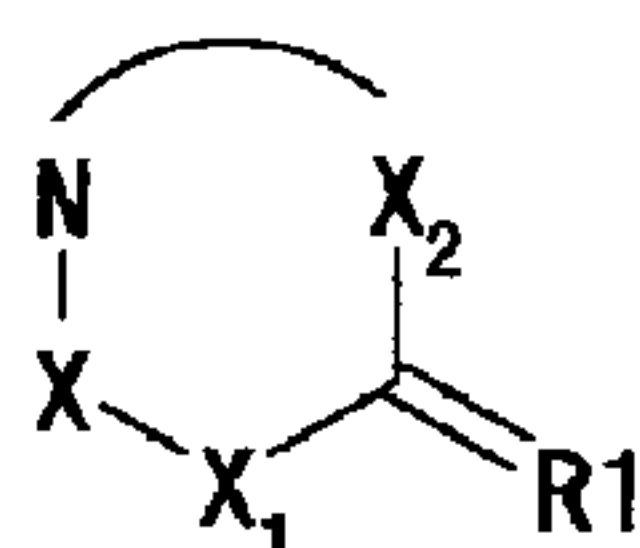




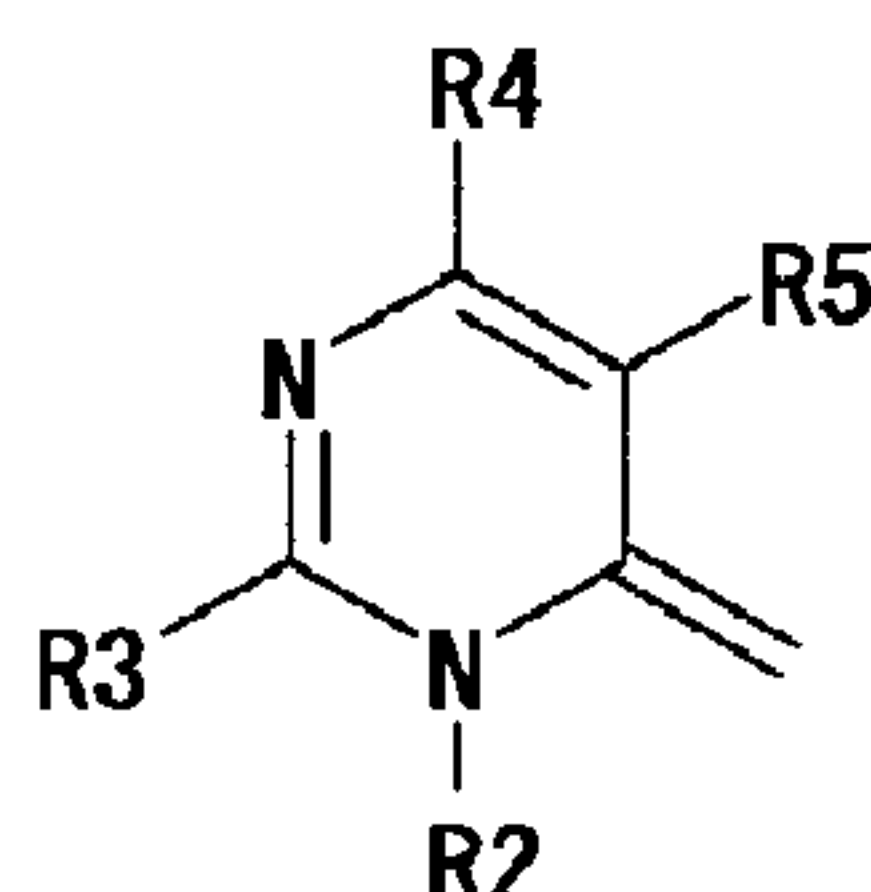
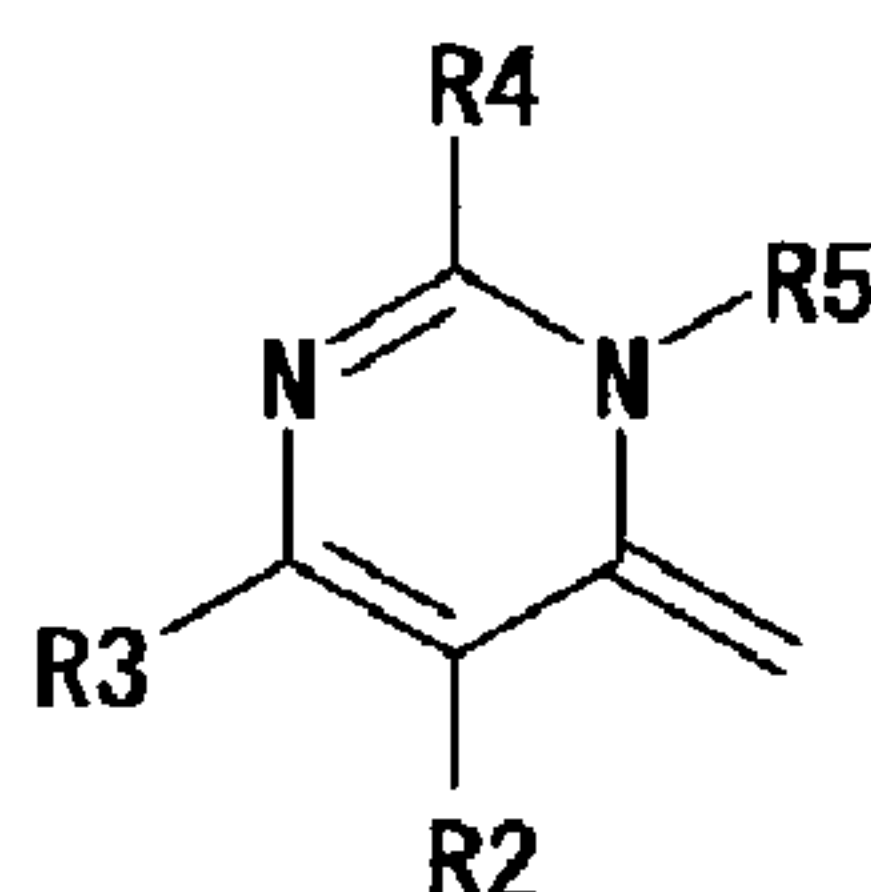
