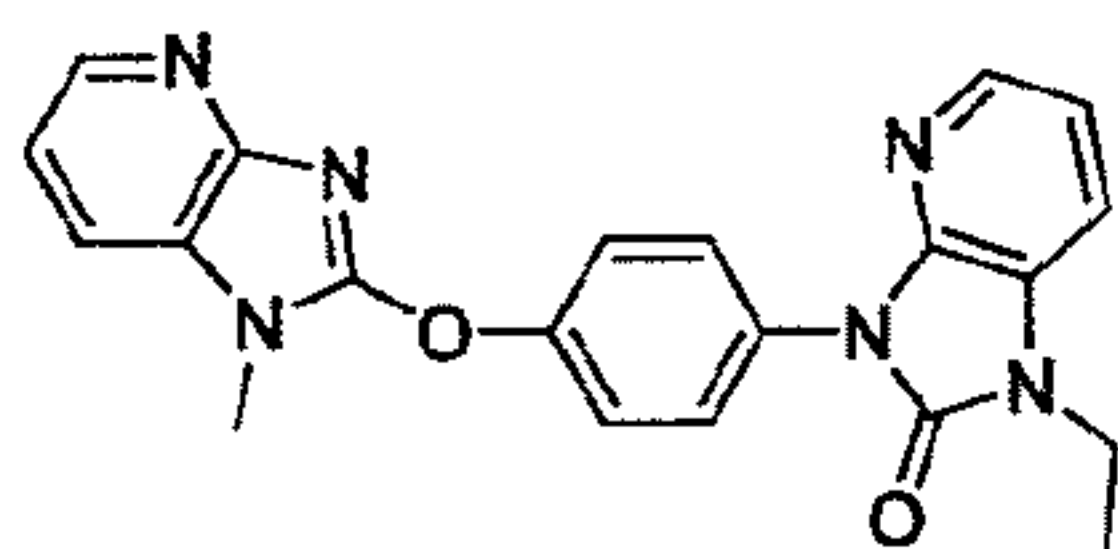
The mixture of 1-methyl-1,3-dihydro-2H-imidazo[4,5-
20 b]pyridin-2-one (1.1 g) and phosphorus oxychloride (6.87 mL)
was stirred at 100°C under a dry atmosphere (CaCl₂ tube) for 5h.
The mixture was neutralized with sat.NaHCO₃ at 0°C and
extracted with EtOAc. The organic layer was separated, washed
with water and brine, dried over MgSO₄ and concentrated in
25 vacuo. The residue was purified by column chromatography (NH
silica gel, eluted with 0% - 50% EtOAc in hexane) to give 2-
chloro-1-methyl-1H-imidazo[4,5-b]pyridine (600 mg) as a white
solid.

MS (API+): [M+H]⁺ 168.0.

30 ¹H NMR (300 MHz, DMSO-d₆) δ 3.83 (3H, s), 7.34 (1H, dd, J = 8.1,
4.9 Hz), 8.06 (1H, dd, J = 8.1, 1.7Hz), 8.42 (1H, dd, J = 4.9,
1.7 Hz).

[0342]

85e) 1-ethyl-3-{4-[(1-methyl-1H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



5 The mixture of sodium hydride (14.32 mg), 2-chloro-1-methyl-1H-imidazo[4,5-b]pyridine (100 mg) and 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (152 mg) in DMF (3 mL) was stirred at 180°C under a dry atmosphere (CaCl₂ tube) for 20 min. The mixture was neutralized with 1N
 10 HCl at 0°C and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 100% EtOAc in hexane) to give 1-ethyl-3-{4-[(1-methyl-1H-imidazo[4,5-
 15 b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (150 mg) as white crystals.

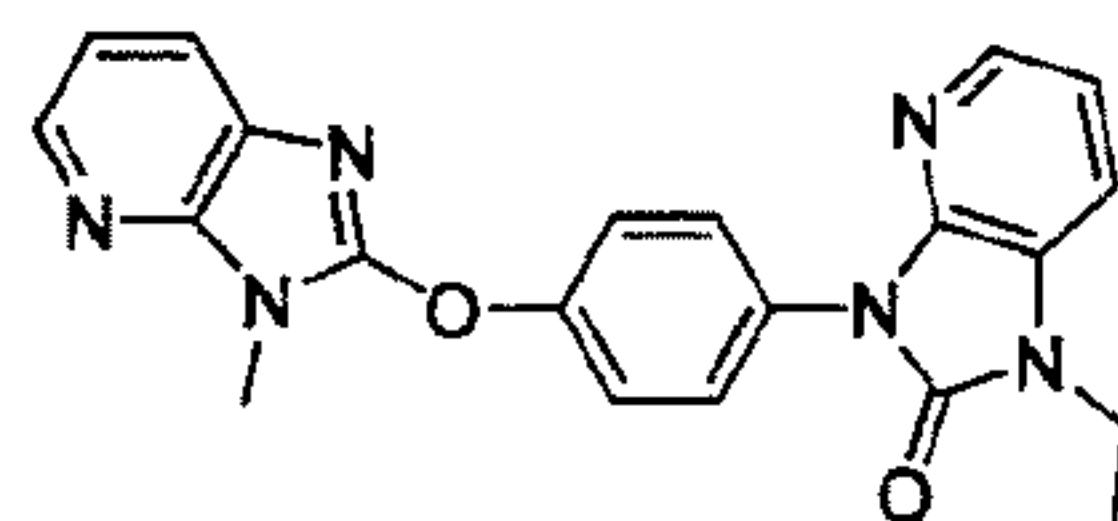
MS (API+): [M+H]⁺ 387.2.

1H NMR (300 MHz, DMSO-d₆) δ 1.31 (3H, t, J = 7.2 Hz), 3.80 (3H, s), 3.99 (2H, q, J = 7.2 Hz), 7.14-7.28 (2H, m), 7.60-7.68 (2H, m),
 20 7.66-7.74 (1H, m), 7.78-7.86 (2H, m), 7.87-7.95 (1H, m), 7.96-8.06 (1H, m), 8.21-8.35 (1H, m).

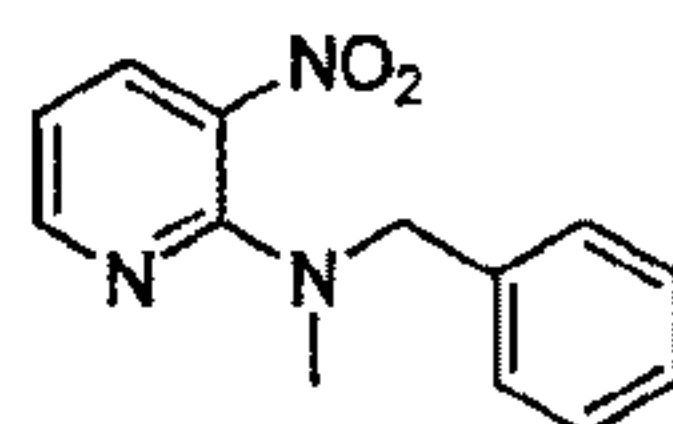
[0343]

Example 86

1-ethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
 25



86a) N-benzyl-N-methyl-3-nitropyridin-2-amine



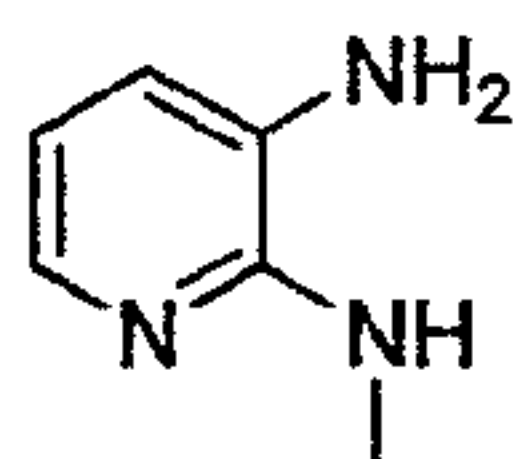
The mixture of 2-chloro-3-nitropyridine (15 g), Na₂CO₃
 30 (10.03 g) and N-methylbenzylamine (24.42 mL) in THF (150 mL)

was stirred at 80°C under a dry atmosphere (CaCl₂ tube) overnight. The mixture was neutralized with 1N HCl at 0°C and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 30% EtOAc in hexane) to give N-benzyl-N-methyl-3-nitropyridin-2-amine (19 g) as yellow oil. MS (API⁺): [M+H]⁺ not detected.

¹H NMR (300 MHz, CDCl₃) δ 2.81 (3H, s), 4.94 (2H, s), 6.59-6.82 (1H, m), 7.21-7.44 (5H, m), 8.09-8.18 (1H, m), 8.27-8.43 (1H, m).

[0344]

86b) N²-methylpyridine-2,3-diamine



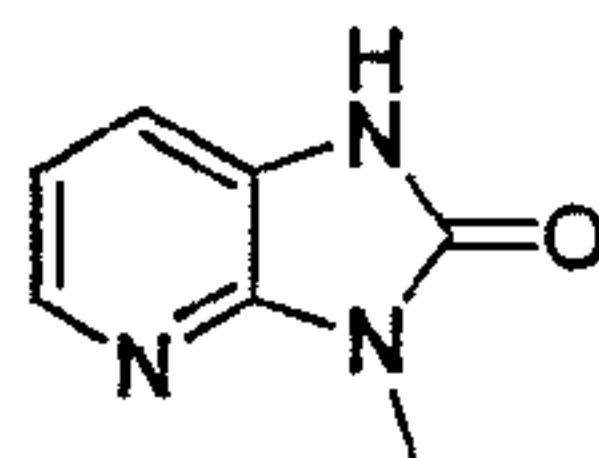
A mixture of N-benzyl-N-methyl-3-nitropyridin-2-amine (15 g) and 10% Pd-C (6.56 g) in EtOH (300 mL) was hydrogenated under balloon pressure at room temperature over weekend. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give N²-methylpyridine-2,3-diamine (7.00 g) as a tan solid.

MS (API⁺): [M+H]⁺ not detected.

¹H NMR (300 MHz, DMSO-d₆) δ 2.81 (3H, d, J = 4.9 Hz), 4.60 (2H, s), 5.56 (1H, q, J = 4.9 Hz), 6.32 (1H, dd, J = 7.2, 4.9 Hz), 6.64 (1H, dd, J = 7.2, 1.7 Hz), 7.37 (1H, dd, J = 4.9, 1.7 Hz).

[0345]

86c) 3-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A solution of N²-methylpyridine-2,3-diamine (7 g) and CDI (13.82 g) in THF (100 mL) was refluxed for 5h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 100%

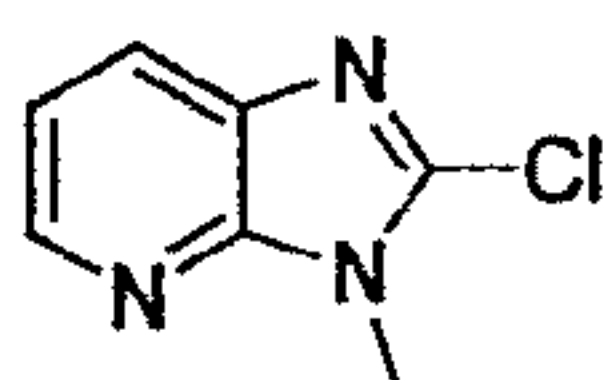
EtOAc in hexane) to give 3-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (7 g) as a light brown solid.

MS (API+): $[M+H]^+$ not detected.

^1H NMR (300 MHz, DMSO- d_6) δ 3.30 (3H, s), 6.96-7.01 (1H, m),
5 7.24-7.34 (1H, m), 7.90-7.98 (1H, m).

[0346]

86d) 2-chloro-3-methyl-3H-imidazo[4,5-b]pyridine



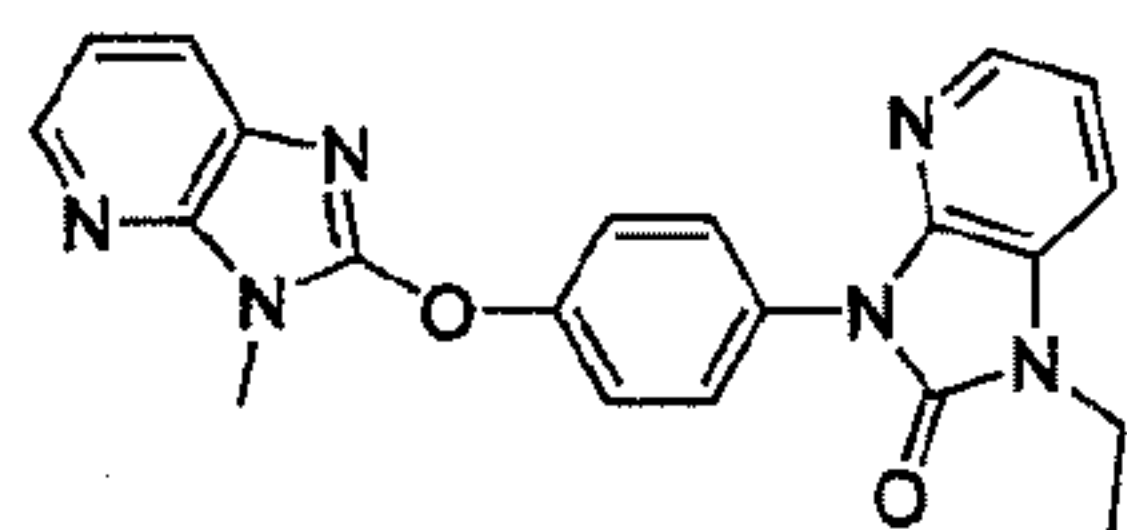
The mixture of 3-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.0 g) in phosphorus oxychloride (10 g) was
10 stirred at 100°C under a dry atmosphere (CaCl_2 tube) for 5h. The mixture was neutralized with sat. NaHCO_3 at 0°C and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO_4 and concentrated in
15 vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 2-chloro-3-methyl-3H-imidazo[4,5-b]pyridine (230 mg) as a white solid.

MS (API+): $[M+H]^+$ 168.0.

20 ^1H NMR (300 MHz, DMSO- d_6) δ 3.80 (3H, s), 7.33 (1H, dd, $J = 8.0, 4.9$ Hz), 8.04 (1H, dd, $J = 8.0, 1.5$ Hz), 8.39 (1H, dd, $J = 4.9, 1.5$ Hz).

[0347]

86e) 1-ethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
25



2-Chloro-3-methyl-3H-imidazo[4,5-b]pyridine (150 mg) was added to a solution of 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (228 mg) and NaH (39.4
30 mg) in DMF (2 mL) at 100°C. The mixture was stirred at 180°C under a dry atmosphere (CaCl_2 tube) for 1h. The mixture was neutralized with 1N HCl at 0°C and extracted with EtOAc. The

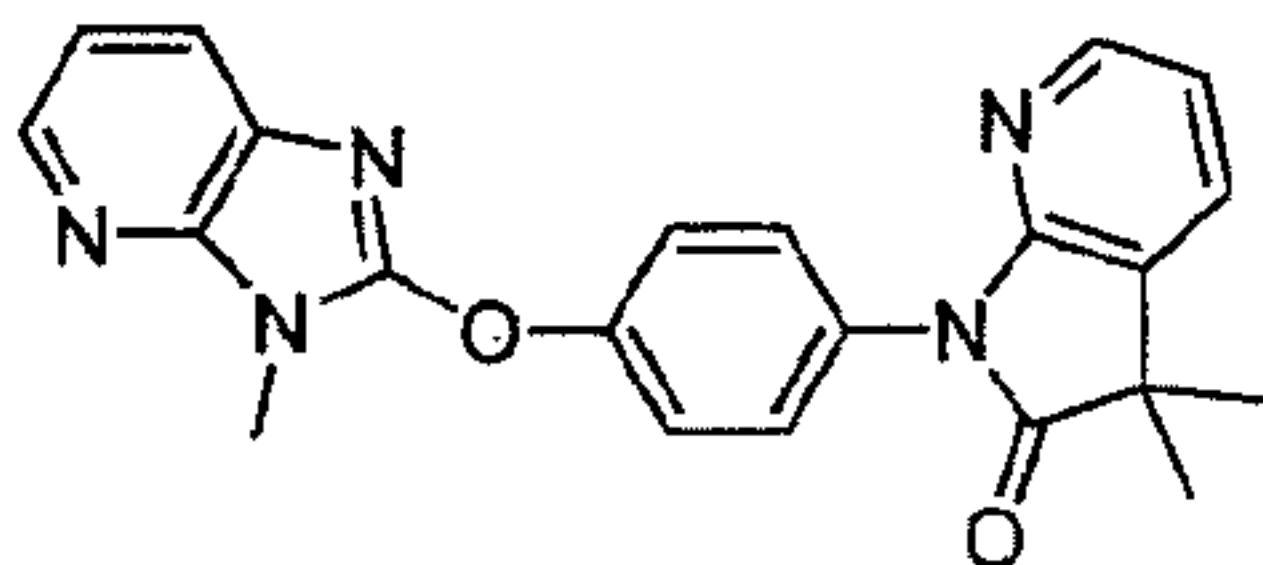
organic layer was separated, washed with water and brine, dried over MgSO_4 and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 100% EtOAc in hexane) to give 1-ethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (200 mg) as white crystals.
 MS (API+): $[\text{M}+\text{H}]^+$ 387.2.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 7.2$ Hz), 3.78 (3H, s), 3.99 (2H, q, $J = 7.2$ Hz), 7.14-7.27 (2H, m), 7.58-7.67 (2H, m), 7.67-7.74 (1H, m), 7.76-7.86 (3H, m), 7.97-8.06 (1H, m), 8.16-8.28 (1H, m).

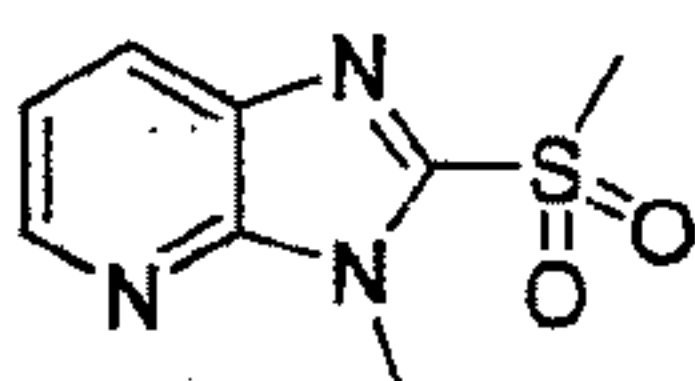
[0348]

Example 96

3,3-dimethyl-1-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one



96a) 3-methyl-2-(methananesulfonyl)-3H-imidazo[4,5-b]pyridine



MeI (44.7 mL) was added to a mixture of K_2CO_3 (148 g) and 1H-imidazo[4,5-b]pyridine-2-thiol (54 g) in DMF (500 mL) at room temperature. The mixture was stirred at room temperature under a dry atmosphere (CaCl_2 tube) overnight. The mixture was poured into water at room temperature and the mixture was extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO_4 and concentrated in vacuo to give 3-methyl-2-(methanesulfanyl)-3H-imidazo[4,5-b]pyridine as a crude product (12 g).

The mixture of 3-methyl-2-(methanesulfanyl)-3H-imidazo[4,5-b]pyridine (12 g) and mCPBA (33.0 g) in EtOAc (200 mL) was stirred at room temperature under a dry atmosphere (CaCl_2 tube) for 3 h. The mixture was neutralized with sat. NaHCO_3 at 0°C and extracted with EtOAc. The organic layer

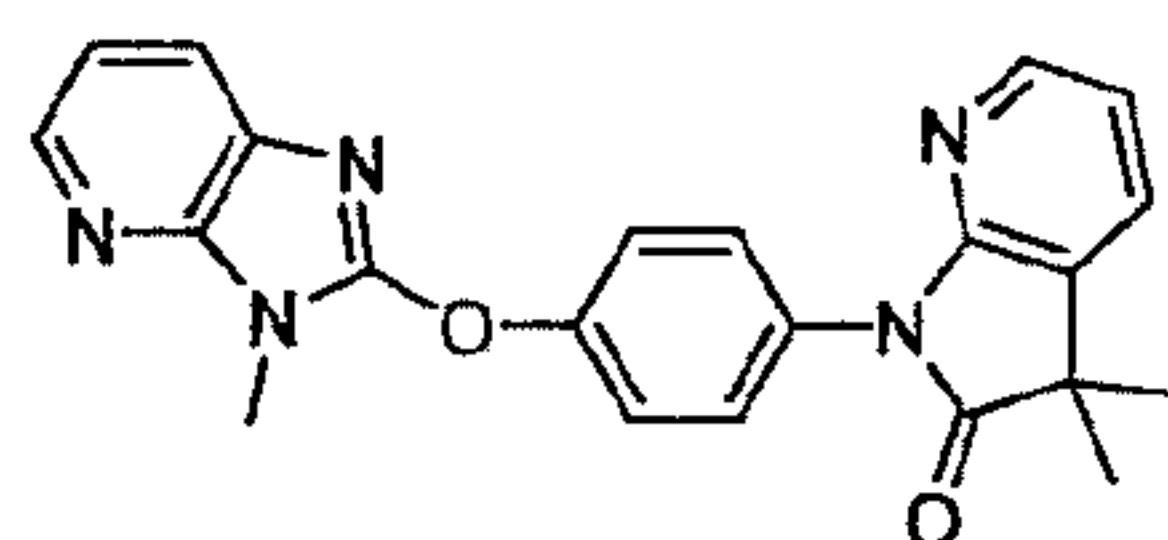
was separated, washed with water and brine, dried over MgSO_4 and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 30% EtOAc in hexane) to give 3-methyl-2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine (10g) as white crystals.

MS (API+): $[\text{M}+\text{H}]^+$ 212.1.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.66 (3H, s), 4.12 (3H, s), 7.43-7.56 (1H, m), 8.25-8.38 (1H, m), 8.56-8.67 (1H, m).

[0349]

96b) 3,3-dimethyl-1-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one



3-Methyl-2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine (90 mg) was added to a solution of 1-(4-hydroxyphenyl)-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (119 mg) and NaH (20.45 mg) in DMF (2 mL) at 100°C. The mixture was heated at 180°C for 30 min under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 3,3-dimethyl-1-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (120 mg) as white crystals.

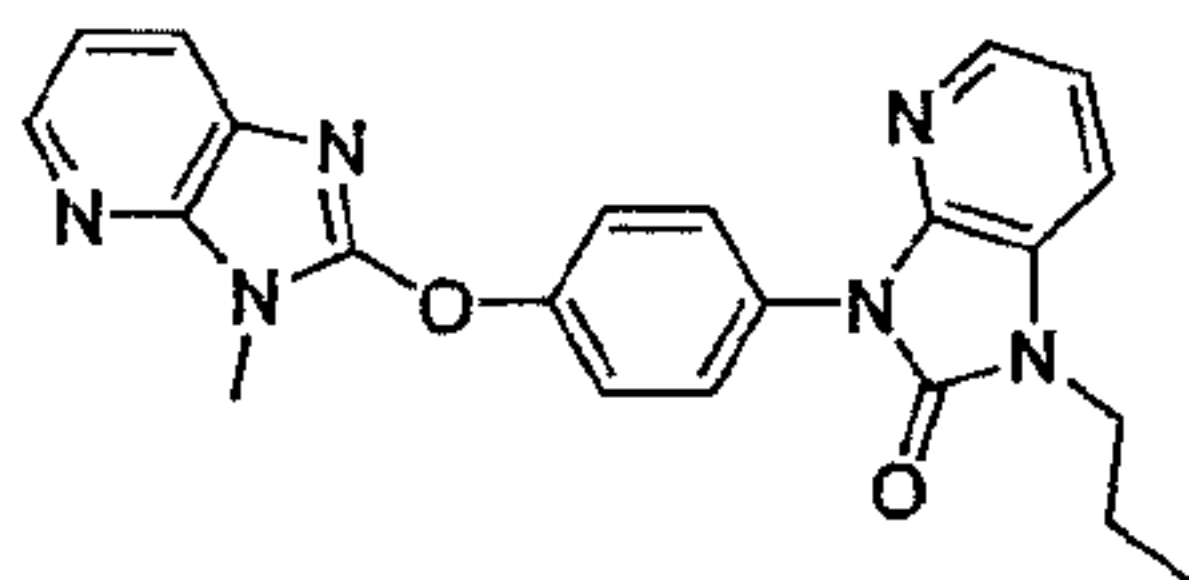
MS (API+): $[\text{M}+\text{H}]^+$ 386.2.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.46 (6H, s), 3.77 (3H, s), 7.09-7.28 (2H, m), 7.55-7.69 (4H, m), 7.75-7.92 (2H, m), 8.13 (1H, m), 8.17-8.28 (1H, m).