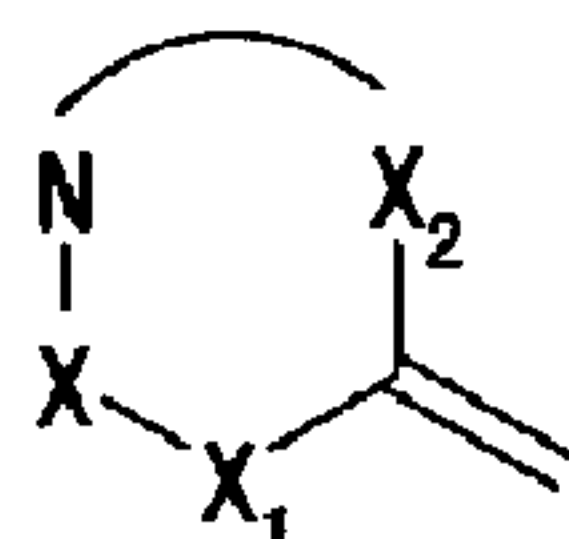
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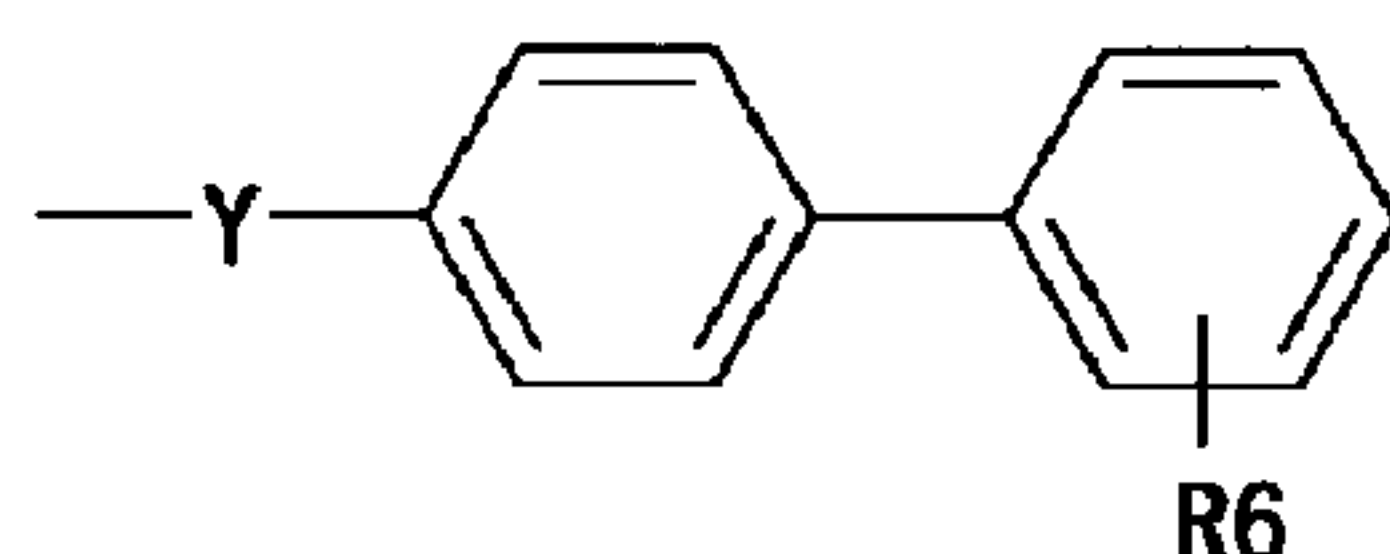