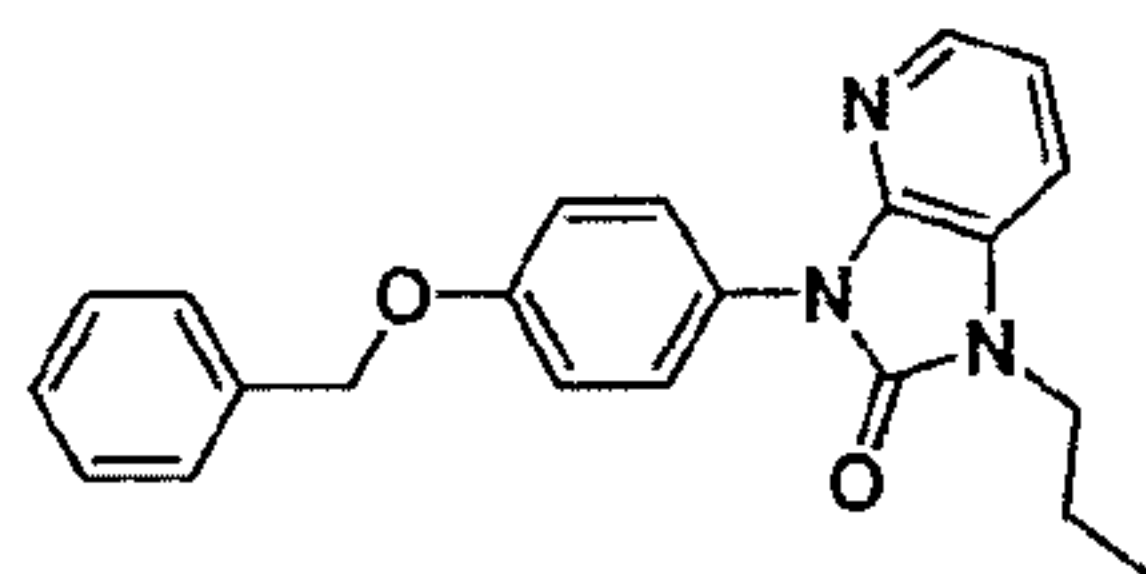
[0350]

Example 97

3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1-propyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



97a) 3-[4-(benzyloxy)phenyl]-1-propyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



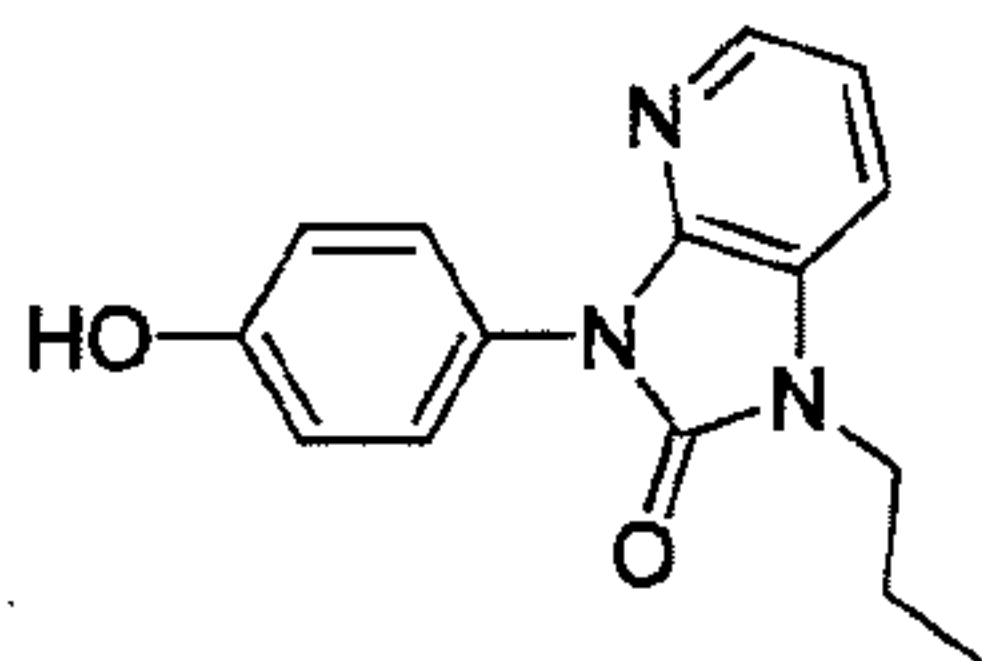
5 NaH (1.260 g) was added to a solution of 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (5 g) and 1-iodopropane (3.07 mL) in DMF (50 mL) at room temperature. The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube) for 1 h. The reaction mixture was
10 diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1-propyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.5 g) as dark yellow oil.

15 MS (API⁺): [M+H]⁺ 360.4.

¹H NMR (300 MHz, DMSO-d₆) δ 0.71-1.12 (3H, m), 1.60-1.88 (2H, m), 3.76-4.02 (2H, m), 5.19 (2H, s), 7.08-7.23 (3H, m), 7.28-7.58 (7H, m), 7.59-7.69 (1H, m), 7.89-8.00 (1H, m).

[0351]

20 97b) 3-(4-hydroxyphenyl)-1-propyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-[4-(benzyloxy)phenyl]-1-propyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.5 g) and 10% Pd-C
25 (0.444 g) in EtOH (40 mL) was hydrogenated under balloon pressure at room temperature for 3h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 3-(4-hydroxyphenyl)-1-propyl-1,3-dihydro-2H-imidazo[4,5-

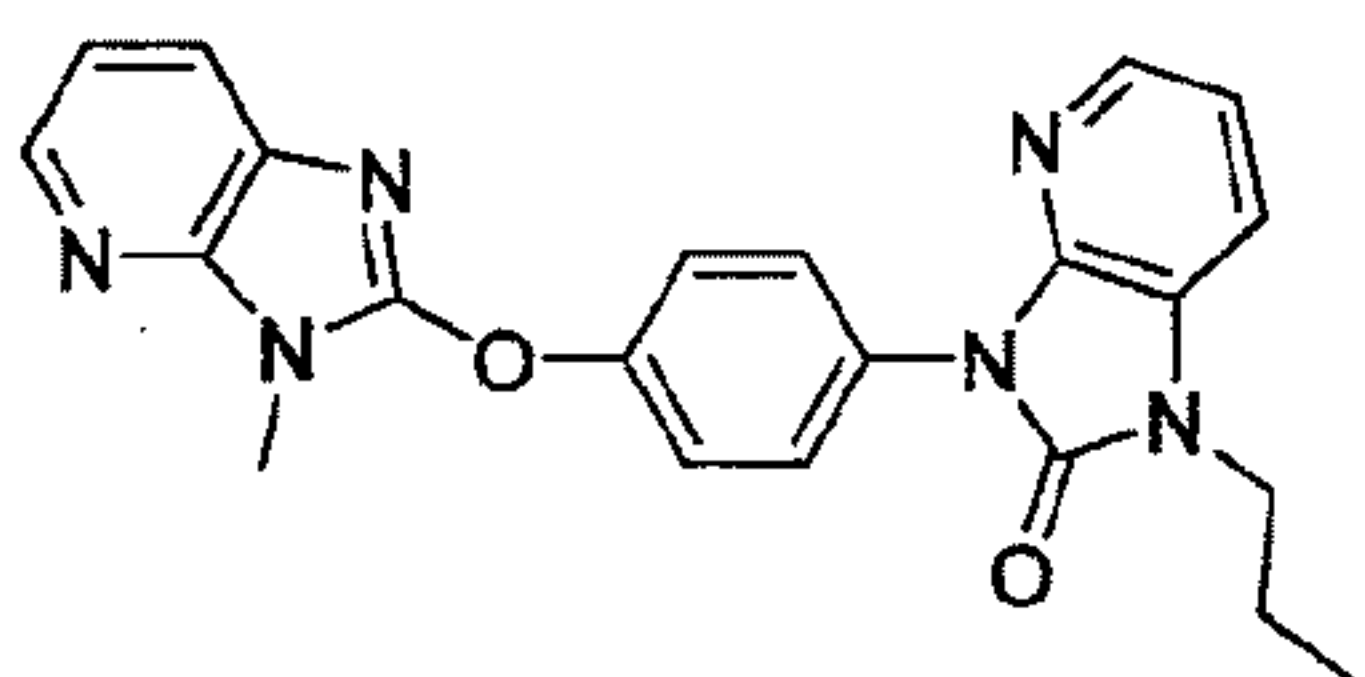
b]pyridin-2-one (1.05 g) as a light brown solid.

MS (API+): $[M+H]^+$ 270.1.

^1H NMR (300 MHz, DMSO- d_6) δ 0.83-0.98 (3H, m), 1.63-1.82 (2H, m), 3.77-3.95 (2H, m), 6.82-6.97 (2H, m), 7.07-7.20 (1H, m),
 5 7.29-7.44 (2H, m), 7.57-7.69 (1H, m), 7.87-8.00 (1H, m), 9.21-10.52 (1H, m).

[0352]

97c) 3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1-propyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-
 10 2-one



3-Methyl-2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine (320 mg) was added to a solution of 3-(4-hydroxyphenyl)-1-propyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (400 mg) and
 15 NaH (65.3 mg) in DMF (5 mL) at 100°C. The mixture was heated at 180°C for 30 min under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 3-{4-[(3-methyl-
 20 3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1-propyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (300 mg) as white crystals.

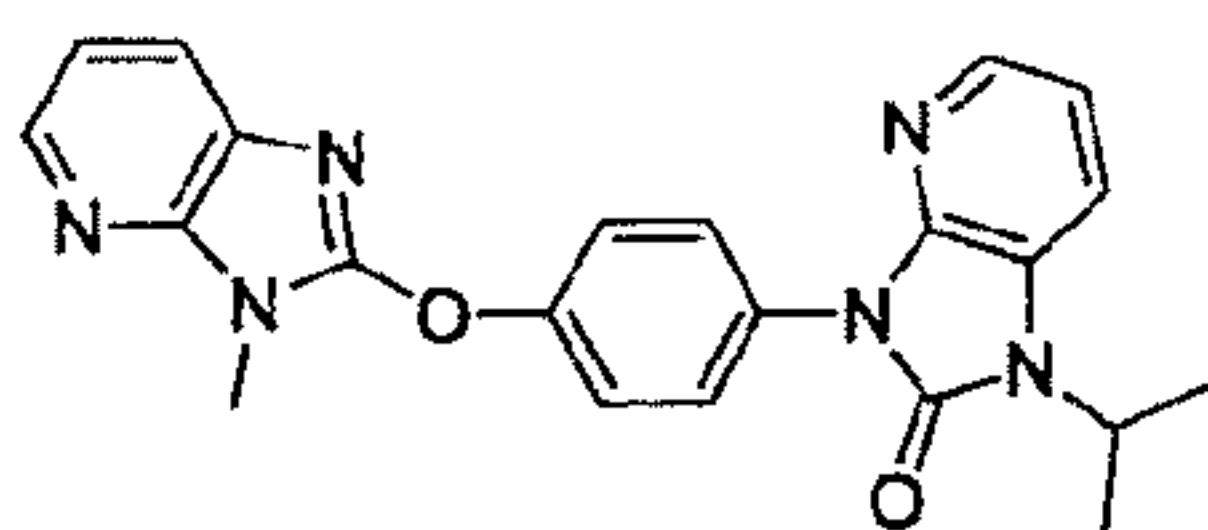
MS (API+): $[M+H]^+$ 401.2.

^1H NMR (300 MHz, DMSO- d_6) δ 0.88-1.00 (3H, m), 1.68-1.86 (2H, m), 3.78 (3H, s), 3.86-3.97 (2H, m), 7.13-7.29 (2H, m), 7.59-
 25 7.66 (2H, m), 7.67-7.73 (1H, m), 7.74-7.86 (3H, m), 7.95-8.06 (1H, m), 8.14-8.29 (1H, m).

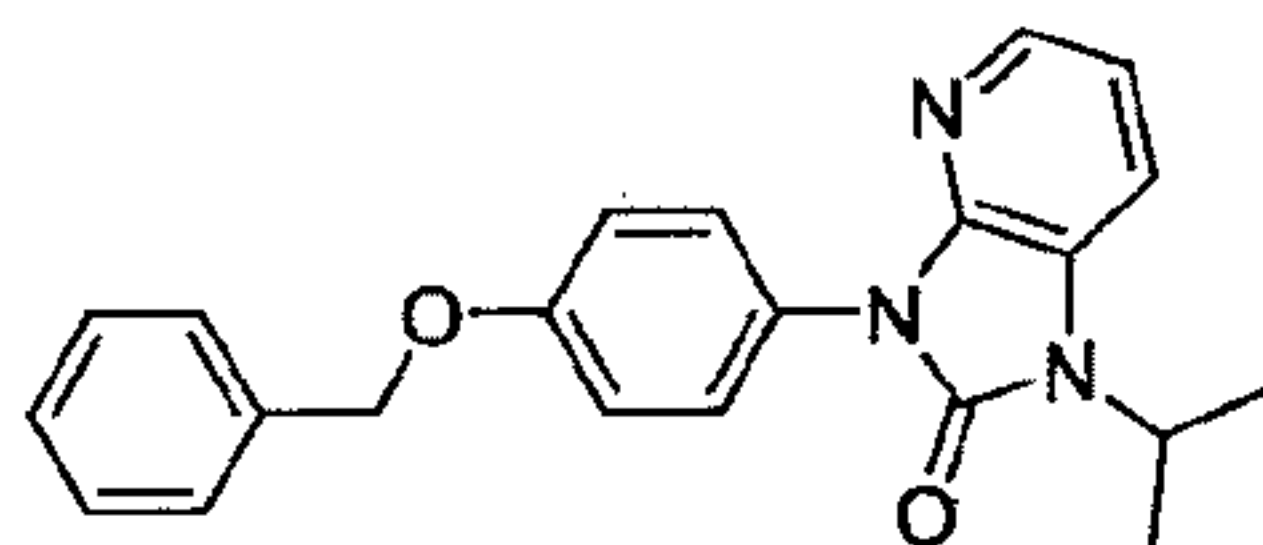
[0353]

Example 98

30 1-(1-methylethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



98a) 3-[4-(benzyloxy)phenyl]-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



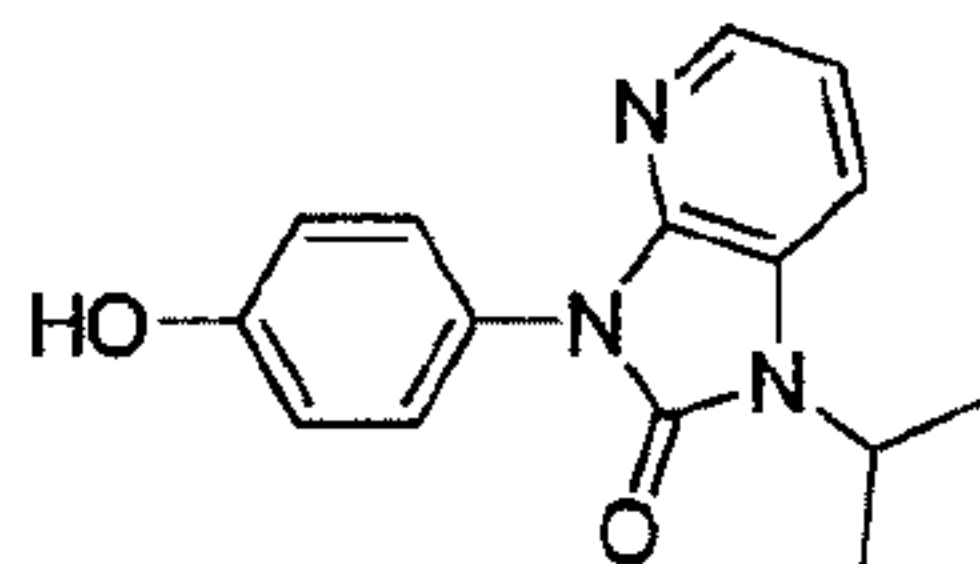
5 NaH (1.260 g) was added to a solution of 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (5 g) and 2-iodopropane (3.15 mL) in DMF (50 mL) at room temperature. The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube) for 1h. The reaction mixture was
10 diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.5 g) as dark yellow oil.

15 MS (API+): [M+H]⁺ 360.4.

¹H NMR (300 MHz, DMSO-d₆) δ 1.50 (6H, d, J = 7.2 Hz), 4.64-4.80 (1H, m), 5.19 (2H, s), 7.05-7.24 (3H, m), 7.28-7.59 (7H, m), 7.70-7.79 (1H, m), 7.87-8.00 (1H, m).

[0354]

20 98b) 3-(4-hydroxyphenyl)-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



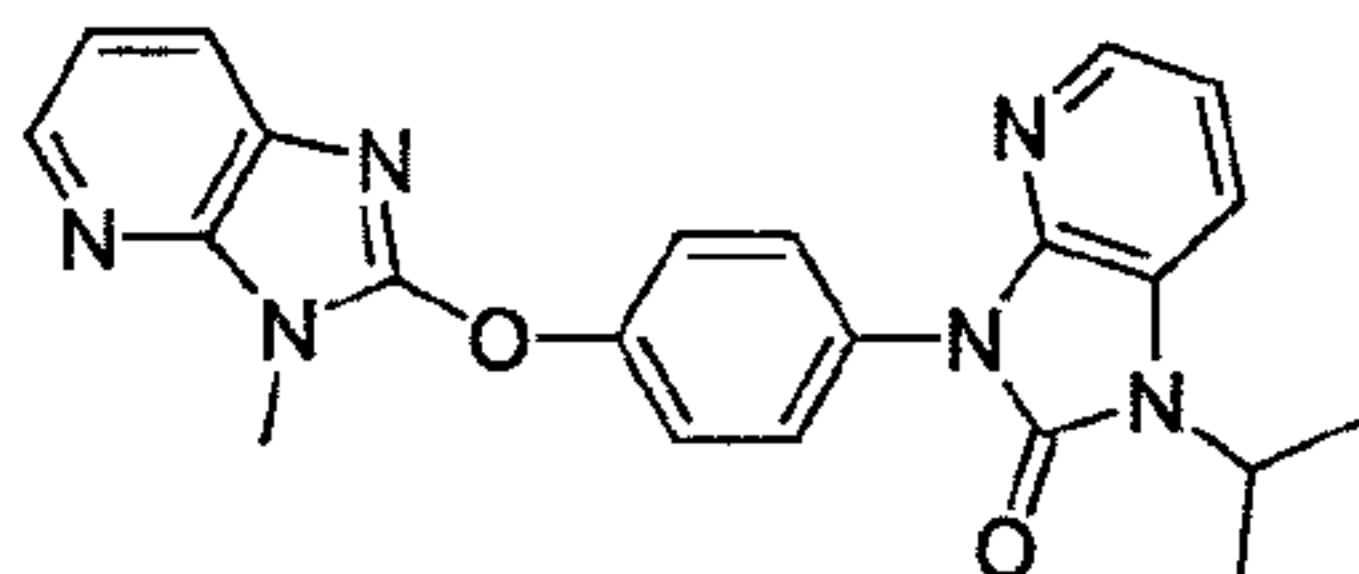
A mixture of 3-[4-(benzyloxy)phenyl]-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1.5g) and 10% Pd-C
25 (0.444 g) in EtOH (40 mL) was hydrogenated under balloon pressure at room temperature for 5 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 3-(4-hydroxyphenyl)-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (670 mg) as a light brown solid.

MS (API+): $[M+H]^+$ 270.1.

^1H NMR (300 MHz, DMSO- d_6) δ 1.40-1.59 (6H, m), 4.62-4.80 (1H, m), 6.81-6.94 (2H, m), 7.04-7.19 (1H, m), 7.29-7.42 (2H, m), 7.63-7.81 (1H, m), 7.87-8.02 (1H, m), 9.52-9.91 (1H, m).

5 [0355]

98c) 1-(1-methylethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



10 3-Methyl-2-(methanesulfonyl)-3H-imidazo[4,5-b]pyridine (270 mg) was added to a solution of 3-(4-hydroxyphenyl)-1-(1-methylethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (330 mg) and NaH (53.9 mg) in DMF (5 mL) at 100°C. The mixture was heated at 180°C for 30 min under microwave irradiation. The
15 reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-(1-methylethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (150
20 mg) as white crystals.

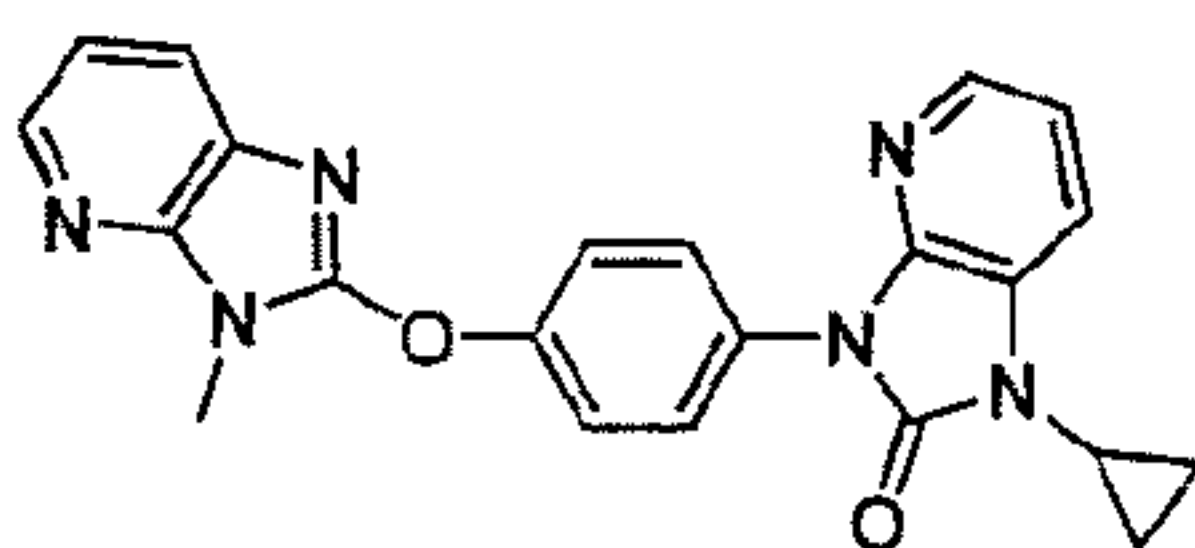
MS (API+): $[M+H]^+$ 401.2.

^1H NMR (300 MHz, DMSO- d_6) δ 1.43-1.67 (6H, m), 3.81 (3H, s), 4.64-4.91 (1H, m), 7.08-7.31 (2H, m), 7.54-7.70 (2H, m), 7.70-7.89 (4H, m), 7.93-8.07 (1H, m), 8.18-8.28 (1H, m).

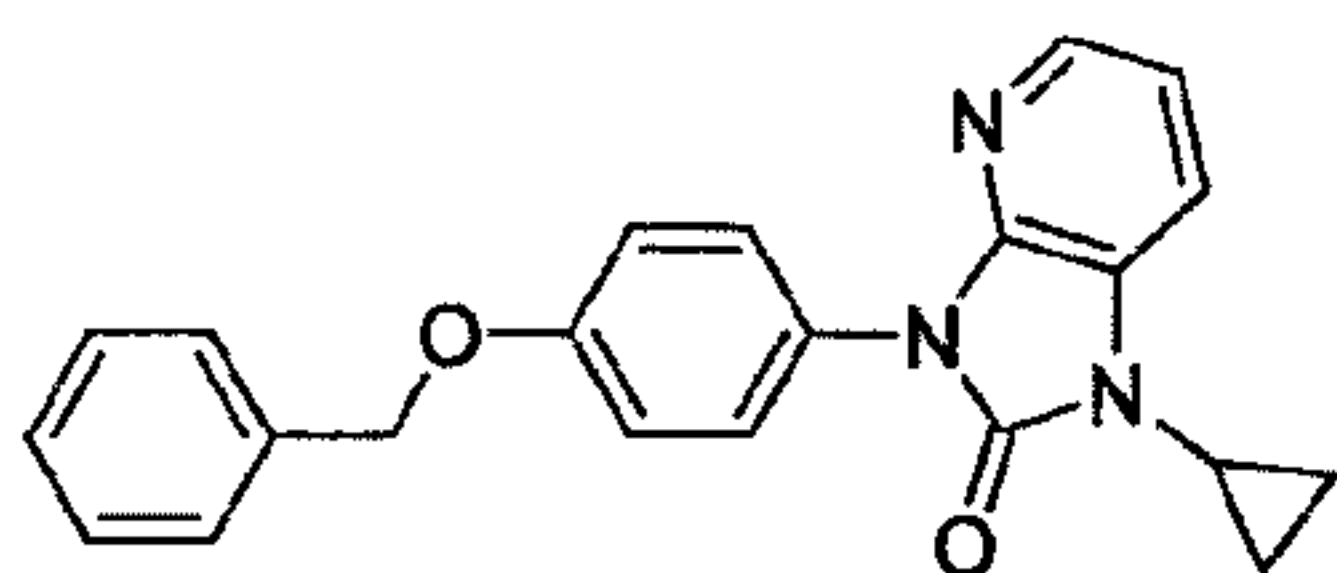
25 [0356]

Example 99

1-cyclopropyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



30 99a) 3-[4-(benzyloxy)phenyl]-1-cyclopropyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



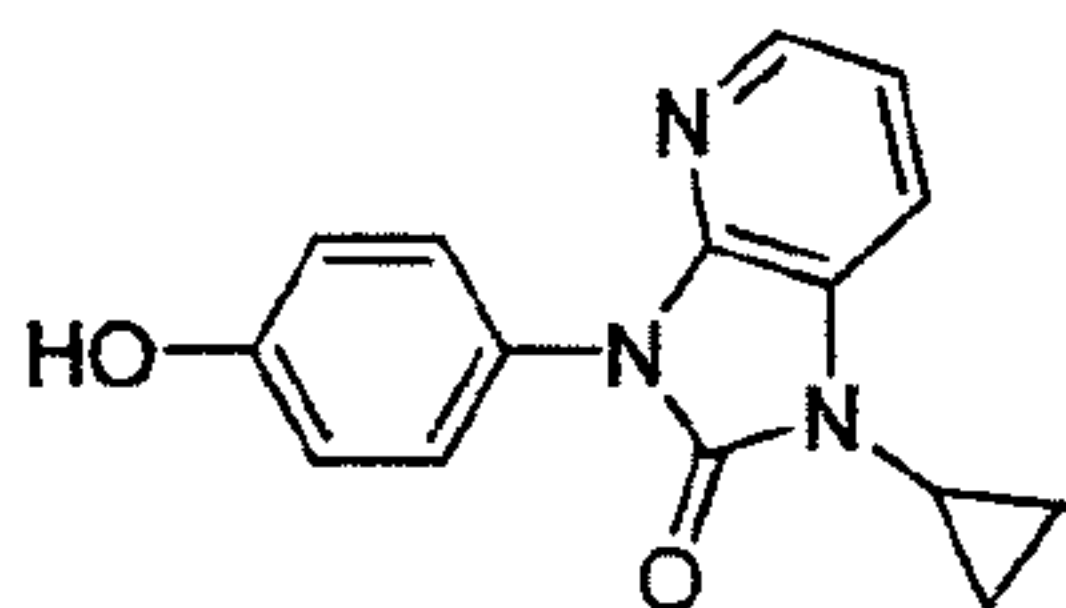
The mixture of 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (300 mg), cyclopropylboronic acid (731 mg), TEA (1976 μ l), pyridine (1835 μ l), copper(II) acetate (1030 mg) and THF (4727 μ l) was heated at 140°C for 30 min under microwave irradiation. The solid was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 30% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1-cyclopropyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (120 mg) as white crystals.

MS (API+): $[M+H]^+$ 358.1.

^1H NMR (300 MHz, DMSO- d_6) δ 0.91-1.01 (2H, m), 1.01-1.11 (2H, m), 2.92-3.07 (1H, m), 5.18 (2H, s), 7.08-7.21 (3H, m), 7.30-7.46 (3H, m), 7.45-7.53 (4H, m), 7.53-7.62 (1H, m), 7.89-8.00 (1H, m).

[0357]

99b) 1-cyclopropyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-[4-(benzyloxy)phenyl]-1-cyclopropyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (120 mg) and 10% Pd-C (17.87 mg) in EtOH (10 mL) was hydrogenated under balloon pressure at room temperature for 2h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 1-cyclopropyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (89 mg) as a white solid.

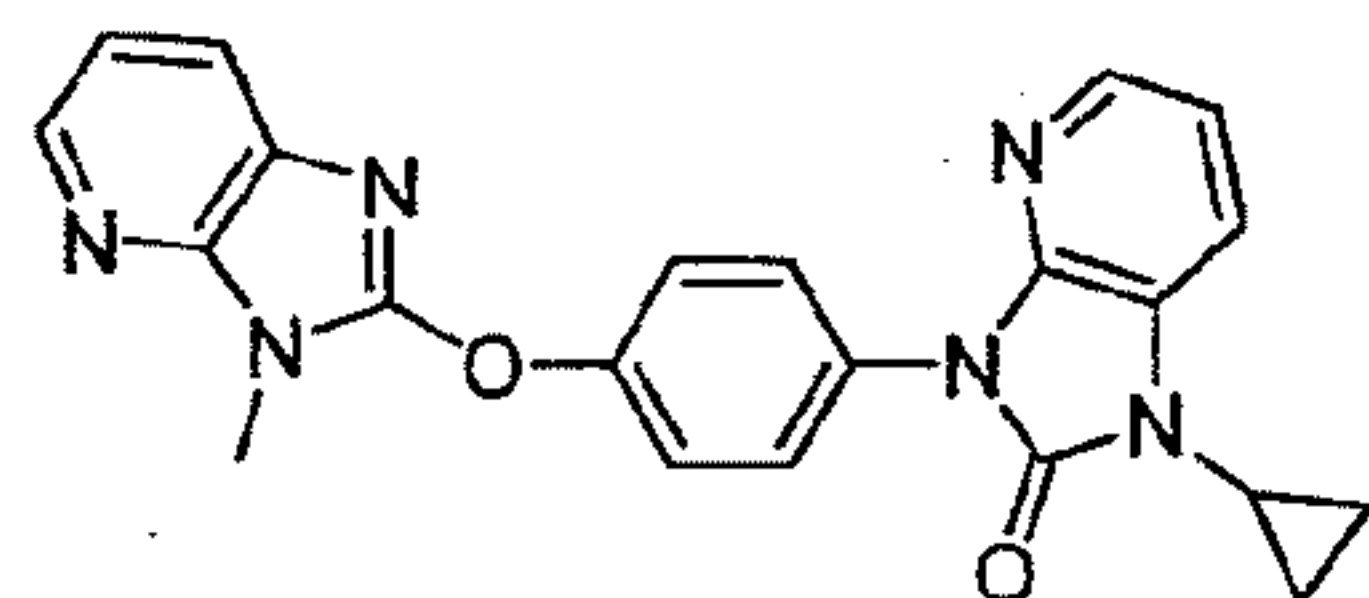
MS (API+): $[M+H]^+$ 268.1.

^1H NMR (300 MHz, DMSO- d_6) δ 0.89-1.00 (2H, m), 1.01-1.11 (2H, m), 2.92-3.07 (1H, m), 6.83-6.95 (2H, m), 7.07-7.20 (1H, m), 7.28-7.40 (2H, m), 7.50-7.62 (1H, m), 7.87-8.00 (1H, m), 9.76

(1H, brs).

[0358]

99c) 1-cyclopropyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



5

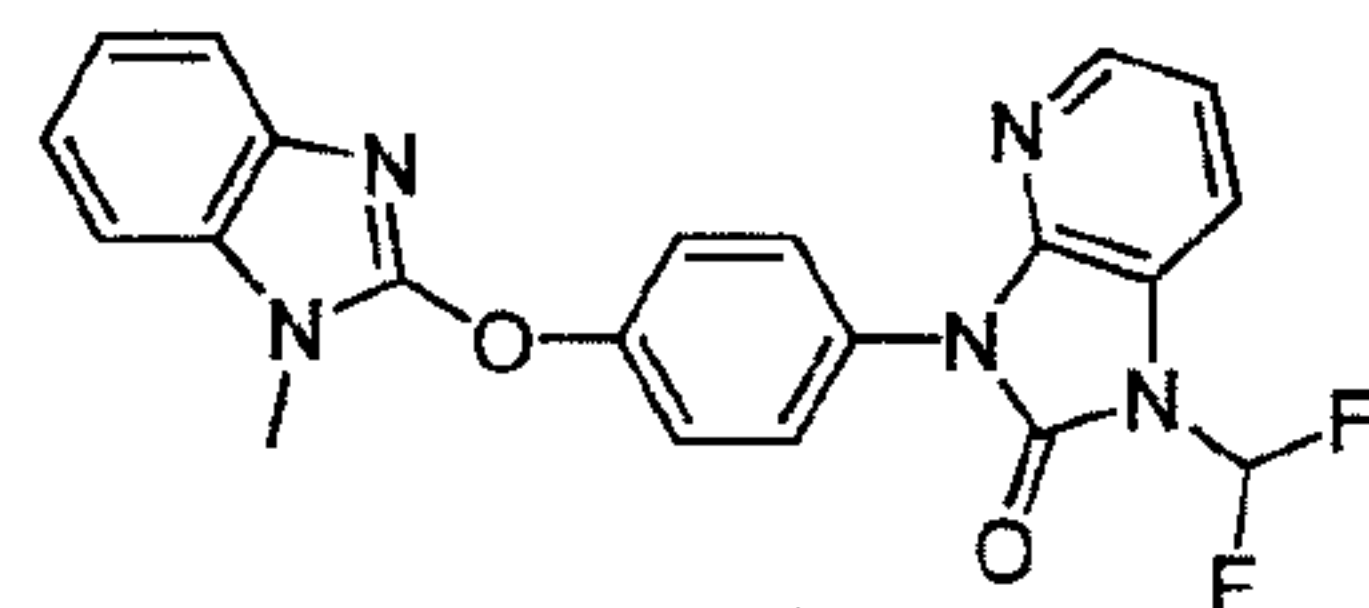
3-Methyl-2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine (79 mg) was added to a solution of 1-cyclopropyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (100 mg) and NaH (17.96 mg) in DMF (2 mL) at 100°C. The mixture was heated at 180°C for 1h under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-cyclopropyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (80 mg) as white crystals.

MS (API+): [M+H]⁺ 399.2.
¹H NMR (300 MHz, DMSO-d₆) δ 0.94-1.03 (2H, m), 1.03-1.13 (2H, m), 2.93-3.10 (1H, m), 3.78 (3H, s), 7.16-7.27 (2H, m), 7.58-7.67 (3H, m), 7.70-7.87 (3H, m), 7.94-8.06 (1H, m), 8.15-8.27 (1H, m).

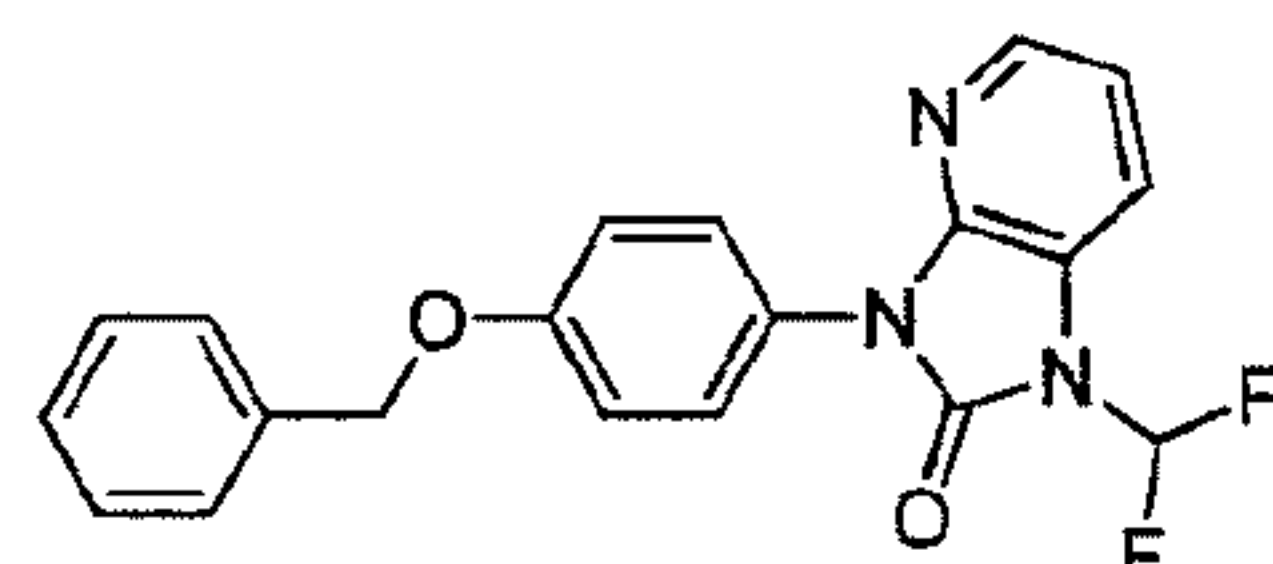
[0359]

Example 100

1-(difluoromethyl)-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



100a) 3-[4-(benzyloxy)phenyl]-1-(difluoromethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



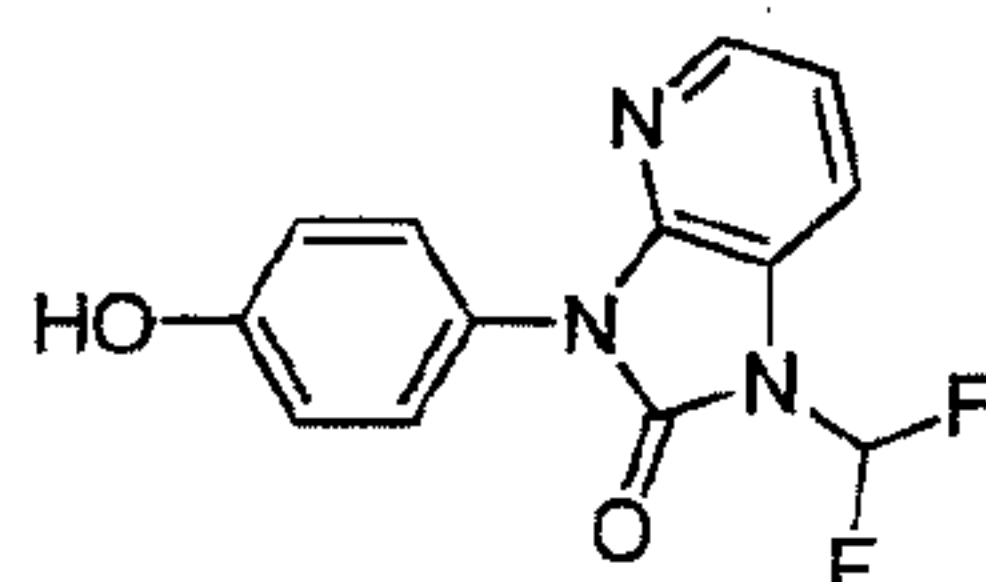
Difluorochloroacetic acid sodium salt (1.922 g) was added to a solution of 3-[4-(benzyloxy)phenyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2 g), lithium bromide (1.095 g) and NaH (0.290 g) in DMF (20 mL) at 0°C. The mixture was stirred
 5 at 140°C under a dry atmosphere (CaCl₂ tube) for 1h. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 30% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1-(difluoromethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (420 mg) as a white solid.

MS (API+): [M+H]⁺ 368.1.

¹H NMR (300 MHz, DMSO-d₆) δ 5.20 (2H, s), 6.99-8.28 (13H, m).

[0360]

100b) 1-(difluoromethyl)-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
 15



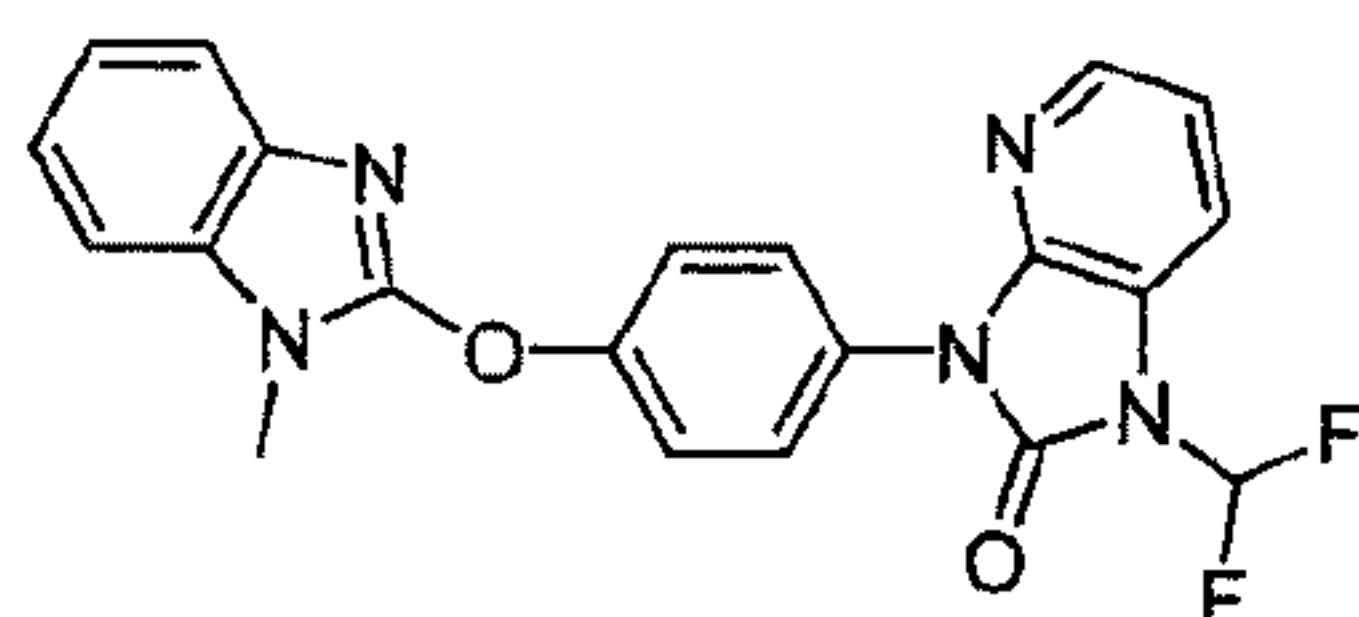
A mixture of 3-[4-(benzyloxy)phenyl]-1-(difluoromethyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (420 mg) and 10% Pd-C (60.8 mg) in EtOH (50 mL) was hydrogenated under balloon
 20 pressure at room temperature for 3h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 1-(difluoromethyl)-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (300 mg) as a white solid.

MS (API+): [M+H]⁺ 278.1.

25 ¹H NMR (300 MHz, DMSO-d₆) δ 6.85-6.98 (2H, m), 7.16-7.29 (1H, m), 7.32-7.45 (2H, m), 7.60-8.04 (2H, m), 8.05-8.16 (1H, m), 9.82 (1H, s).

[0361]

100c) 1-(difluoromethyl)-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
 30



2-Chloro-1-methyl-1H-benzimidazole (70 mg) was added to a solution of 1-(difluoromethyl)-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (122 mg) and NaH (25.2 mg) in DMF (3 mL) at 100°C. The mixture was heated at 180°C for 1h under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-(difluoromethyl)-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (80 mg) as white crystals.

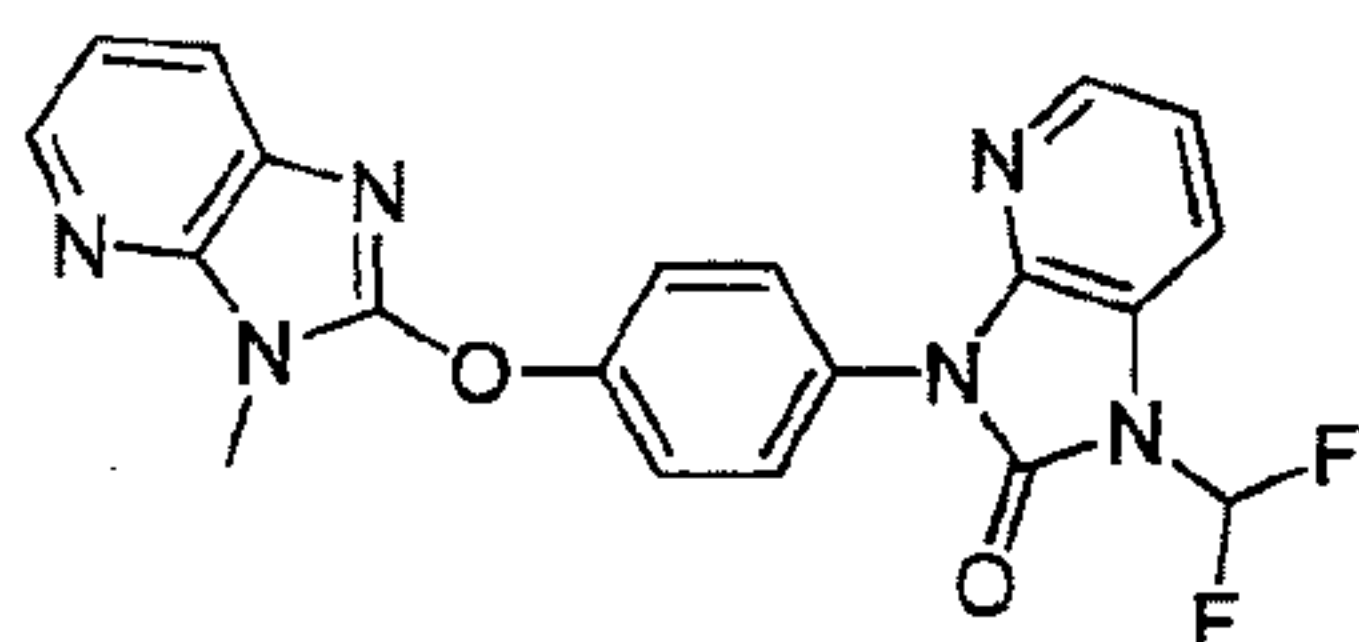
MS (API+): $[M+H]^+$ 408.1.

^1H NMR (300 MHz, DMSO- d_6) δ 3.77 (3H, s), 7.08-7.34 (3H, m), 7.37-7.54 (2H, m), 7.57-7.67 (2H, m), 7.66-8.09 (4H, m), 8.12-8.19 (1H, m).

[0362]

Example 101

1-(difluoromethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



3-Methyl-2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine (90 mg) was added to a solution of 1-(difluoromethyl)-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (124 mg) and NaH (25.6 mg) in DMF (3 mL) at 100°C. The mixture was heated at 180°C for 1h under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-(difluoromethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (50 mg) as white crystals.

MS (API+): $[M+H]^+$ 409.1.

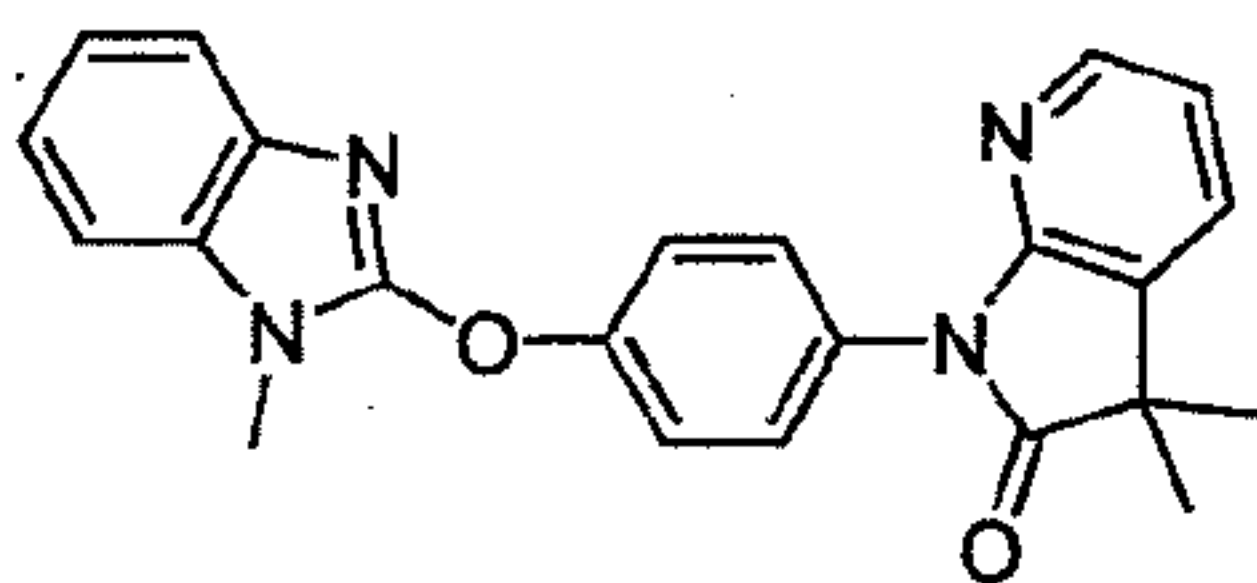
^1H NMR (300 MHz, DMSO- d_6) δ 3.78 (3H, s), 7.07-7.37 (2H, m),

7.54-8.37 (9H, m).

[0363]

Example 102

3,3-dimethyl-1-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-
5 1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one



NaH (17.28 mg) was added to a solution of 1-[4-(1H-benzimidazol-2-yloxy)phenyl]-3,3-dimethyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (40 mg) and MeI (10.13 μ l) in
10 DMF (1 mL) at room temperature. The mixture was stirred at room temperature under a dry atmosphere (CaCl_2 tube) for 1h. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 3,3-
15 dimethyl-1-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (35 mg) as white crystals.

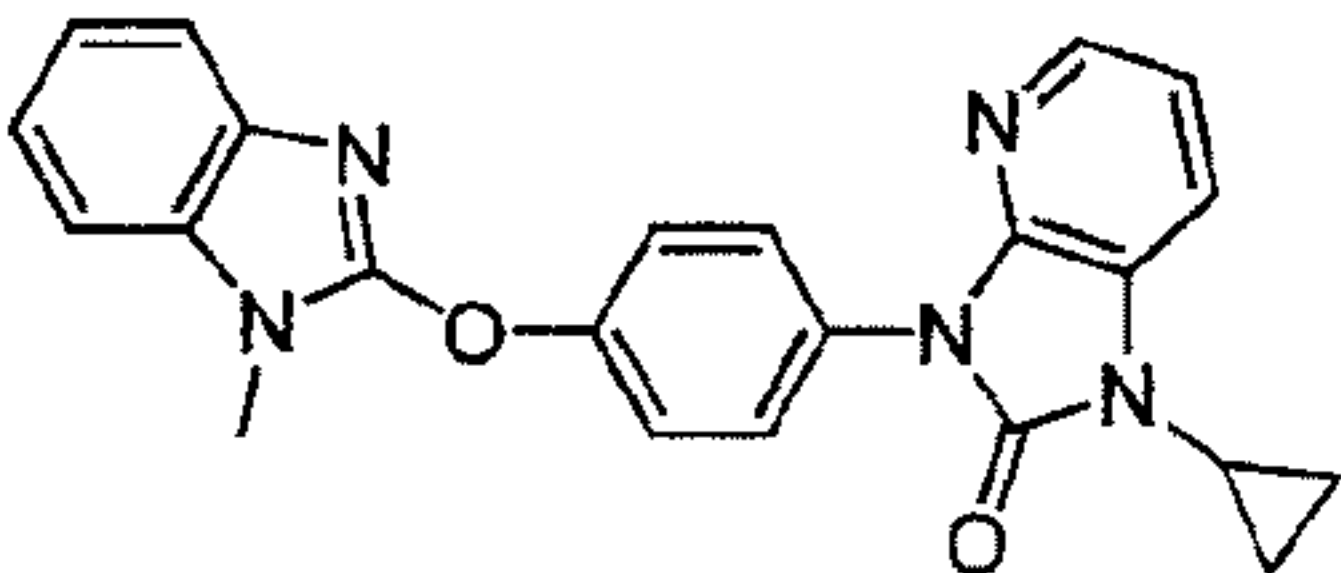
MS (API+): $[M+H]^+$ 385.2.

^1H NMR (300 MHz, DMSO-d_6) δ 1.45 (6H, s), 3.76 (3H, s), 7.09-
20 7.25 (3H, m), 7.37-7.52 (2H, m), 7.53-7.66 (4H, m), 7.80-7.93 (1H, m), 8.06-8.20 (1H, m).

[0364]

Example 103

1-cyclopropyl-3-{4-[(1-methyl-1H-benzimidazol-2-
25 yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



2-Chloro-1-methyl-1H-benzimidazole (15 mg) was added to a solution of 1-cyclopropyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (24.06 mg) and NaH (5.40 mg) in
30 DMF (1 mL) at 100°C. The mixture was heated at 180°C for 1 h under microwave irradiation. The reaction mixture was diluted

with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-cyclopropyl-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (5.0 mg) as white crystals.