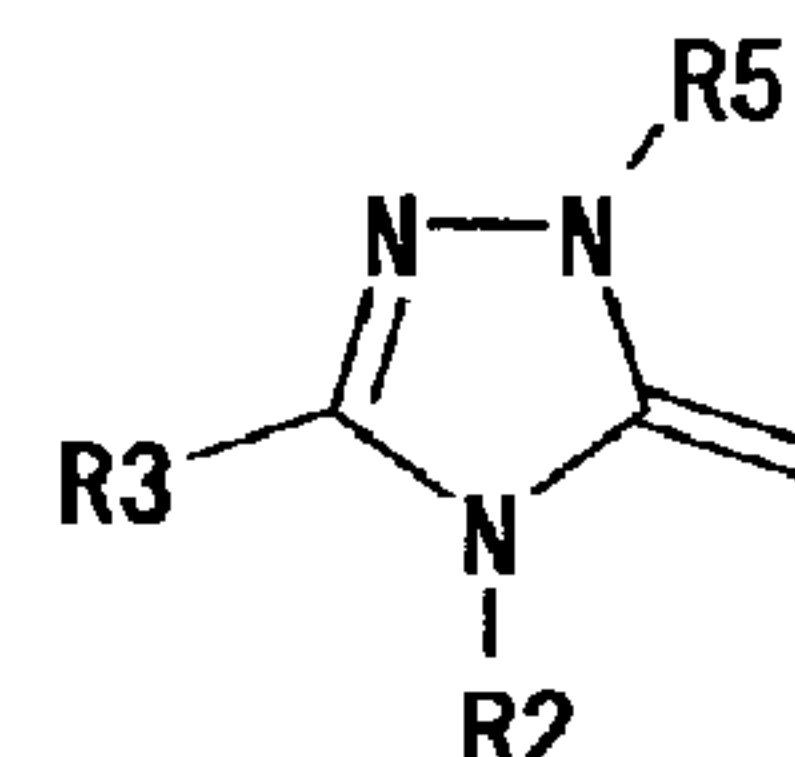
(54) Titre : COMPOSE HETEROMONOCYCLIQUE ET SES UTILISATIONS
(54) Title: HETEROMONOCYCLIC COMPOUND AND USE THEREOF