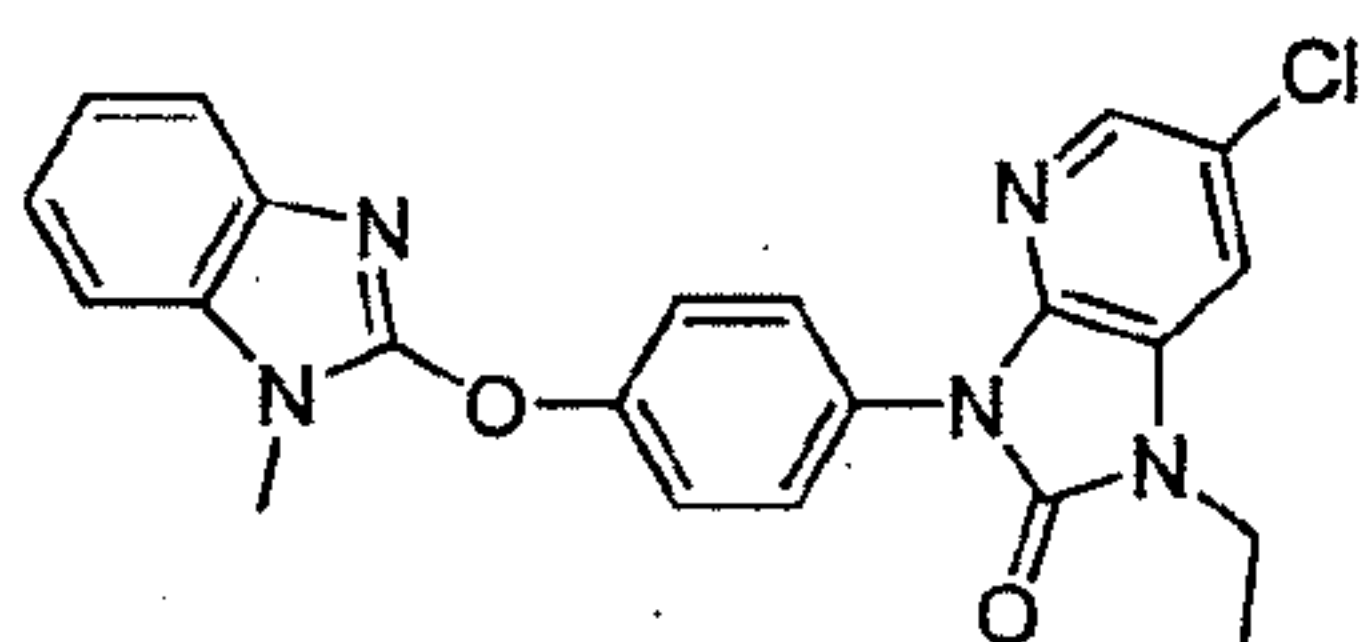
MS (API+): $[M+H]^+$ 398.2.

^1H NMR (300 MHz, DMSO- d_6) δ 0.94-1.04 (2H, m), 1.04-1.13 (2H, m), 2.96-3.08 (1H, m), 3.77 (3H, s), 7.10-7.29 (3H, m), 7.38-7.51 (2H, m), 7.54-7.67 (3H, m), 7.67-7.79 (2H, m), 7.95-8.06 (1H, m).

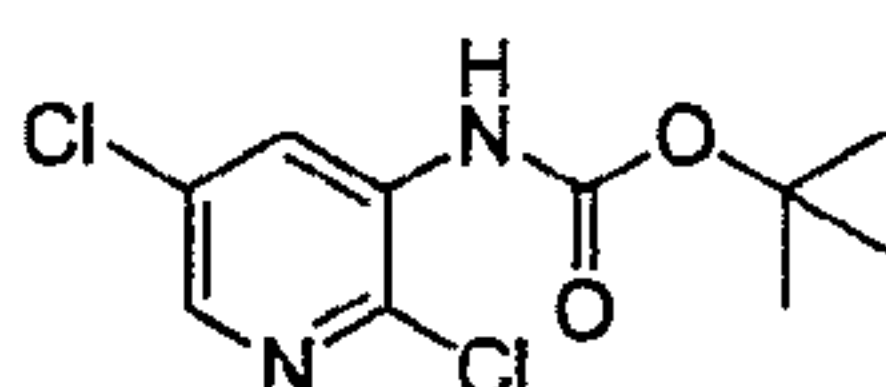
[0365]

Example 106

6-chloro-1-ethyl-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



106a) tert-butyl (2,5-dichloropyridin-3-yl)carbamate



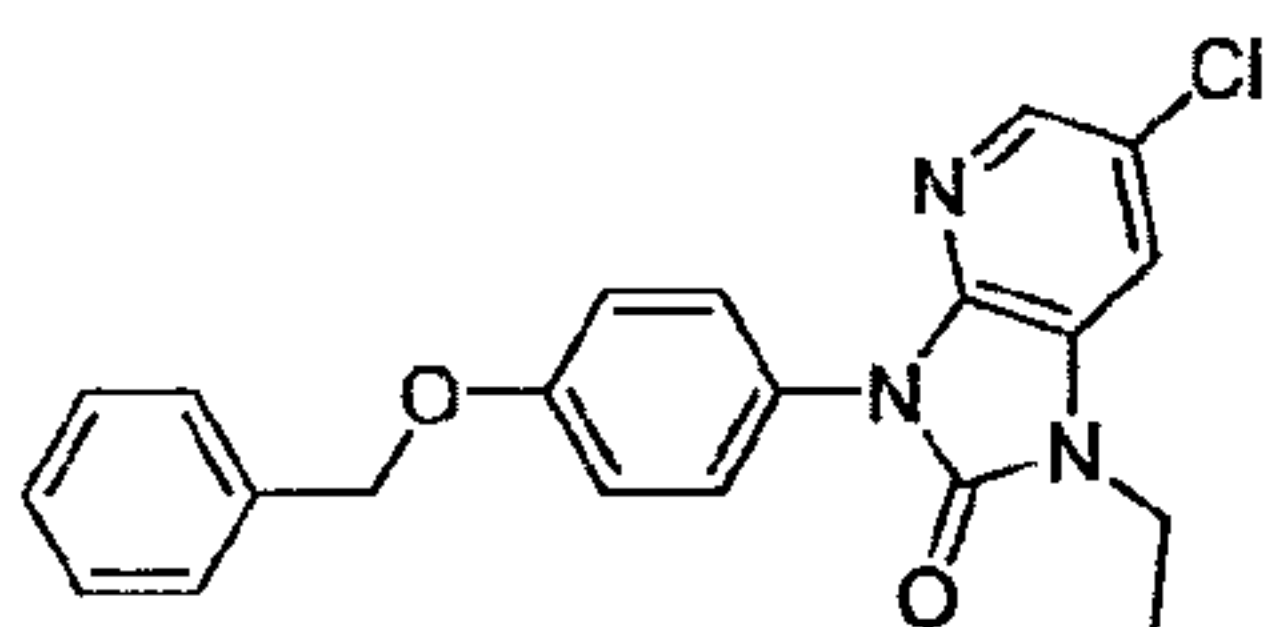
Boc₂O (17.05 mL) was added to a solution of 2,5-dichloropyridin-3-amine (11.4 g) and NaHMDS (1.9M, 81 mL) in THF (200 mL) at 0°C. The mixture was stirred at 0°C under a dry atmosphere (CaCl₂ tube) for 1h. The mixture was neutralized with 1N HCl at 0°C and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 20% EtOAc in hexane) to give tert-butyl (2,5-dichloropyridin-3-yl)carbamate (15.6 g) as colorless oil.

MS (API+): $[M+H]^+$ not detected.

^1H NMR (300 MHz, DMSO- d_6) δ 1.48 (9H, s), 8.20-8.23 (1H, m), 8.23-8.26 (1H, m), 9.07-9.11 (1H, m).

[0366]

106b) 3-[4-(benzyloxy)phenyl]-6-chloro-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



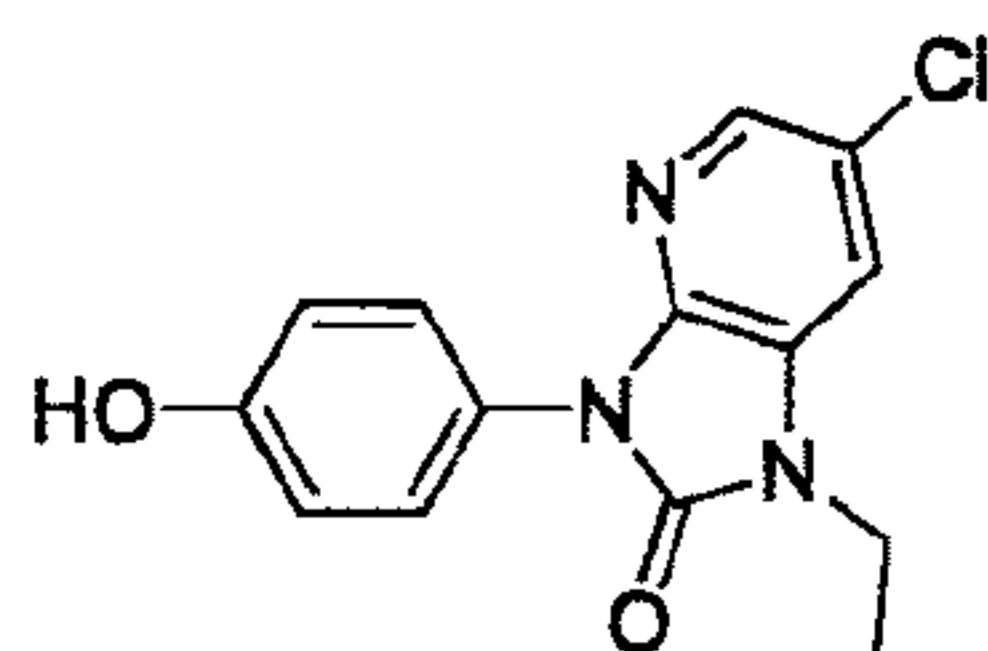
The mixture of tert-butyl (2,5-dichloropyridin-3-yl)carbamate (7.0 g), 4-(benzyloxy)aniline (7.95 g), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (1.231 g), Pd₂(dba)₃ (0.974 g) and sodium tert-butoxide (3.58 g) in toluene (160 mL) - 2-propanol (40.0 mL) was stirred at 100°C under Ar overnight. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 100% EtOAc in hexane) to give intermediate. To the intermediate in DMF (100 mL) were added NaH (3.19 g) and ethyl iodide (20.75 g). The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube) for 1h. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-6-chloro-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (2 g) as a colorless solid.

MS (API+): [M+H]⁺ 380.2.

¹H NMR (300 MHz, DMSO-d₆) δ 1.21-1.36 (3H, m), 3.88-4.02 (2H, m), 5.18 (2H, s), 7.10-7.21 (2H, m), 7.29-7.56 (7H, m), 7.85-7.93 (1H, m), 7.94-8.00 (1H, m).

[0367]

106c) 6-chloro-1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



A mixture of 3-[4-(benzyloxy)phenyl]-6-chloro-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (500 mg) and 10%

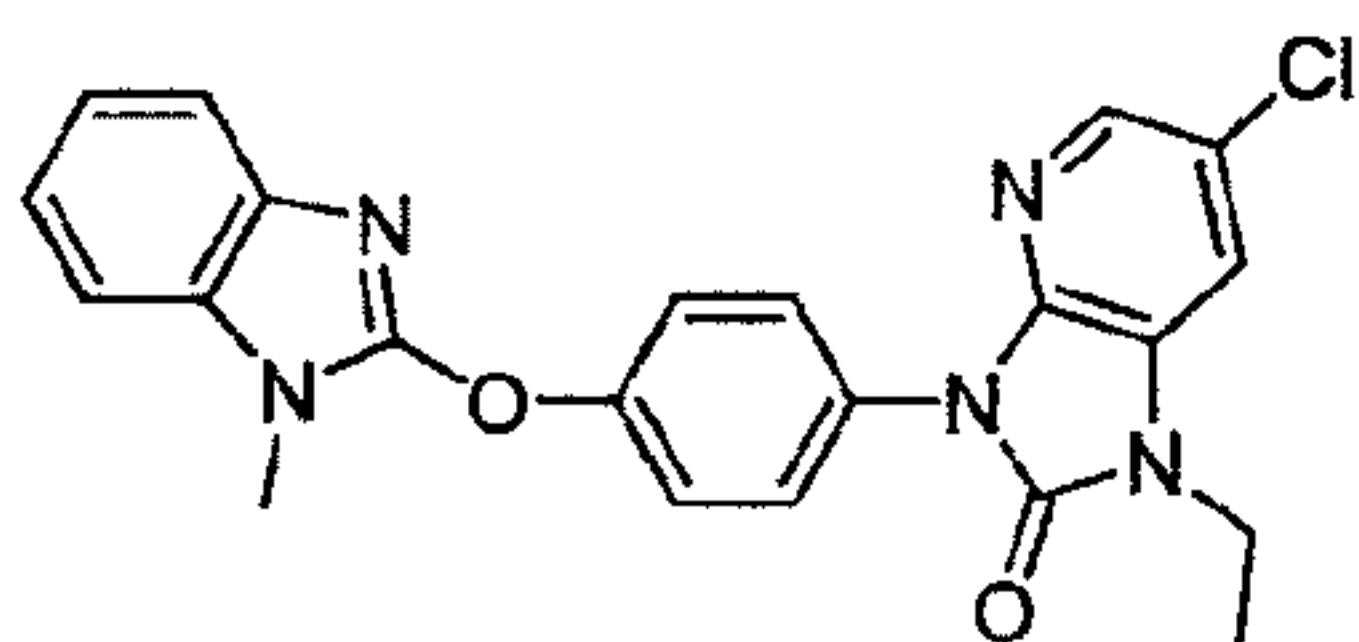
Pd-C (140 mg) in EtOAc (10 mL) was hydrogenated under balloon pressure at room temperature for 3h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel,
 5 eluted with 0% - 50% EtOAc in hexane) to give 6-chloro-1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (70 mg) as a white solid.

MS (API+): [M+H]⁺ 290.1.

¹H NMR (300 MHz, DMSO-d₆) δ 1.22-1.32 (3H, m), 3.86-4.01 (2H, m),
 10 6.83-6.96 (2H, m), 7.26-7.46 (2H, m), 7.84-7.94 (1H, m), 7.92-8.04 (1H, m), 9.74 (1H, s).

[0368]

106d) 6-chloro-1-ethyl-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



15

2-Chloro-1-methyl-1H-benzimidazole (50 mg) was added to a solution of 6-chloro-1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (90 mg) and NaH (13.2 mg) in DMF (2 mL) at room temperature. The mixture was heated at 180°C
 20 for 30 min under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 6-chloro-1-ethyl-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (100 mg) as colorless crystals.
 25

MS (API+): [M+H]⁺ 420.1.

¹H NMR (300 MHz, DMSO-d₆) δ 1.25-1.34 (3H, m), 3.76 (3H, s),
 3.92-4.04 (2H, m), 7.09-7.29 (2H, m), 7.37-7.52 (2H, m), 7.54-7.65 (2H, m), 7.69-7.81 (2H, m), 7.93-7.99 (1H, m), 7.99-8.07
 30 (1H, m).

Anal. Calcd for

C₂₂H₁₈N₅O₂Cl: C, 62.93; H, 4.32; N, 16.68; Cl, 8.44. Found: C, 62.74; H, 4.38;

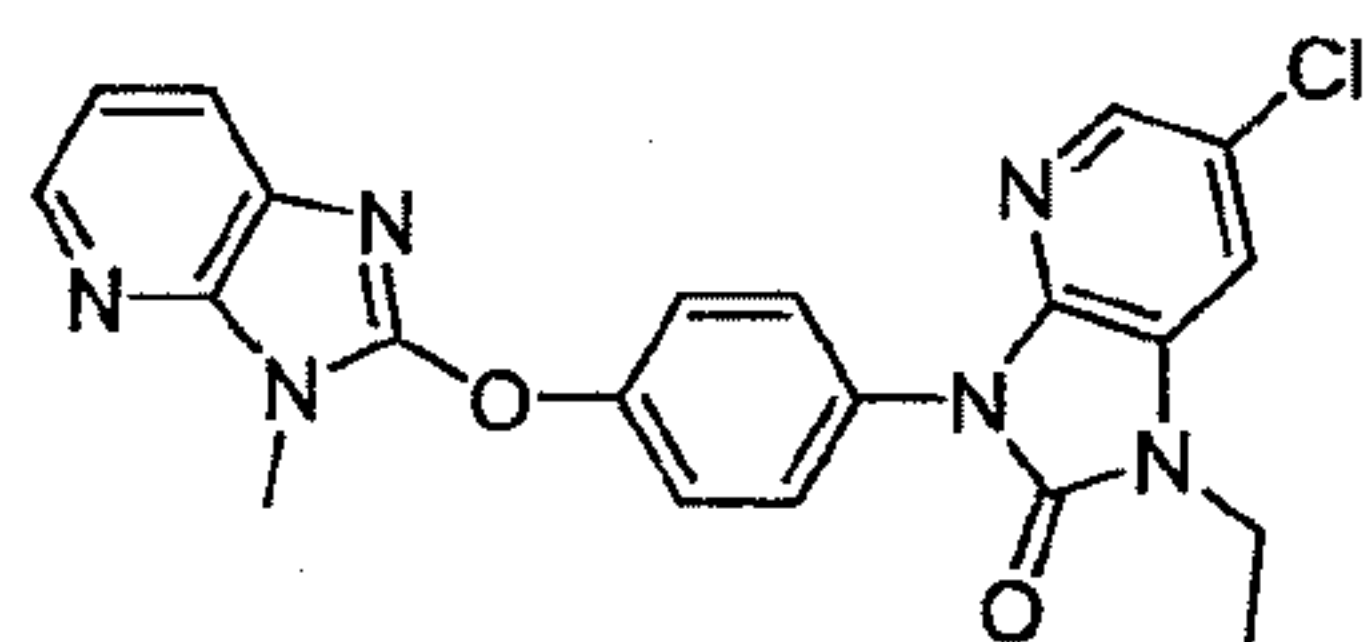
N, 16.40; Cl, .

Mp: 208-210°C

[0369]

Example 107

5 6-chloro-1-ethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



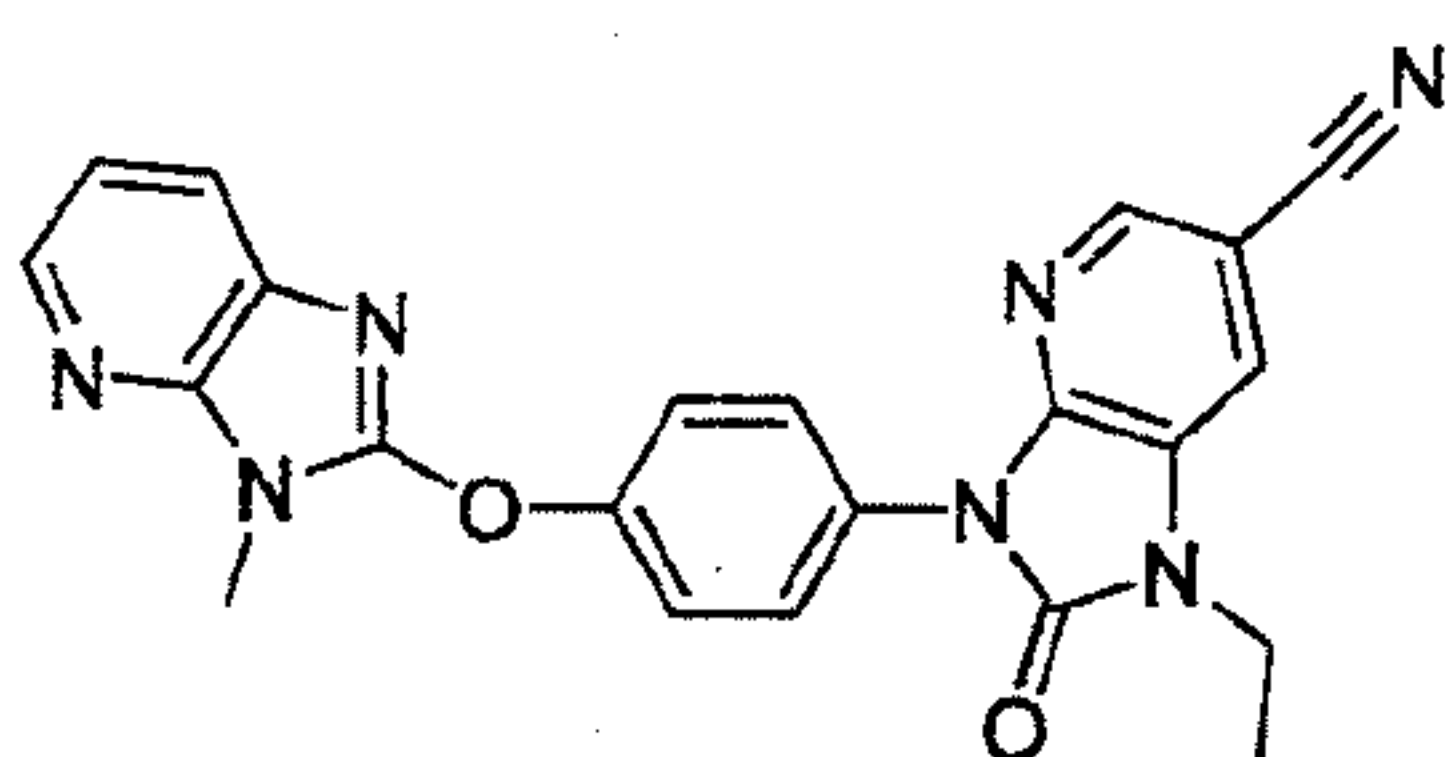
3-Methyl-2-(methylsulfonyl)-3H-imidazo[4,5-b]pyridine (90 mg) was added to a solution of 6-chloro-1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (127 mg) and NaH (18.74 mg) in DMF (2 mL) at room temperature. The mixture was heated at 180°C for 30 min under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 6-chloro-1-ethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (40 mg) as colorless crystals. MS (API+): [M+H]⁺ 421.1.

20 ¹H NMR (300 MHz, DMSO-d₆) δ 1.24-1.41 (3H, m), 3.77 (3H, s), 3.93-4.03 (2H, m), 7.15-7.28 (1H, m), 7.60-7.68 (2H, m), 7.72-7.86 (3H, m), 7.94-7.99 (1H, m), 7.99-8.08 (1H, m), 8.18-8.27 (1H, m).

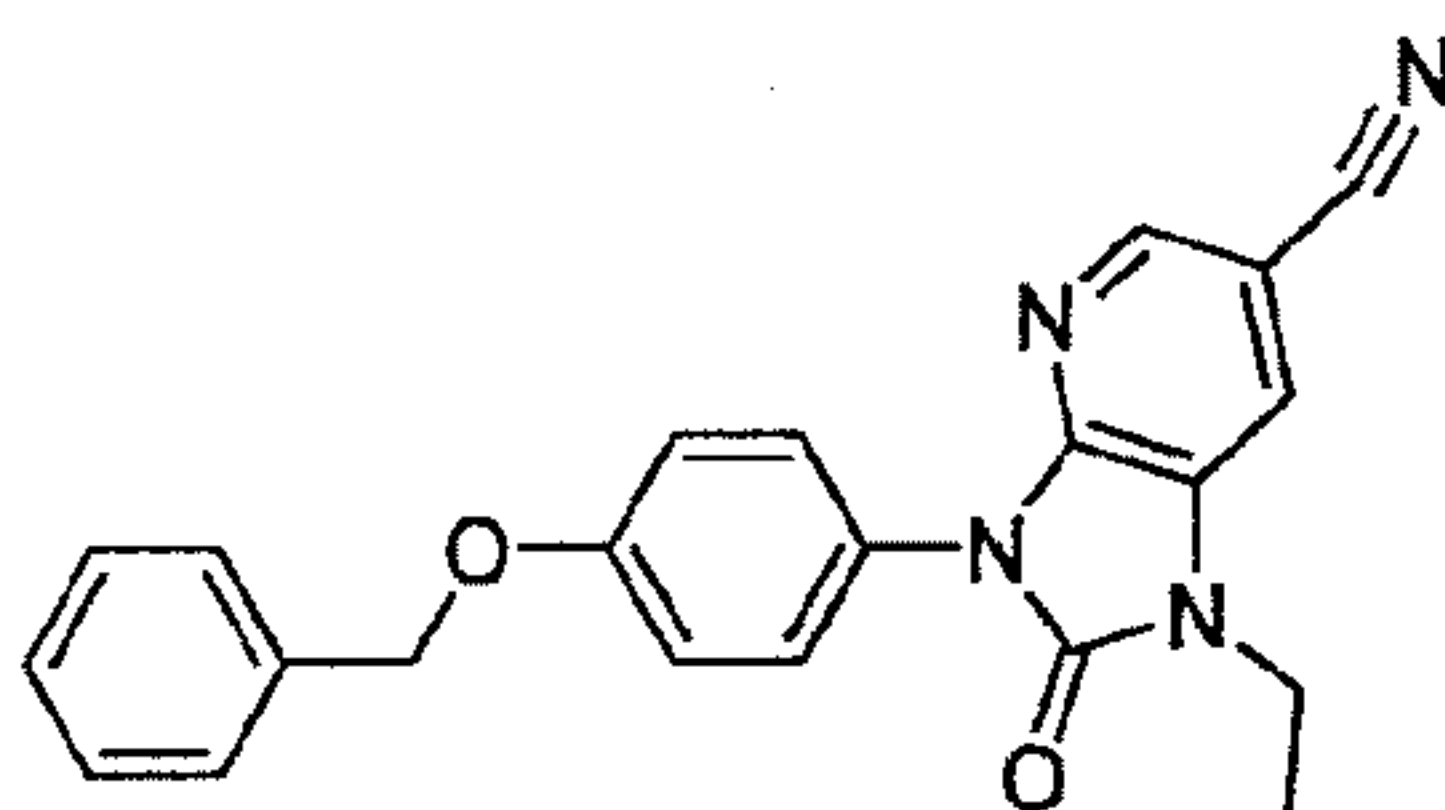
[0370]

Example 108

1-ethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile



108a) 3-[4-(benzyloxy)phenyl]-1-ethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile



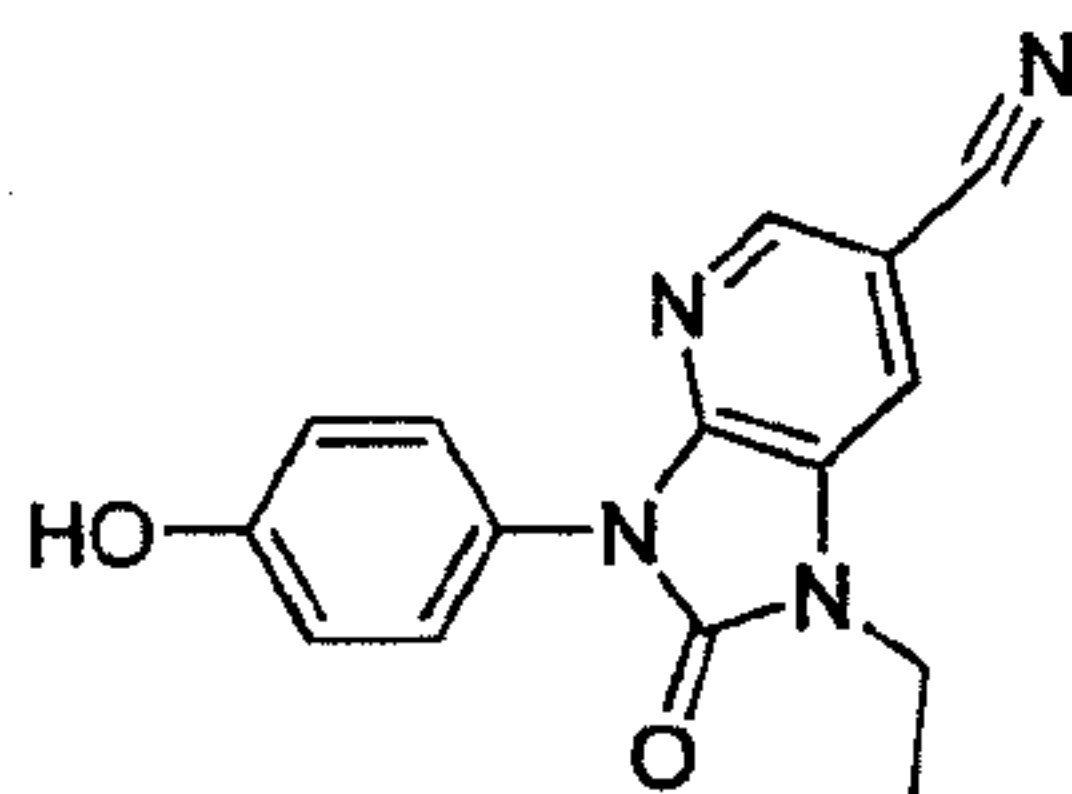
The mixture of 3-[4-(benzyloxy)phenyl]-6-chloro-1-ethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (1 g), zinc cyanide (2.474 g), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (0.216 g), Pd₂(dba)₃ (0.241 g) and DMF (20 mL) was heated at 150°C for 1h under microwave irradiation. The solid was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 50% EtOAc in hexane) to give 3-[4-(benzyloxy)phenyl]-1-ethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile (710 mg) as colorless oil.

15 MS (API⁺): [M+H]⁺ 371.2.

¹H NMR (300 MHz, DMSO-d₆) δ 1.25-1.35 (3H, m), 3.85-4.09 (2H, m), 5.19 (2H, s), 7.08-7.24 (2H, m), 7.28-7.57 (7H, m), 8.11-8.22 (1H, m), 8.38-8.50 (1H, m).

[0371]

20 108b) 1-ethyl-3-(4-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile



A mixture of 3-[4-(benzyloxy)phenyl]-1-ethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile (500 mg) and 10% Pd-C (71.8 mg) in EtOAc (50 mL) was hydrogenated under balloon pressure at room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-

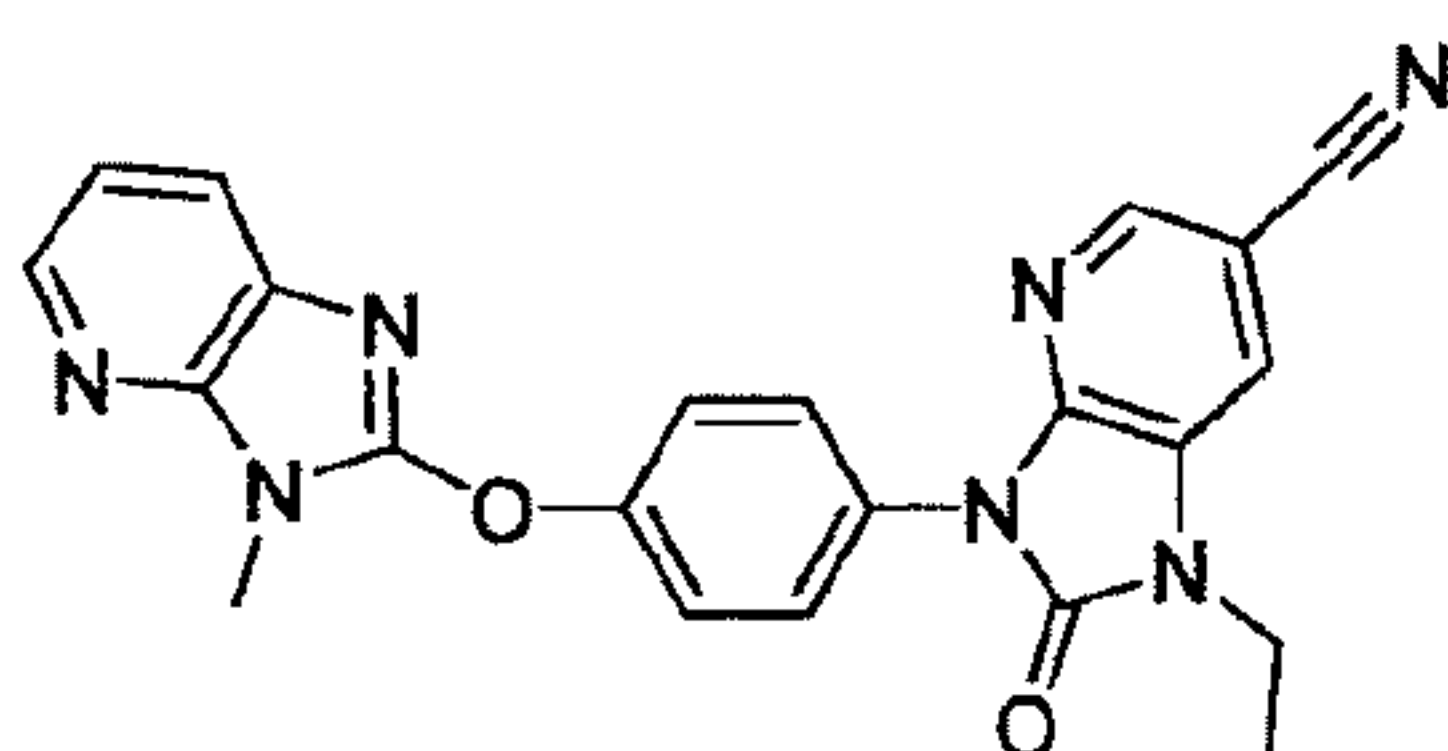
ethyl-3-(4-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile (90 mg) as a white solid.

MS (API+): $[M+H]^+$ 281.2.

^1H NMR (300 MHz, DMSO- d_6) δ 1.24-1.34 (3H, m), 3.90-4.01 (2H, m), 6.81-6.99 (2H, m), 7.29-7.39 (2H, m), 8.12-8.19 (1H, m), 8.38-8.48 (1H, m), 9.71-9.84 (1H, m).

[0372]

108c) 1-ethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile



3-Methyl-2-(methanesulfonyl)-3H-imidazo[4,5-b]pyridine (45 mg) was added to a solution of 1-ethyl-3-(4-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile (61.5 mg) and NaH (9.0 mg) in DMF (1 mL) at room temperature. The mixture was heated at 180°C for 30 min under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 50% EtOAc in hexane) to give 1-ethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile (11 mg) as white crystals.

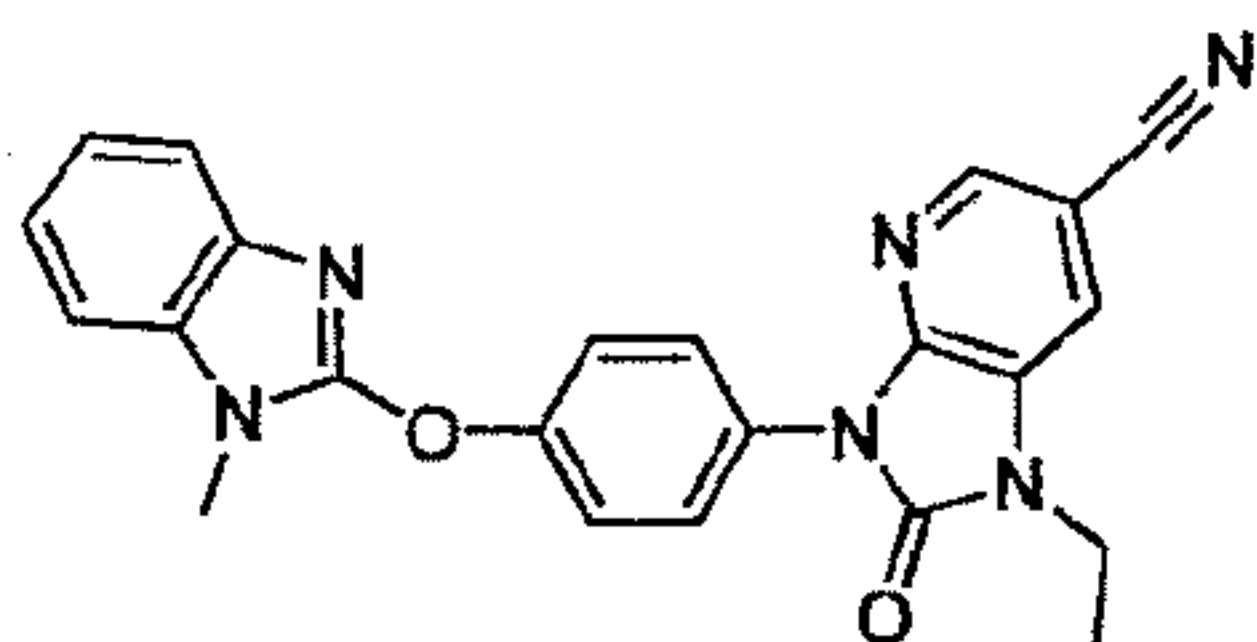
MS (API+): $[M+H]^+$ 412.2.

^1H NMR (300 MHz, DMSO- d_6) δ 1.27-1.40 (3H, m), 3.78 (3H, s), 3.94-4.08 (2H, m), 7.14-7.26 (1H, m), 7.60-7.71 (2H, m), 7.71-7.88 (3H, m), 8.18-8.30 (2H, m), 8.44-8.54 (1H, m).

[0373]

Example 109

1-ethyl-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile



2-Chloro-1-methyl-1H-benzimidazole (15 mg) was added to a solution of 1-ethyl-3-(4-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile (25.5 mg) and sodium hydride (4.0 mg) in DMF (1.0 mL) at room temperature. The mixture was heated at 180°C for 30min under microwave irradiation. The reaction mixture was diluted with MeOH and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0% - 30% EtOAc in hexane) to give 1-ethyl-3-{4-[(1-methyl-1H-benzimidazol-2-yl)oxy]phenyl}-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbonitrile (5 mg) as white crystals.

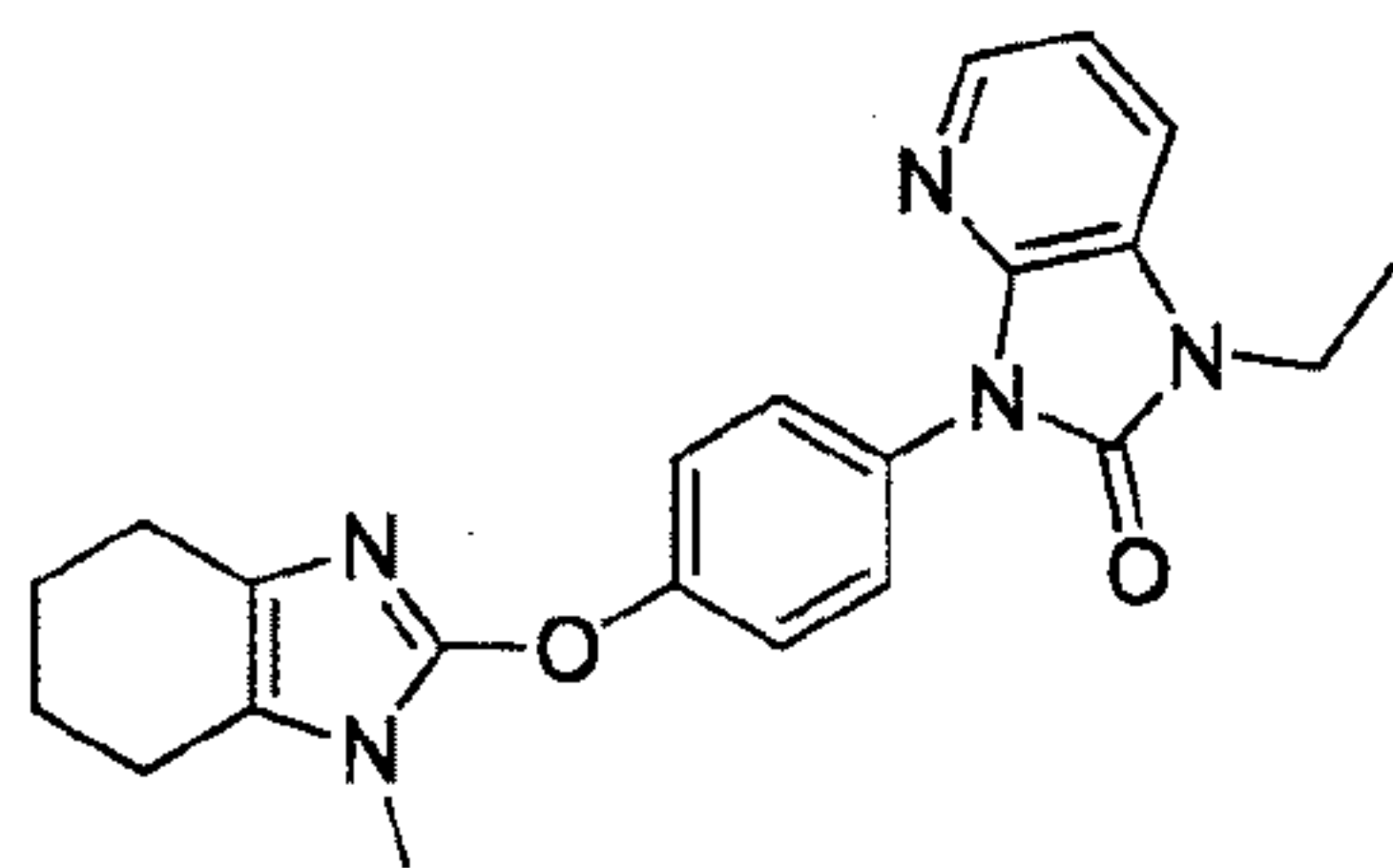
MS (API+): [M+H]⁺ 411.2.

¹H NMR (300 MHz, DMSO-d₆) δ 1.27-1.36 (3H, m), 3.77 (3H, s), 3.92-4.09 (2H, m), 7.08-7.33 (2H, m), 7.38-7.53 (2H, m), 7.55-7.67 (2H, m), 7.68-7.82 (2H, m), 8.12-8.31 (1H, m), 8.41-8.59 (1H, m).

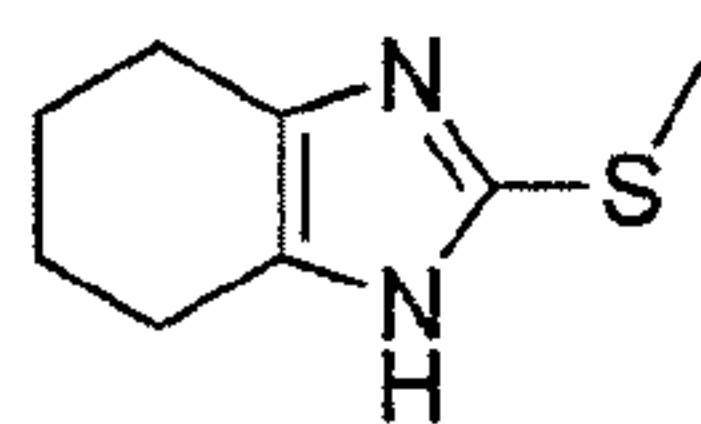
[0374]

Example 112

1-ethyl-3-{4-[(1-methyl-4,5,6,7-tetrahydro-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



112a) 2-(methanethio)-4,5,6,7-tetrahydro-1H-benzimidazole



To a solution of 4,5,6,7-tetrahydro-1H-benzimidazole-2-thiol (500 mg) in acetone (5 mL) were added K₂CO₃ (1344 mg) and

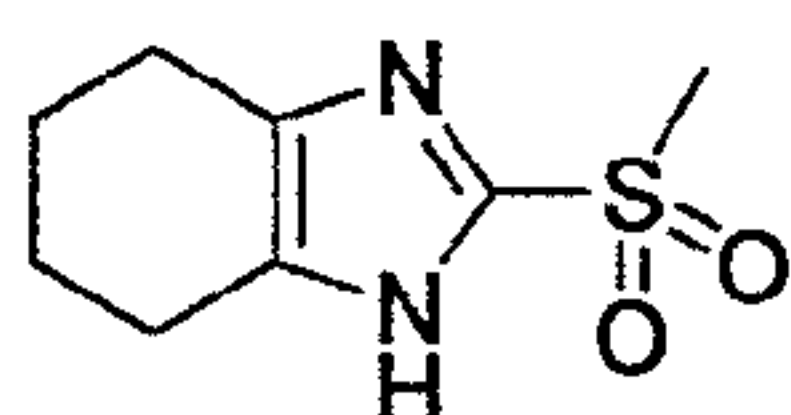
MeI (0.223 mL) at room temperature. After stirring for 1 h, the mixture was quenched with water, and extracted with ethyl acetate, and the extract was washed with brine and dried over magnesium sulfate. The residue was purified by column chromatography (silica gel, eluted with 40% - 90% EtOAc in hexane) to give 2-(methylsulfanyl)-4,5,6,7-tetrahydro-1H-benzimidazole (545 mg) as a white solid.

MS (API+): $[M+H]^+$ 169.0.

^1H NMR (300 MHz, DMSO- d_6) δ 1.69 (4 H, br. s.), 2.47 - 2.65 (4 H, m), 3.33 (3 H, s), 11.43 - 11.98 (1 H, m).

[0375]

112b) 2-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-benzimidazole



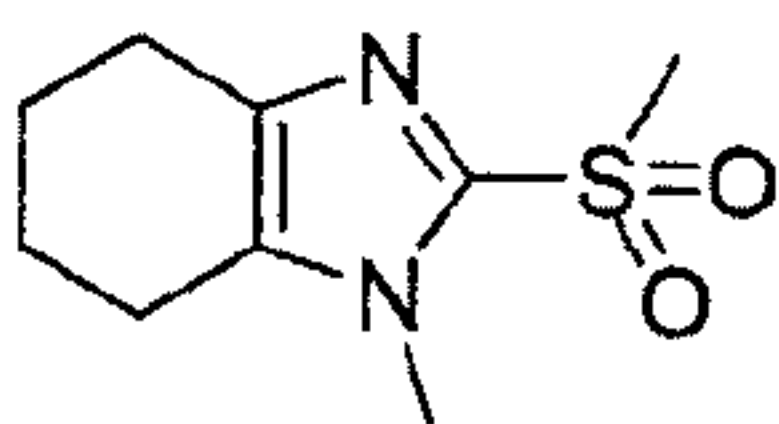
To a solution of 2-(methylsulfanyl)-4,5,6,7-tetrahydro-1H-benzimidazole (280 mg) in EtOAc (5 mL) was added mCPBA (766 mg) at 0°C. After stirring for 10 h, the mixture was quenched with water, and extracted with ethyl acetate, and the extract was washed with brine, and dried over magnesium sulfate. The residue was purified by column chromatography (silica gel, eluted with 20% - 80% EtOAc in hexane) to give 2-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-benzimidazole (200 mg) as white crystals.

MS (API+): $[M+H]^+$ 201.0.

^1H NMR (300 MHz, DMSO- d_6) δ 1.67 - 1.88 (4 H, m), 2.51 - 2.65 (4 H, m), 3.23 (3 H, s), 13.17 (1 H, none)

[0376]

112c) 1-methyl-2-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-benzimidazole



Sodium hydride (55.8 mg) (60% in mineral oil) was added to a solution of 2-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-

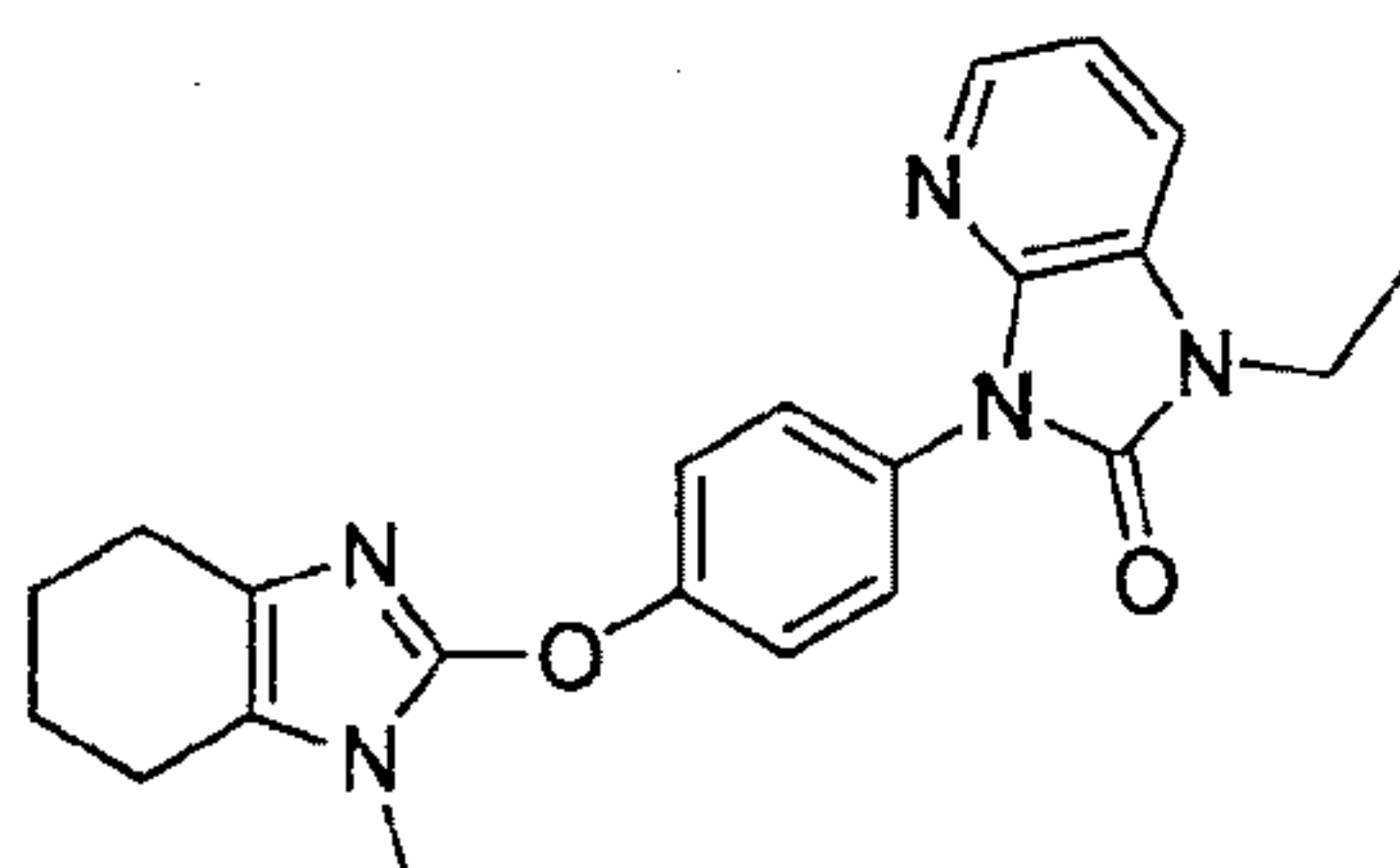
benzimidazole (233 mg) and MeI (0.080 mL) in DMF(dry) (10 mL) at room temperature. The mixture was stirred at room temperature under a dry atmosphere (CaCl₂ tube) for 1h. The reaction mixture was diluted with MeOH (2 mL), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0% - 30% EtOAc in hexane) to give 1-methyl-2-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-benzimidazole (200 mg) as a white solid.

MS (API+): [M+H]⁺ 215.0.

¹H NMR (300 MHz, DMSO-d₆) δ 1.59 - 1.93 (3 H, m), 2.50 (5 H, br. s.), 3.18 - 3.43 (6 H, m)

[0377]

112d) 1-ethyl-3-{4-[(1-methyl-4,5,6,7-tetrahydro-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



1-Methyl-2-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-benzimidazole (84 mg) was added to a solution of 1-ethyl-3-(4-hydroxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (100 mg) and NaH (18.8 mg) (60% in mineral oil) in DMA (3 mL) in a microwave vessel. The vessel was sealed and subjected to microwave irradiation (at 120°C set by IR sensor, fixed hold time : on, Absorption level : High) for 1 h in a Biotage Initiator 60EXP. The mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluted with 20% - 100% EtOAc in hexane) to give 1-ethyl-3-{4-[(1-methyl-4,5,6,7-tetrahydro-1H-benzimidazol-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (8.90 mg) as white crystals.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

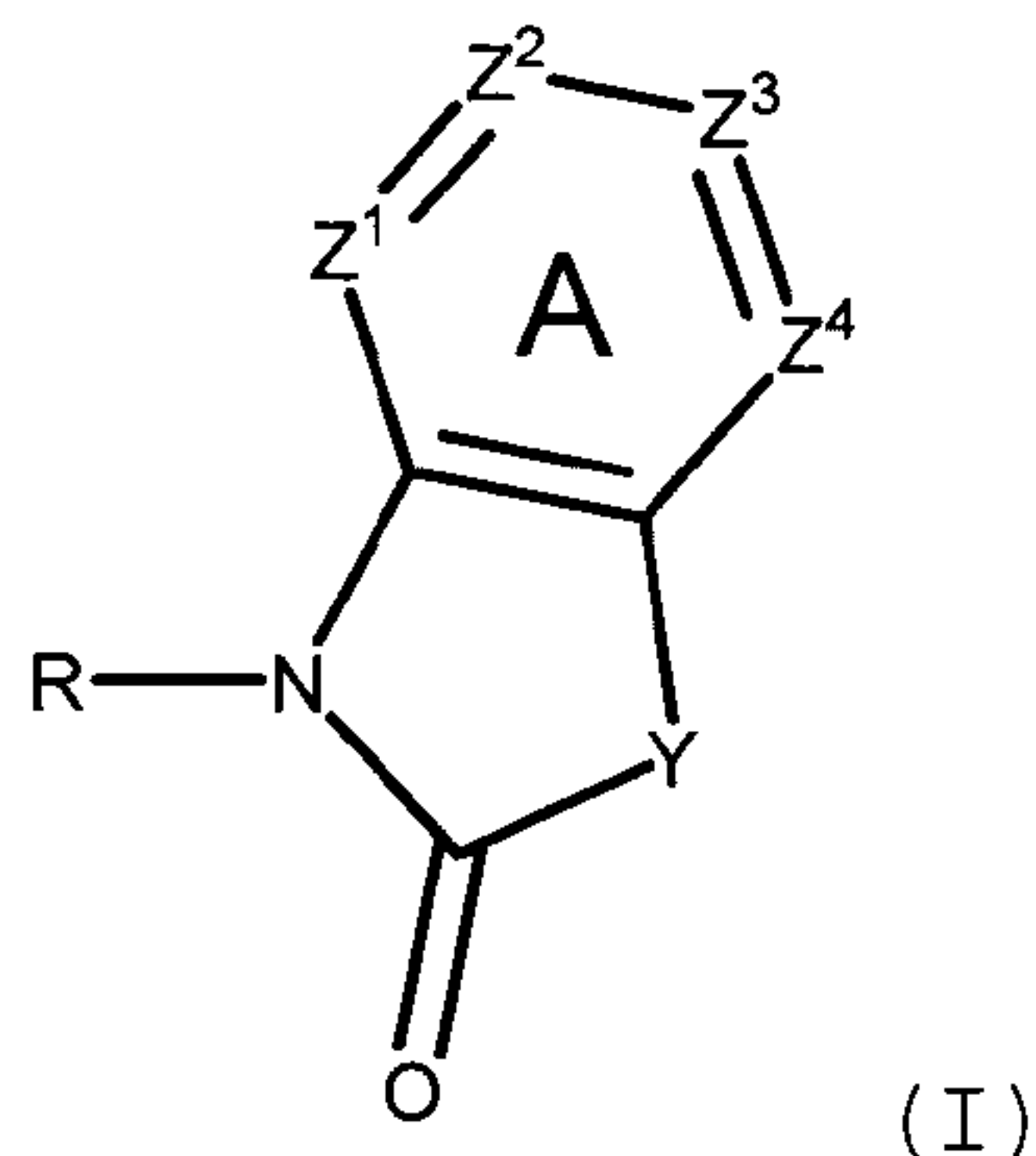
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

CLAIMS:

1. A compound represented by the formula (I):



5 wherein

ring A represents a 6-membered ring optionally substituted by
substituent(s) selected from the group consisting of

- (1) a halogen atom,
- (2) cyano,

10 (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of (a) a halogen
atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carboxyloxy group, and
(4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen
atoms, any one or two of Z¹ to Z⁴ represent -N=, and the others
15 represent -CH=;

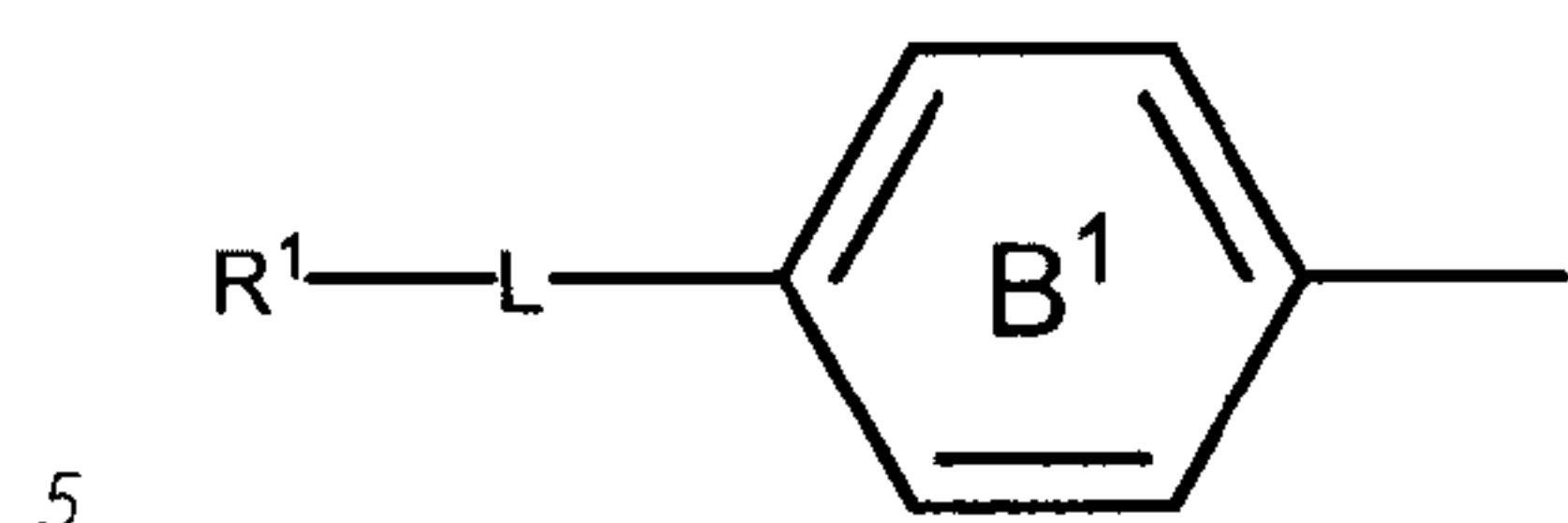
Y represents

- (1) an oxygen atom,
- (2) a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl
group(s), wherein the two substituents for the methylene group
20 optionally form, together with the adjacent carbon atom, a C₃₋₆
cycloalkane, or
- (3) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl
group optionally substituted by 1 to 3 substituents selected
from the group consisting of a halogen atom, a hydroxy group, a
25 C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆

alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇ cycloalkyl group; and

R represents

a group represented by the formula:

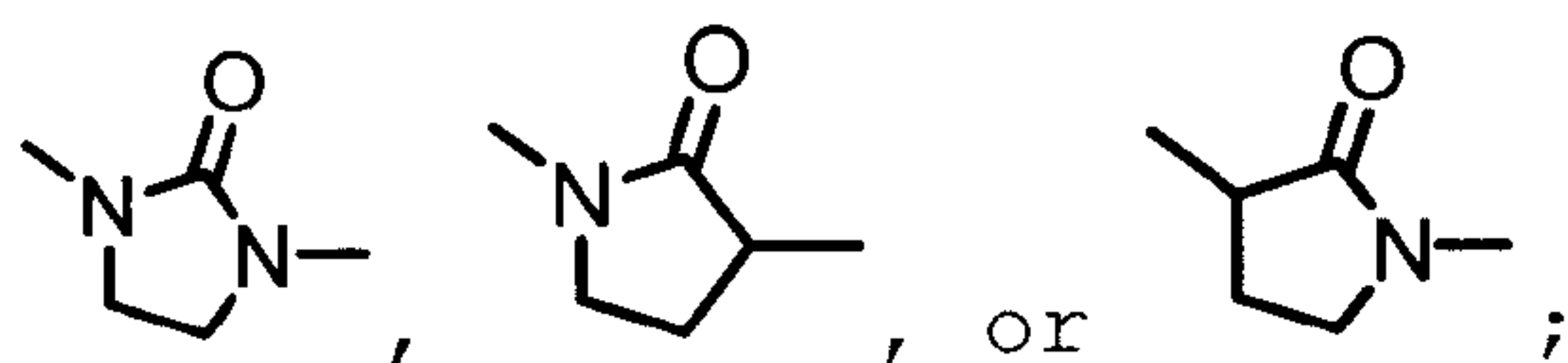


wherein

R¹ represents a phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted by substituent(s) selected from the group consisting of

- 10 (a) a halogen atom,
 (b) a C₁₋₆ alkoxy-carbonyl group,
 (c) a C₁₋₆ alkyl group optionally substituted by one or more substituents selected from the group consisting of
 (i) a halogen atom,
 15 (ii) a hydroxy group, and
 (iii) a C₁₋₆ alkoxy group optionally substituted by trimethylsilyl,
 (d) a C₆₋₁₄ aryl group, and
 (e) a C₁₋₆ alkyl-carbonyl group;

- 20 L represents a sulfur atom, an oxygen atom, a methylene group, -CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-, -NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



- R^a and R^b are the same or different and each represents a
 25 hydrogen atom, or a C₁₋₆ alkyl group, or
 L and R¹ in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom,
(b) a C₁₋₆ alkoxy-carbonyl group,
(c) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl group(s), and

5 (d) an oxo group; and

ring B¹ represents a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted by substituent(s) selected from the group consisting of

10 (a) a halogen atom, and

(b) a C₁₋₆ alkyl group;

provided that

3,3'-benzene-1,4-diylbis(1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one),

15 3-(4-phenoxyphenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, and

3,3'-benzene-1,4-diylbis(1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one)

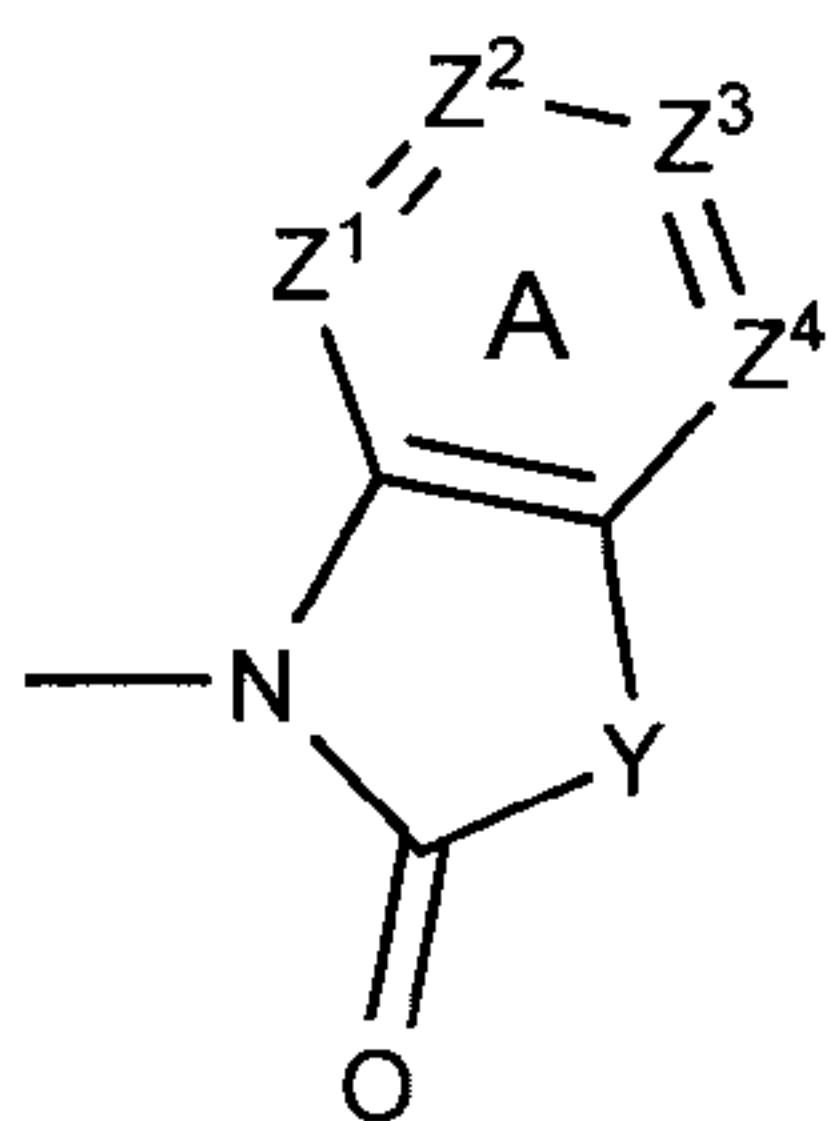
are excluded;

20 or a salt thereof.

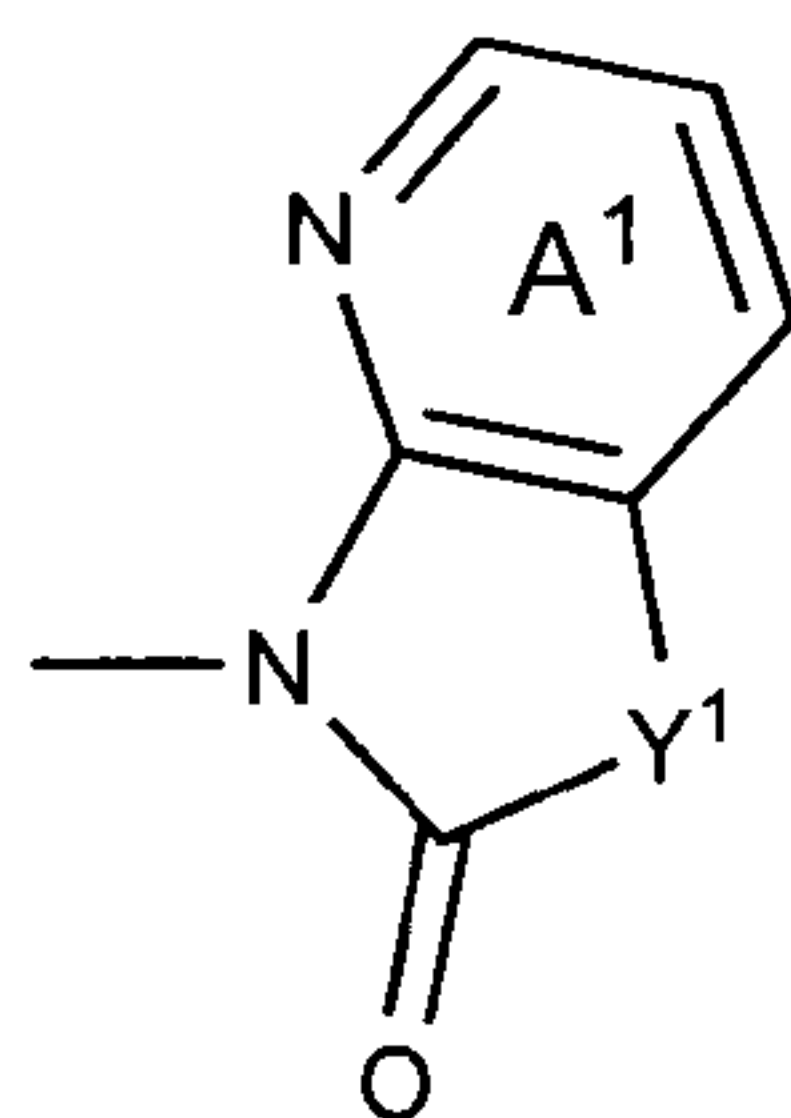
2. The compound according to claim 1, wherein any one of Z¹ to Z⁴ is -N=, and the others are -CH=, or a salt thereof.

25

3. The compound according to claim 1, wherein the partial structure of formula (I):



is a group represented by the formula:



wherein

5 Y¹ represents

(1) a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl group(s), wherein the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane, or

10 (2) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆ alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇
15 cycloalkyl group, and

ring A¹ represents a pyridine ring optionally substituted by substituent(s) selected from the group consisting of

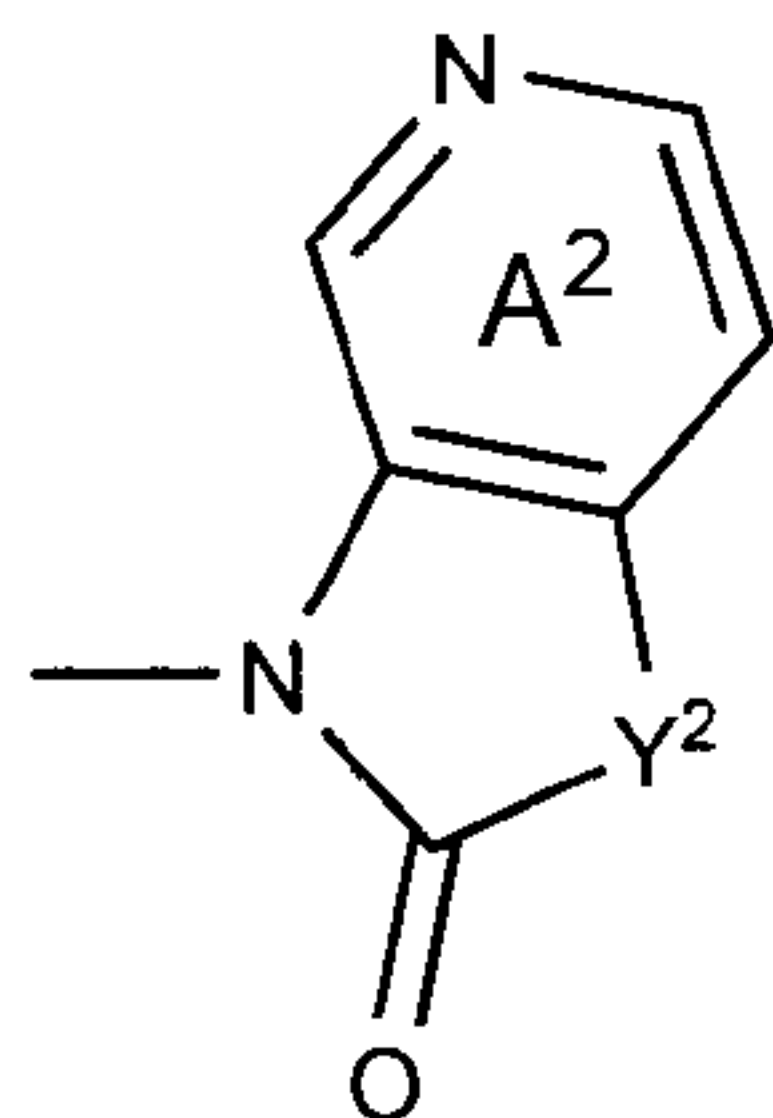
(1) a halogen atom,

(2) cyano,

20 (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carboxyloxy group, and

(4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, or

a group represented by the formula:



5 wherein

Y² represents -NR^d-,

R^d represents (i) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆ alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (ii) a C₃₋₇ cycloalkyl group, and ring A² represents a pyridine ring optionally substituted by substituent(s) selected from the group consisting of

(1) a halogen atom,

15 (2) cyano,

(3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carboxyloxy group, and

(4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen

20 atoms,

or a salt thereof.

4. The compound according to claim 1, wherein L is an oxygen atom, or -NR^a- wherein R^a represents a hydrogen atom or a C₁₋₆ alkyl group, or

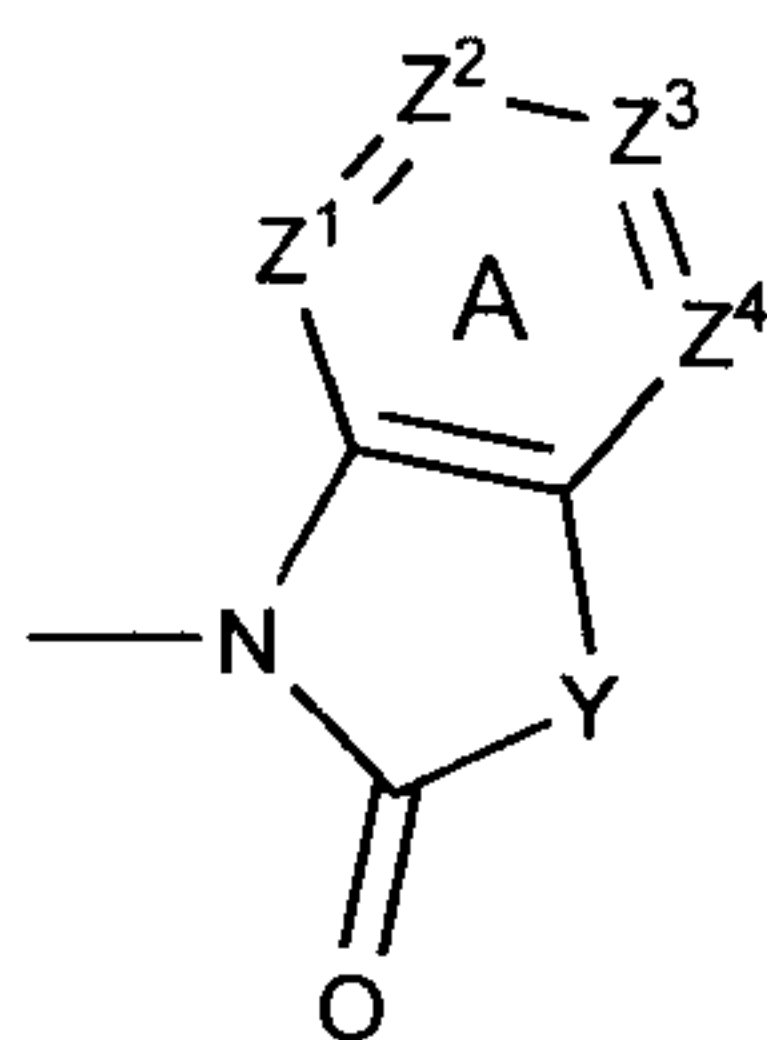
25

L and R¹ in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by substituent(s) selected from the group consisting of

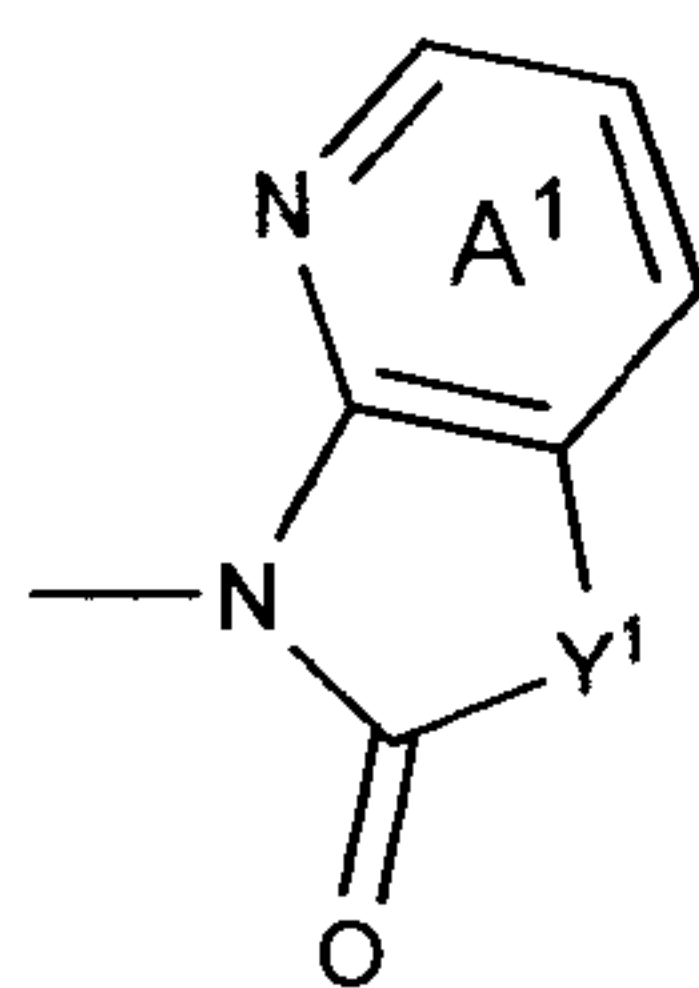
- (a) a halogen atom,
5 (b) a C₁₋₆ alkoxy-carbonyl group,
(c) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl
group(s), and
(d) an oxo group,
or a salt thereof.

10

5. The compound according to claim 3, wherein the partial structure of formula (I):

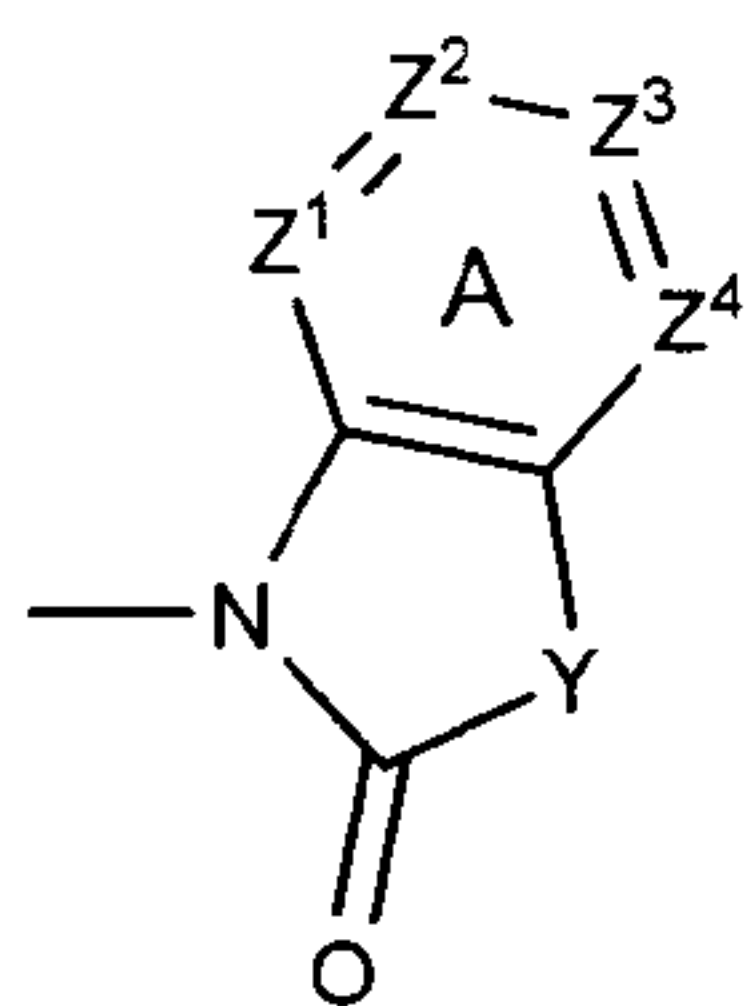


is a group represented by the formula:

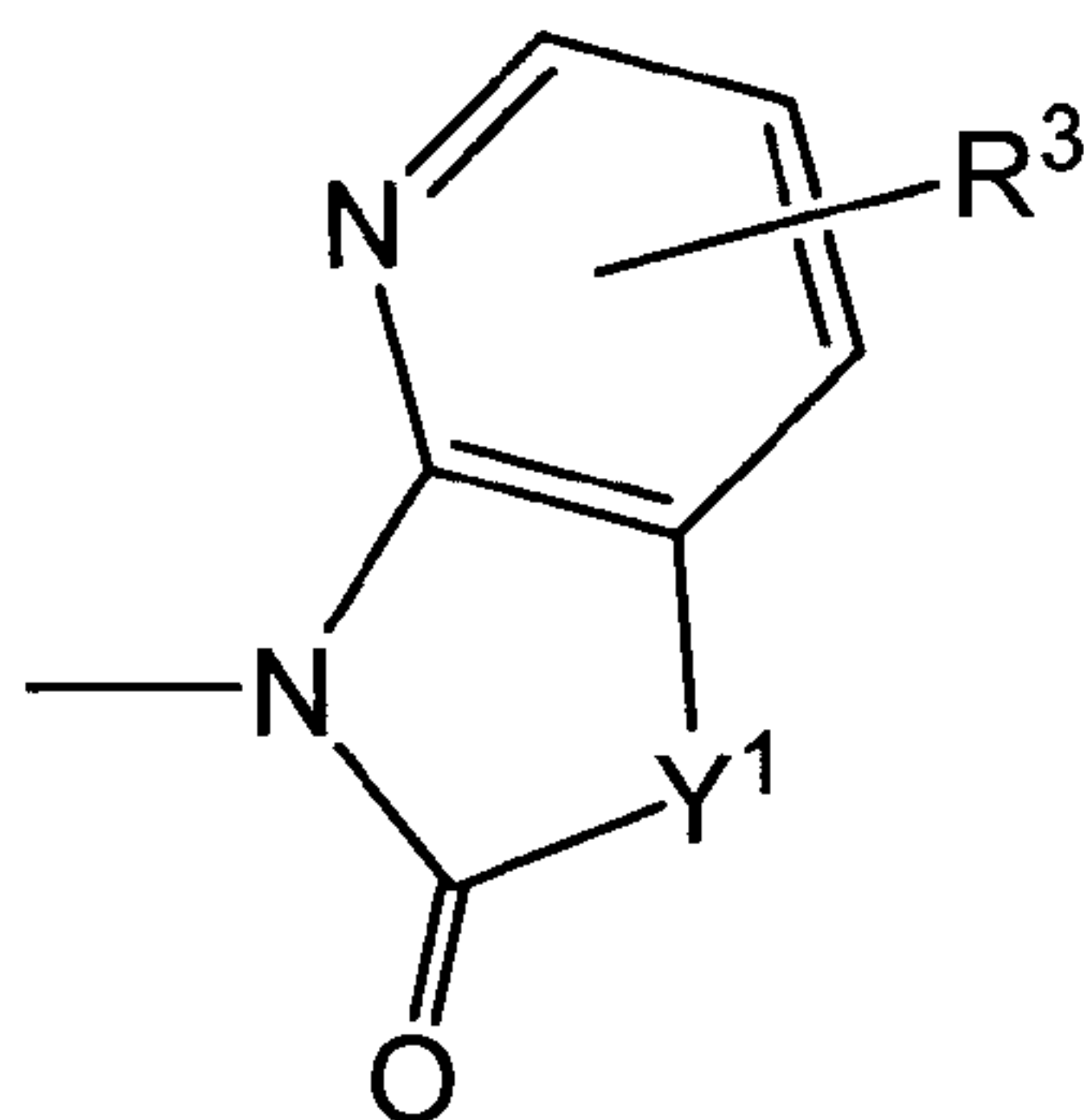


wherein each symbol is as defined in claim 3,
or a salt thereof.

6. The compound according to claim 3, wherein the partial
20 structure of formula (I):



is a group represented by the formula:



wherein

5 R^3 represents

(1) a halogen atom,

(2) a cyano group,

(3) a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or

10 (4) a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms, and

Y^1 is as defined in claim 3,

or a salt thereof.

15 7. The compound according to claim 1, wherein ring B^1 is a benzene ring optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom, and

(b) a C_{1-6} alkyl group, or a salt thereof.

8. The compound according to claim 1, wherein R^1 is a 5- to 10-membered heterocyclic group optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom,

5 (b) a C_{1-6} alkoxy-carbonyl group,

(c) a C_{1-6} alkyl group optionally substituted by one or more substituents selected from the group consisting of

(i) a halogen atom,

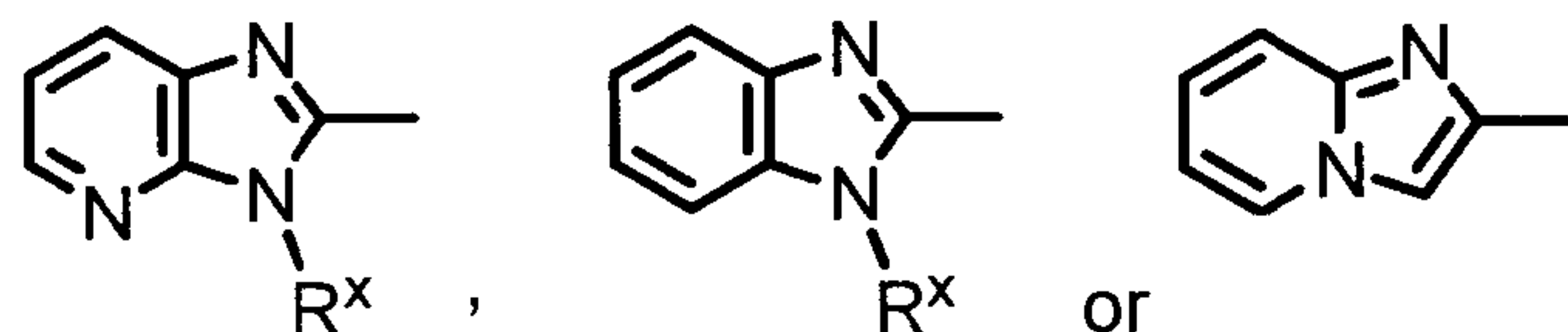
(ii) a hydroxy group, and

10 (iii) a C_{1-6} alkoxy group optionally substituted by trimethylsilyl,

(d) a C_{6-14} aryl group, and

(e) a C_{1-6} alkyl-carbonyl group, or a salt thereof.

15 9. The compound according to claim 8, wherein R^1 is a group represented by the formula:



wherein R^x represents a hydrogen atom or a C_{1-6} alkyl group, or a salt thereof.

20

10. 1-Ethyl-6-methyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

25 11. 1-Ethyl-6-methoxy-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

12. 1-Ethyl-7-methyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

5 13. 6-Methyl-1-(1-methylethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

14. 1-Ethyl-6-fluoro-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a
10 salt thereof.

15. 1,7-Dimethyl-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a
15 salt thereof.

16. 1-Ethyl-7-(hydroxymethyl)-3-{4-[(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)oxy]phenyl}-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, or a salt thereof.

20

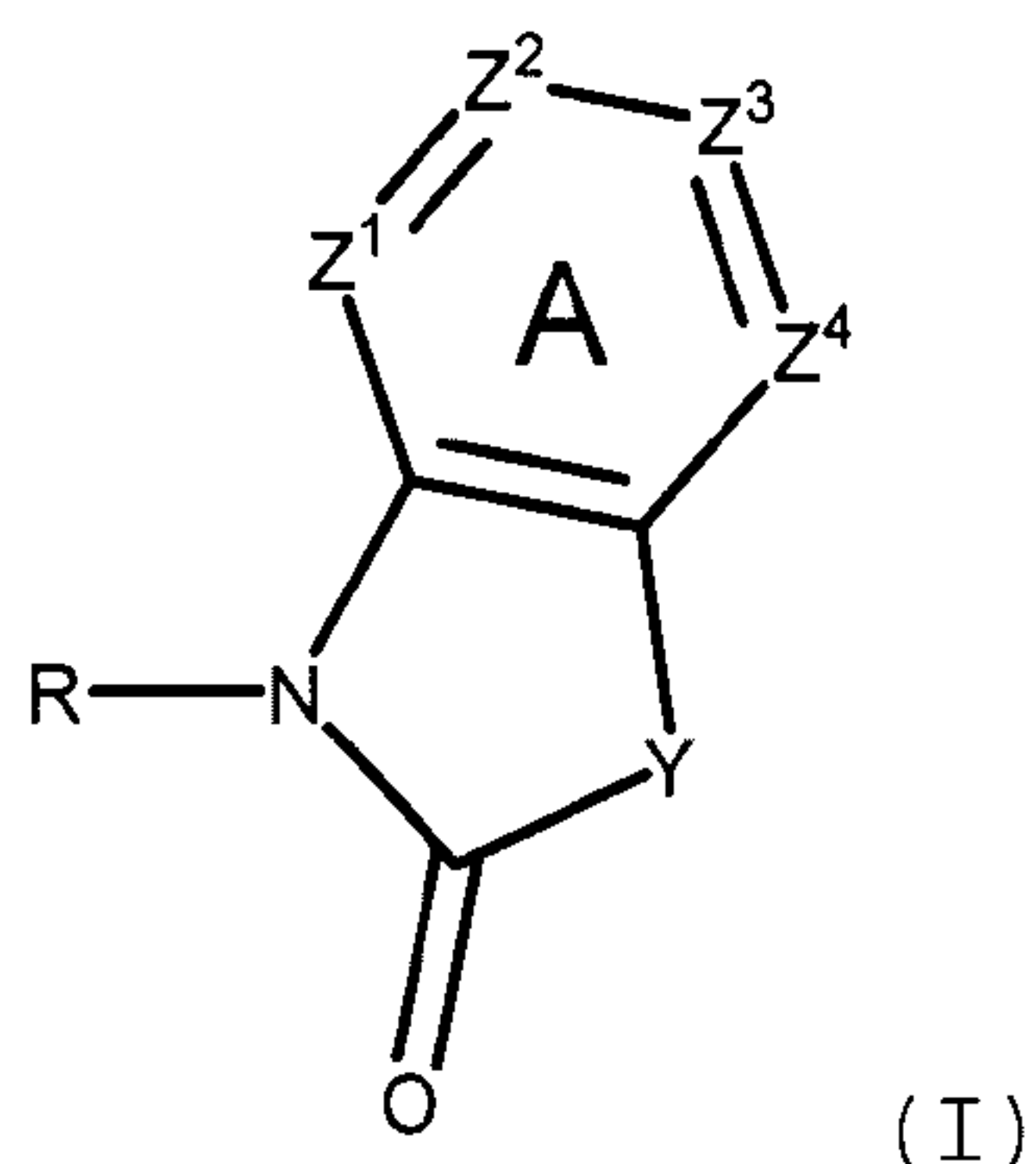
17. A medicament comprising the compound according to claim 1, or a pharmacologically acceptable salt thereof and a pharmaceutically acceptable carrier.

25 18. The medicament according to claim 17, which is a phosphodiesterase 10A inhibitor.

19. The medicament according to claim 17, which is an agent for preventing or treating schizophrenia, autism, Alzheimer's
30 disease, bipolar disorders, Parkinson's disease, Huntington's

disease, obesity, drug addiction or attention deficit/hyperactivity disorder.

20. Use of a compound represented by the formula (I):



wherein

ring A represents a 6-membered ring optionally substituted by substituent(s) selected from the group consisting of

- (1) a halogen atom,
- 10 (2) cyano,
- (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carbonyloxy group, and
- (4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen
- 15 atoms, any one or two of Z¹ to Z⁴ represent -N=, and the others represent -CH=;

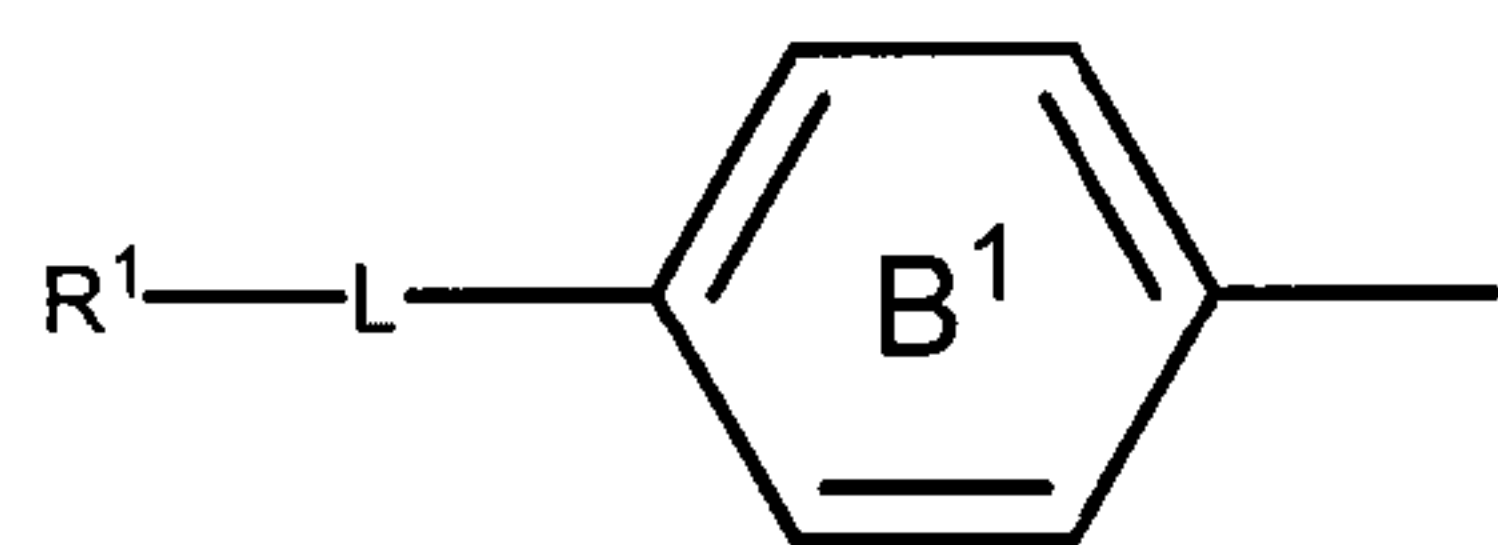
Y represents

- (1) an oxygen atom,
- (2) a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl
- 20 group(s), wherein the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane, or
- (3) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected
- 25 from the group consisting of a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆

alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇ cycloalkyl group; and

R represents

a group represented by the formula:

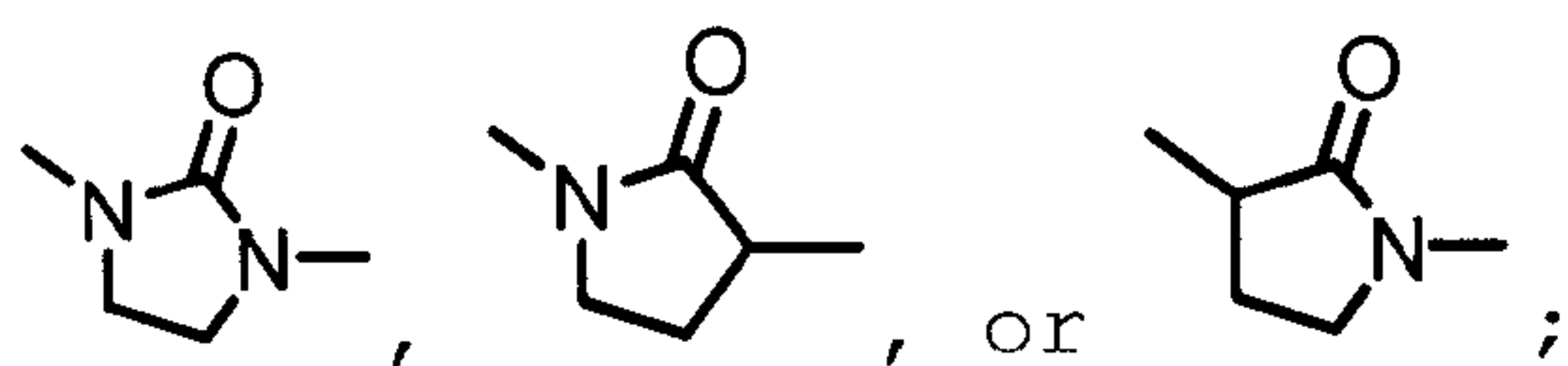


wherein

R¹ represents a phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted by substituent(s) selected from the group consisting of

- 10 (a) a halogen atom,
 (b) a C₁₋₆ alkoxy-carbonyl group,
 (c) a C₁₋₆ alkyl group optionally substituted by one or more substituents selected from the group consisting of
 (i) a halogen atom,
 15 (ii) a hydroxy group, and
 (iii) a C₁₋₆ alkoxy group optionally substituted by trimethylsilyl,
 (d) a C₆₋₁₄ aryl group, and
 (e) a C₁₋₆ alkyl-carbonyl group;

20 L represents a sulfur atom, an oxygen atom, a methylene group, -CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-, -NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



R^a and R^b are the same or different and each represents a
 25 hydrogen atom, or a C₁₋₆ alkyl group, or
 L and R¹ in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by substituent(s) selected from the group consisting of

- (a) a halogen atom,
- (b) a C₁₋₆ alkoxy-carbonyl group,
- (c) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl group(s), and

5 (d) an oxo group; and

ring B¹ represents a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted by substituent(s) selected from the group consisting of

10 (a) a halogen atom, and

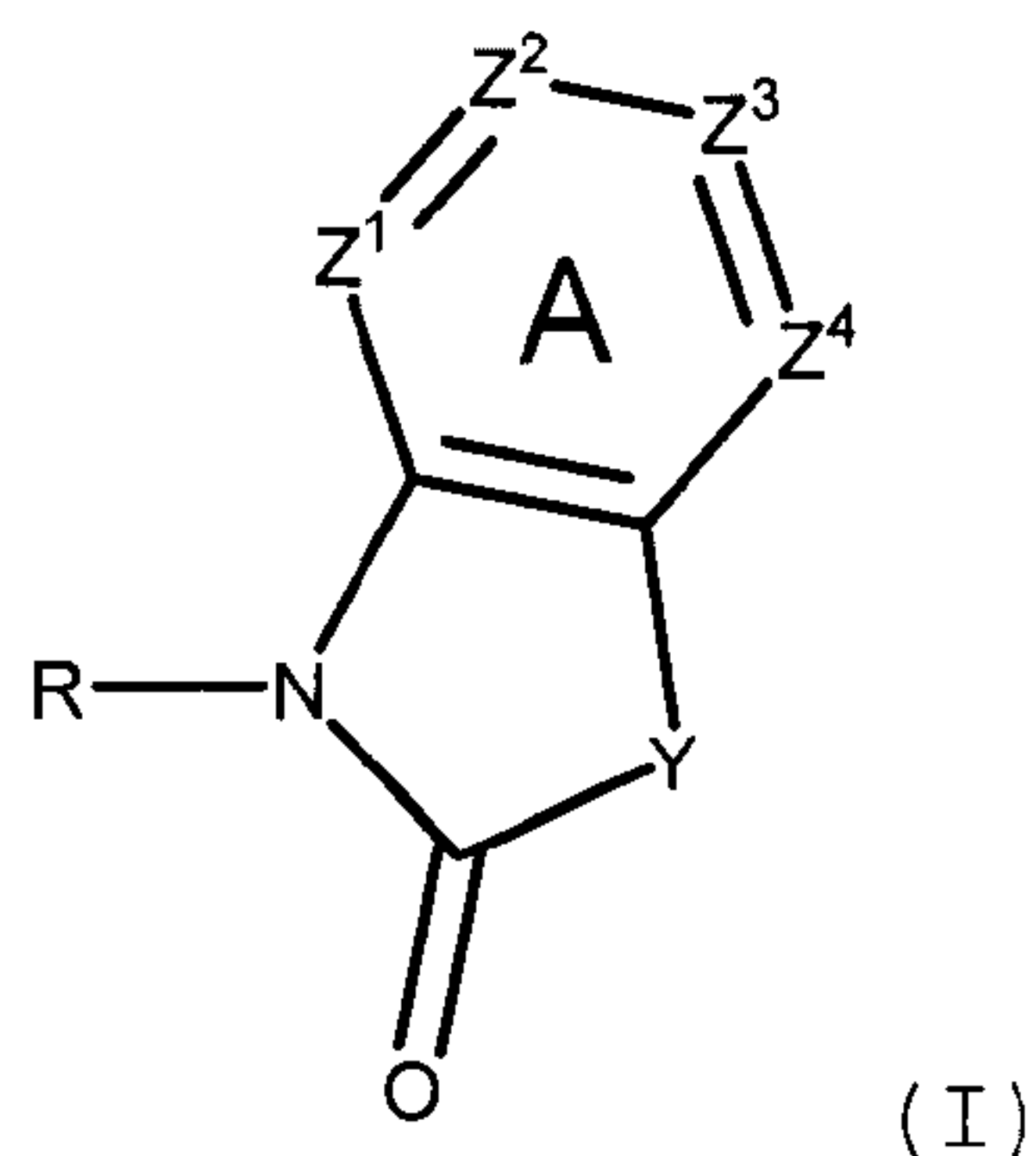
(b) a C₁₋₆ alkyl group;

or a pharmacologically acceptable salt thereof,

for the prevention or treatment of schizophrenia, autism, Alzheimer's disease, bipolar disorders, Parkinson's disease,

15 Huntington's disease, obesity, drug addiction or attention deficit/hyperactivity disorder, in a mammal.

21. Use of a compound represented by the formula (I):



20 wherein

ring A represents a 6-membered ring optionally substituted by substituent(s) selected from the group consisting of

- (1) a halogen atom,
- (2) cyano,

(3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carbonyloxy group, and

(4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, any one or two of Z¹ to Z⁴ represent -N=, and the others represent -CH=;

Y represents

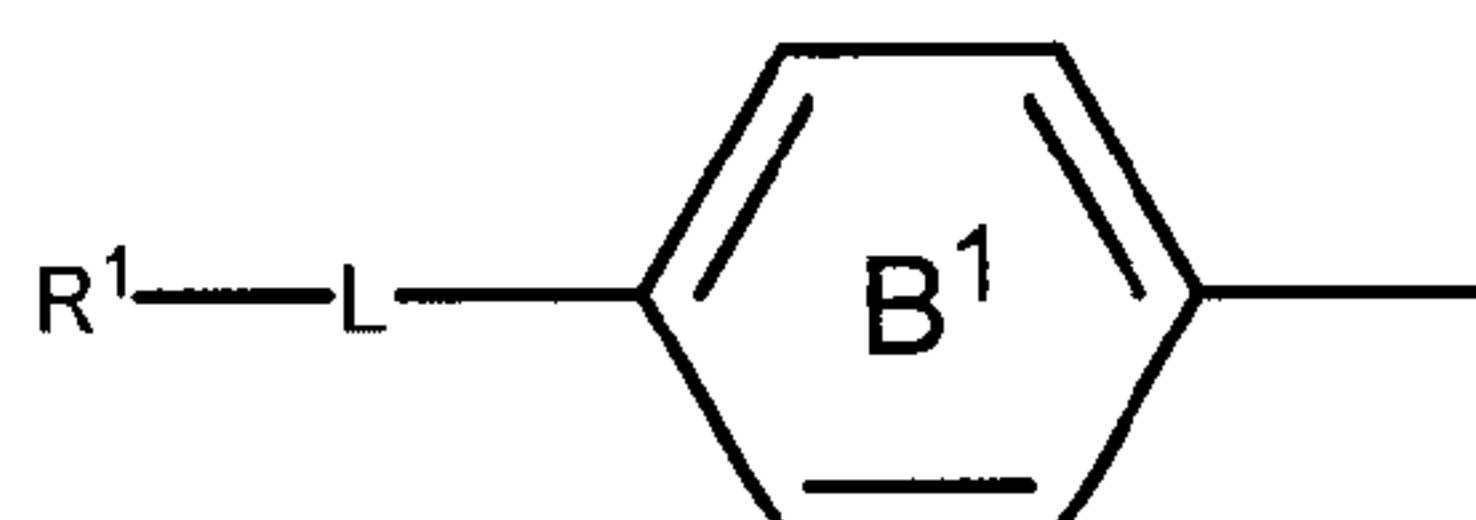
(1) an oxygen atom,

(2) a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl group(s), wherein the two substituents for the methylene group optionally form, together with the adjacent carbon atom, a C₃₋₆ cycloalkane, or

(3) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆ alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇ cycloalkyl group; and

R represents

a group represented by the formula:



wherein

R¹ represents a phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom,

(b) a C₁₋₆ alkoxy-carbonyl group,

(c) a C₁₋₆ alkyl group optionally substituted by one or more substituents selected from the group consisting of

(i) a halogen atom,

(ii) a hydroxy group, and

(iii) a C₁₋₆ alkoxy group optionally substituted by trimethylsilyl,

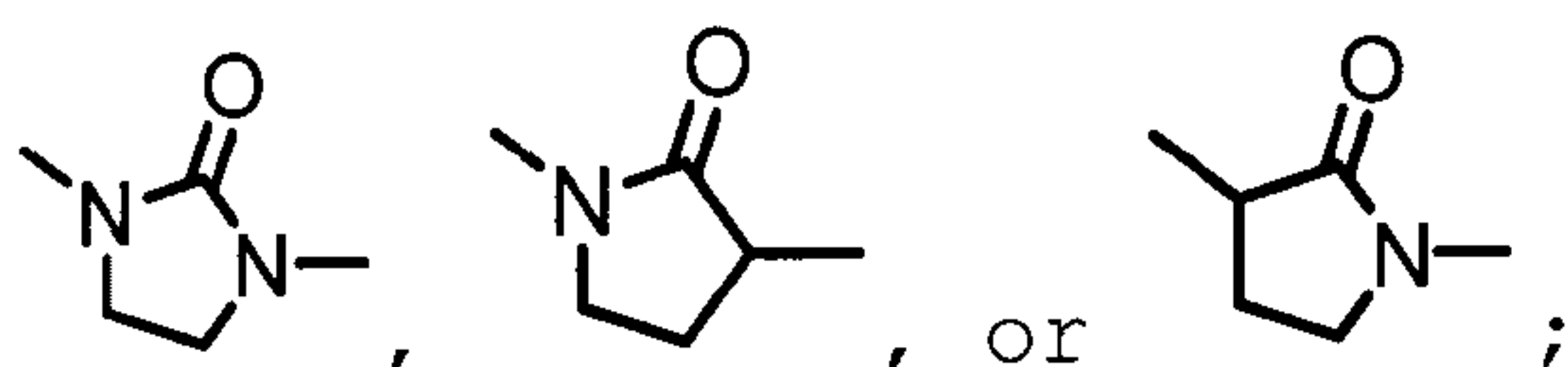
(d) a C₆₋₁₄ aryl group, and

5 (e) a C₁₋₆ alkyl-carbonyl group;

L represents a sulfur atom, an oxygen atom, a methylene group,

-CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-,

-NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



10 R^a and R^b are the same or different and each represents a hydrogen atom, or a C₁₋₆ alkyl group, or

L and R¹ in combination optionally form a bi- or tri-cyclic fused heterocyclic group optionally substituted by substituent(s) selected from the group consisting of

15 (a) a halogen atom,

(b) a C₁₋₆ alkoxy-carbonyl group,

(c) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl group(s), and

(d) an oxo group; and

20 ring B¹ represents a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, each of which is optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom, and

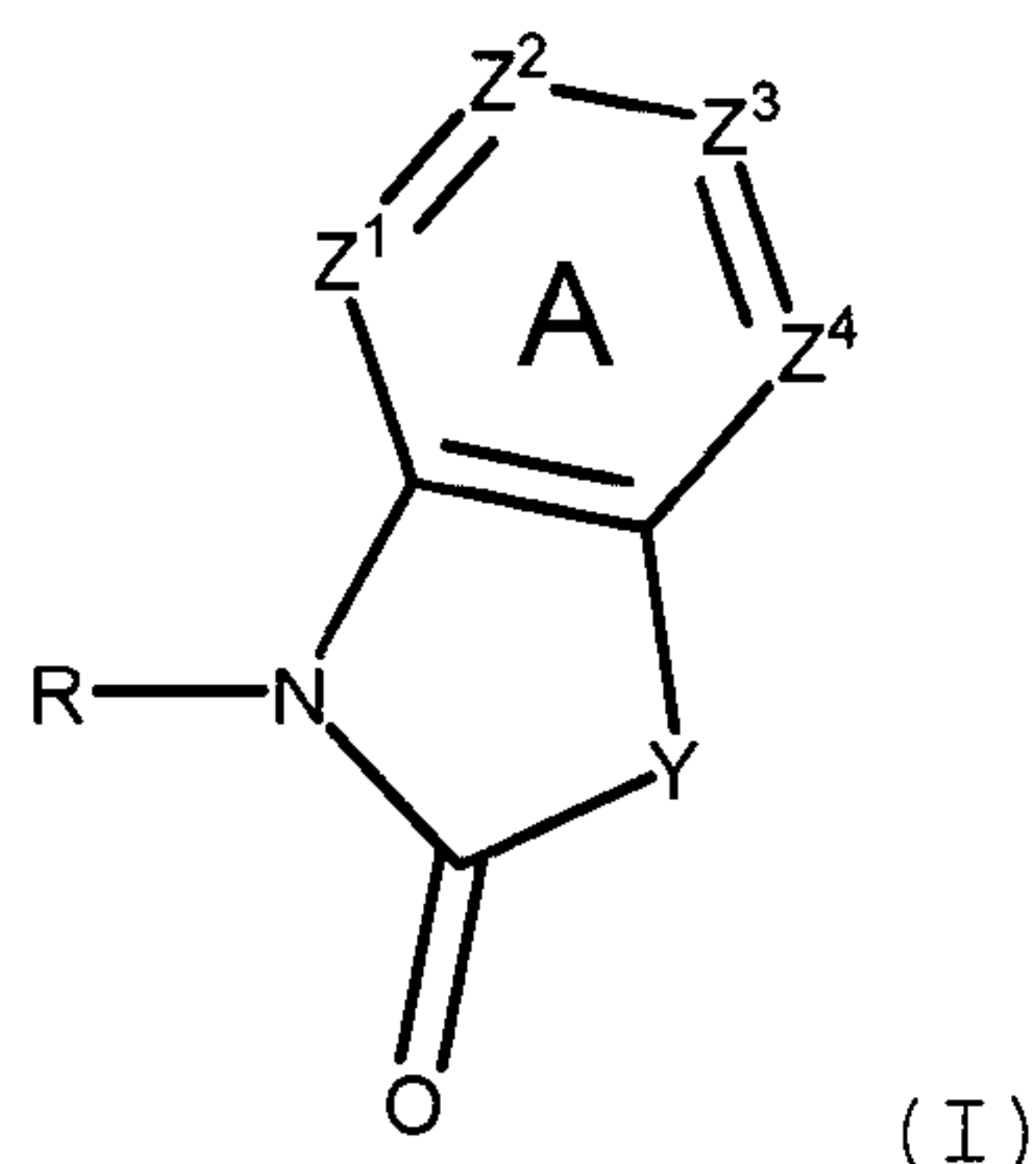
25 (b) a C₁₋₆ alkyl group;

or a pharmacologically acceptable salt thereof,

for the production of a medicament for prevention or treatment of schizophrenia, autism, Alzheimer's disease, bipolar disorders, Parkinson's disease, Huntington's disease, obesity, drug

30 addiction or attention deficit/hyperactivity disorder.

22. A compound represented by the formula (I):

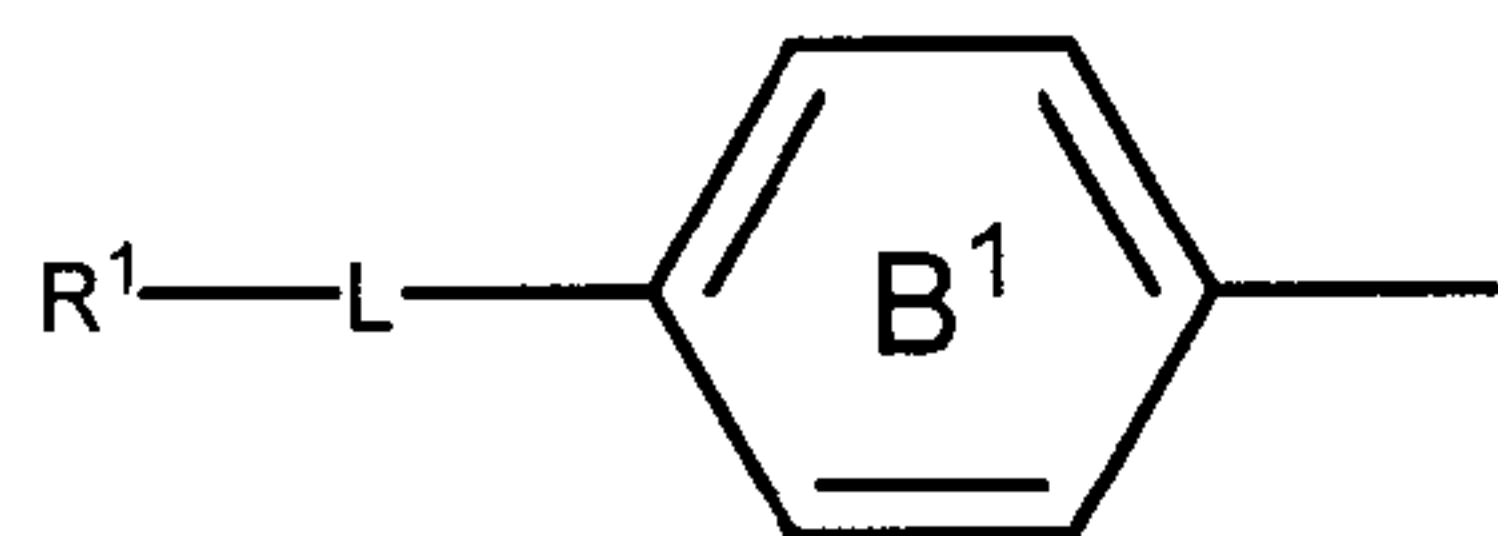


wherein

- 5 ring A represents a 6-membered ring optionally substituted by
 substituent(s) selected from the group consisting of
 (1) a halogen atom,
 (2) cyano,
 (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3
 10 substituents selected from the group consisting of (a) a halogen
 atom, (b) hydroxy and (c) a C₁₋₆ alkyl-carbonyloxy group, and
 (4) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen
 atoms, any one or two of Z¹ to Z⁴ represent -N=, and the others
 represent -CH=;
- 15 Y represents
 (1) an oxygen atom,
 (2) a methylene group optionally substituted by 1 or 2 C₁₋₆ alkyl
 group(s), wherein the two substituents for the methylene group
 optionally form, together with the adjacent carbon atom, a C₃₋₆
 20 cycloalkane, or
 (3) -NR^c- wherein R^c is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl
 group optionally substituted by 1 to 3 substituents selected
 from the group consisting of a halogen atom, a hydroxy group, a
 C₃₋₇ cycloalkyl group, a C₁₋₆ alkoxy group, a trimethylsilyl-C₁₋₆
 25 alkoxy group and a C₁₋₆ alkoxy-carbonyl group, or (iii) a C₃₋₇
 cycloalkyl group; and

R represents

a group represented by the formula:



wherein

5 R¹ represents a phenyl group or 5- to 10-membered heterocyclic group, each of which is optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom,

(b) a C₁₋₆ alkoxy-carbonyl group,

10 (c) a C₁₋₆ alkyl group optionally substituted by one or more substituents selected from the group consisting of

(i) a halogen atom,

(ii) a hydroxy group, and

(iii) a C₁₋₆ alkoxy group optionally substituted by

15 trimethylsilyl,

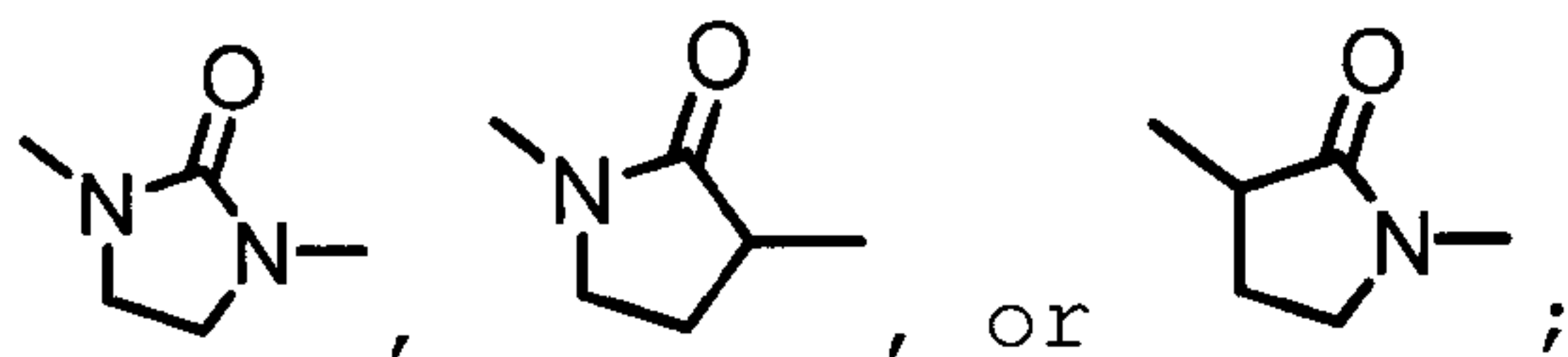
(d) a C₆₋₁₄ aryl group, and

(e) a C₁₋₆ alkyl-carbonyl group;

L represents a sulfur atom, an oxygen atom, a methylene group,

-CO-, -NR^a-, -CH₂O-, -OCH₂-, -NR^aCOO-, -OCONR^a-, -NR^aCONR^b-,

20 -NR^aCOCH₂-, -CH₂CONR^a-, -NR^aCO-, -CONR^a-,



R^a and R^b are the same or different and each represents a hydrogen atom, or a C₁₋₆ alkyl group, or

L and R¹ in combination optionally form a bi- or tri-cyclic fused
25 heterocyclic group optionally substituted by substituent(s) selected from the group consisting of

(a) a halogen atom,

(b) a C₁₋₆ alkoxy-carbonyl group,

(c) a C₁₋₆ alkyl group optionally substituted by C₆₋₁₄ aryl group(s), and

(d) an oxo group; and

ring B¹ represents a benzene ring, a pyridine ring, a pyrimidine
5 ring, a pyrazine ring or a pyridazine ring, each of which is
optionally substituted by substituent(s) selected from the group
consisting of

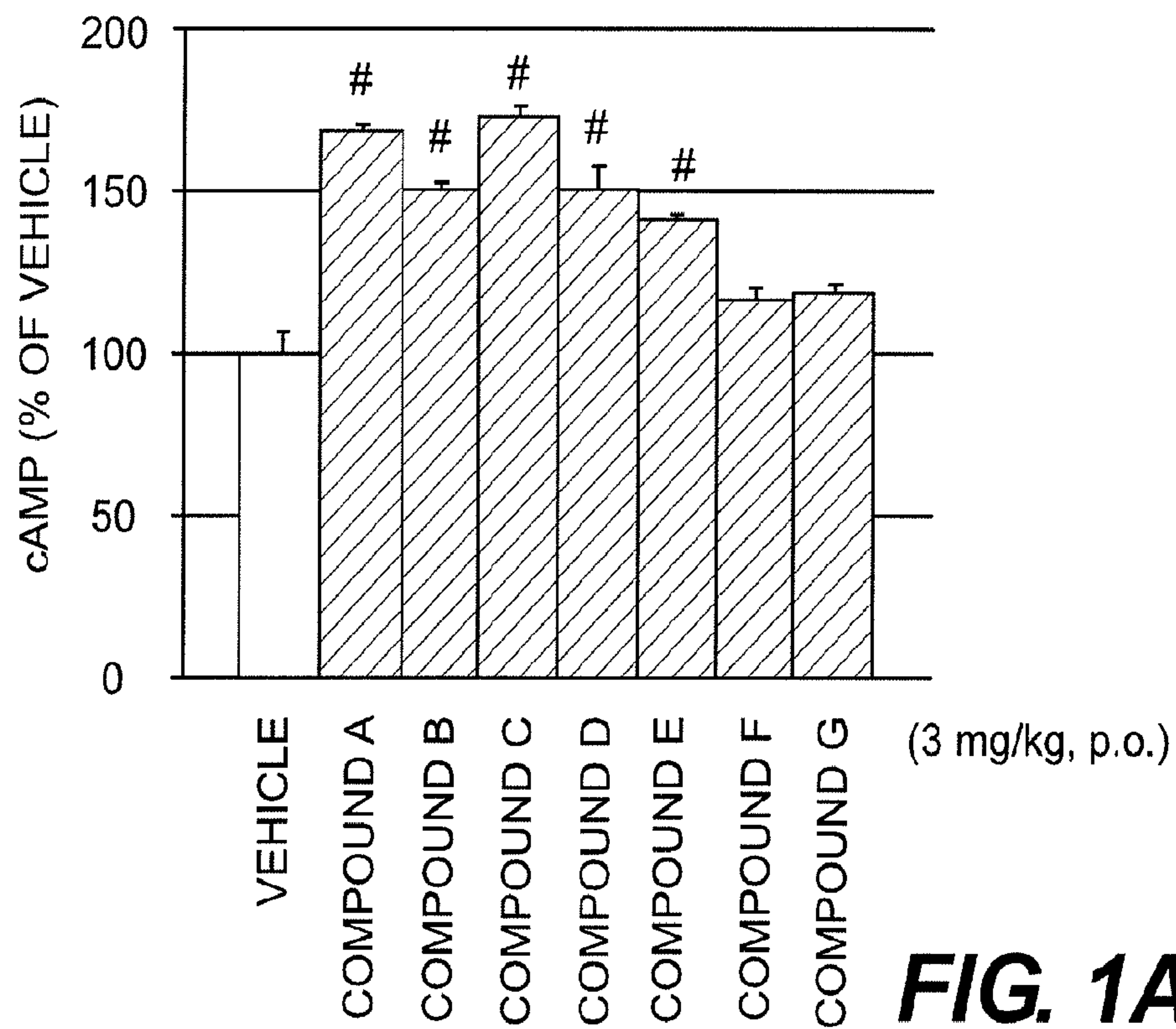
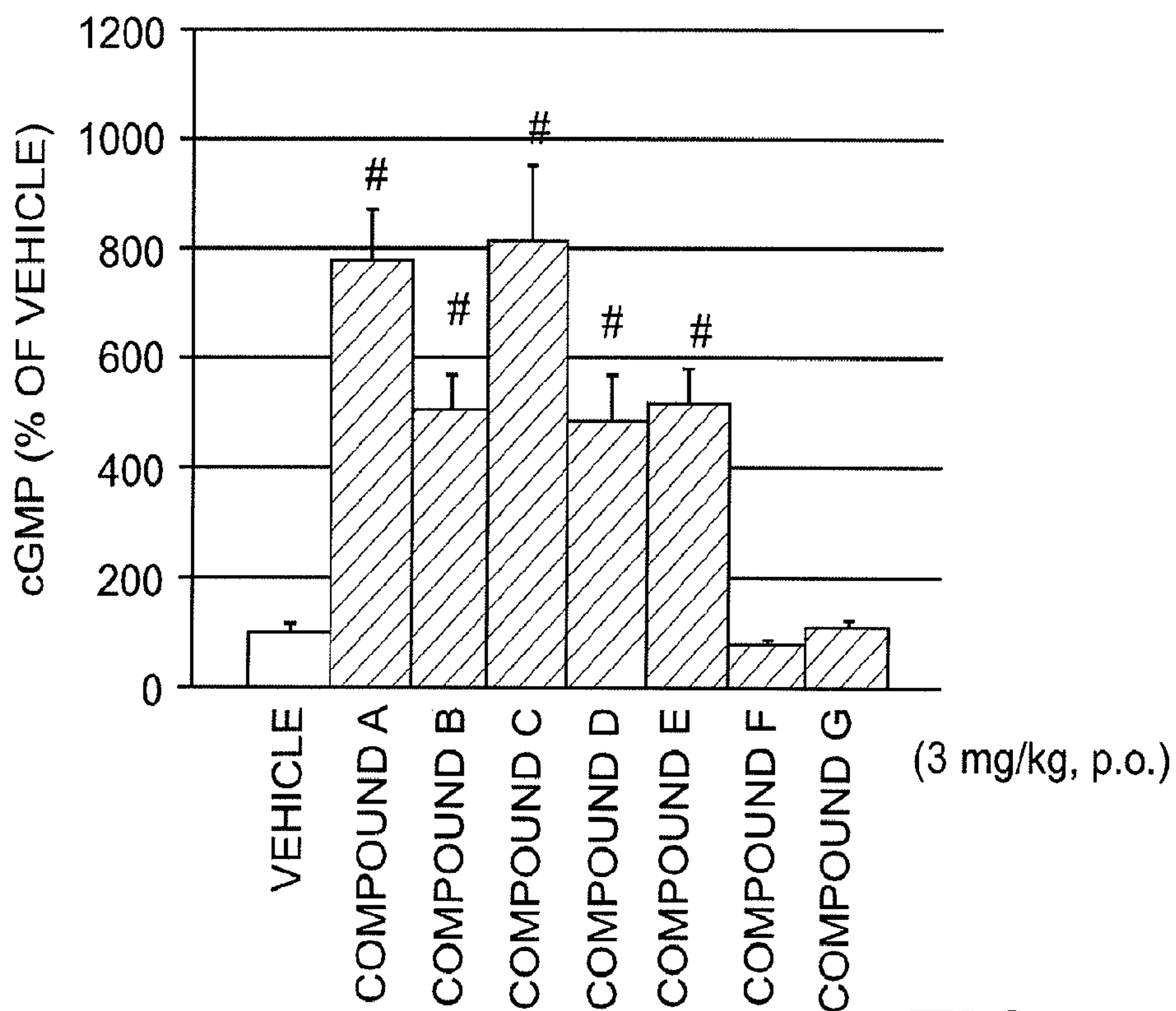
(a) a halogen atom, and

(b) a C₁₋₆ alkyl group;

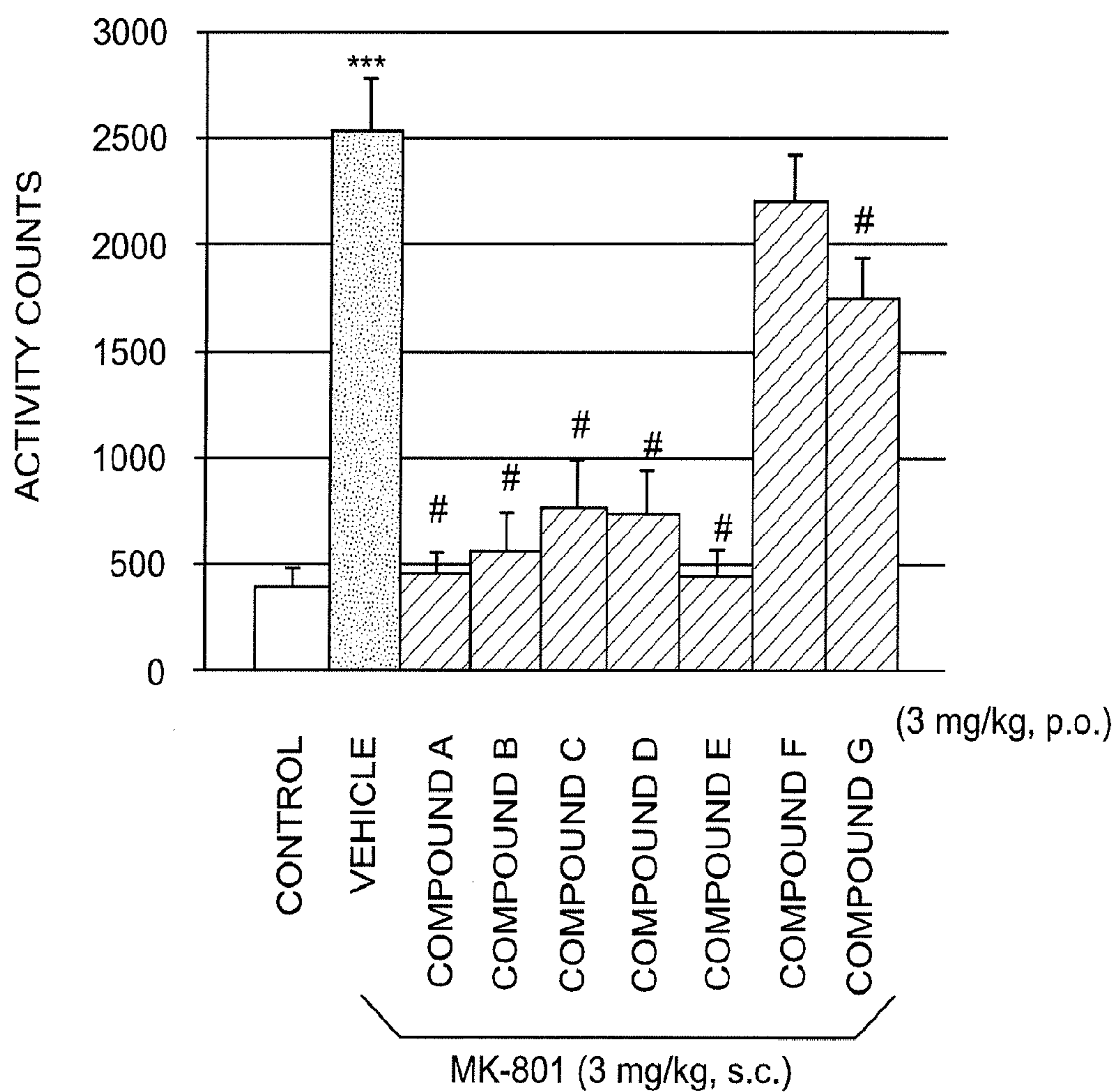
10 or a pharmacologically acceptable salt thereof,

for use in prevention or treatment of schizophrenia, autism,
Alzheimer's disease, bipolar disorders, Parkinson's disease,
Huntington's disease, obesity, drug addiction or attention
deficit/hyperactivity disorder.

1/2

**FIG. 1A****FIG. 1B**

2/2

**FIG. 2**