(I)



or



(57) Abrégé/Abstract:

A compound represented by the formula (I): wherein R1 is an oxo group, =N-R or the like; a group represented by the formula: is a group represented by the formula:; R2 is a group represented by the formula: or a salt thereof. The compound of the present



(57) **Abrégé(suite)/Abstract(continued):**

invention is useful as a drug for the prophylaxis or treatment of circulatory diseases, metabolic diseases and/or central nervous system diseases.

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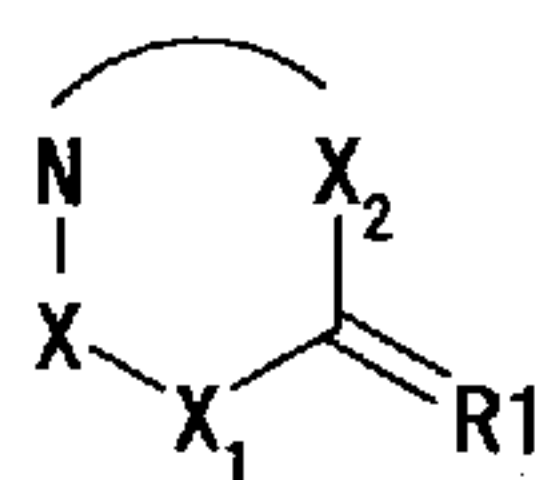
(71) Applicant (for all designated States except US): **TAKEDA PHARMACEUTICAL COMPANY LIMITED** [JP/JP];
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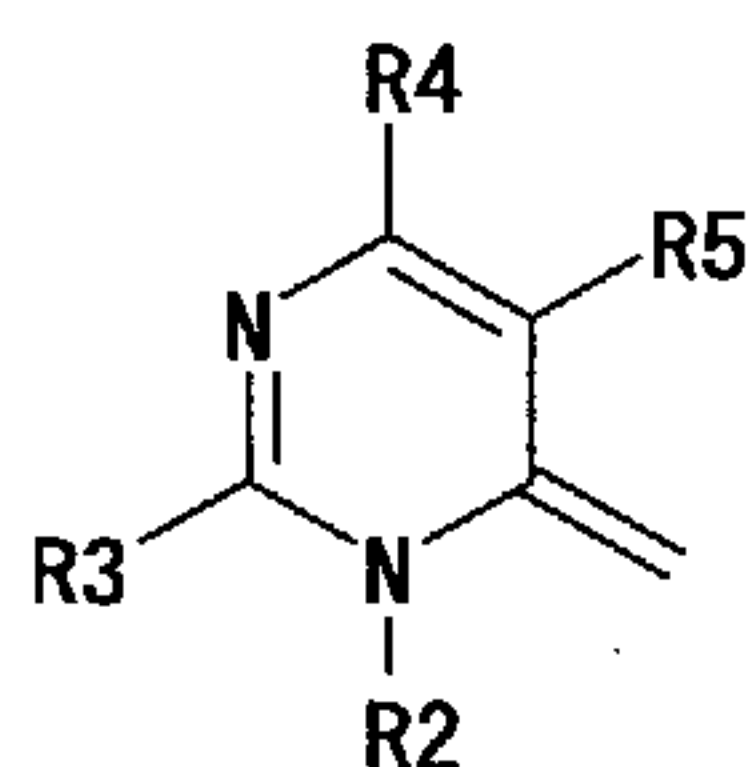
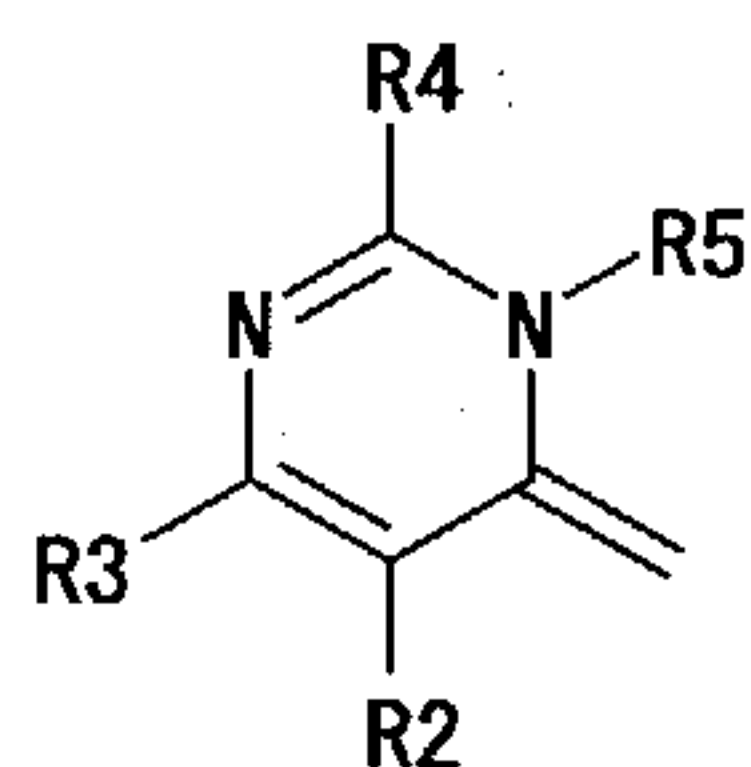
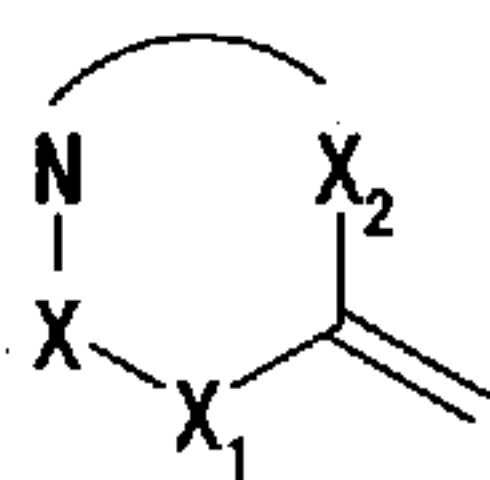
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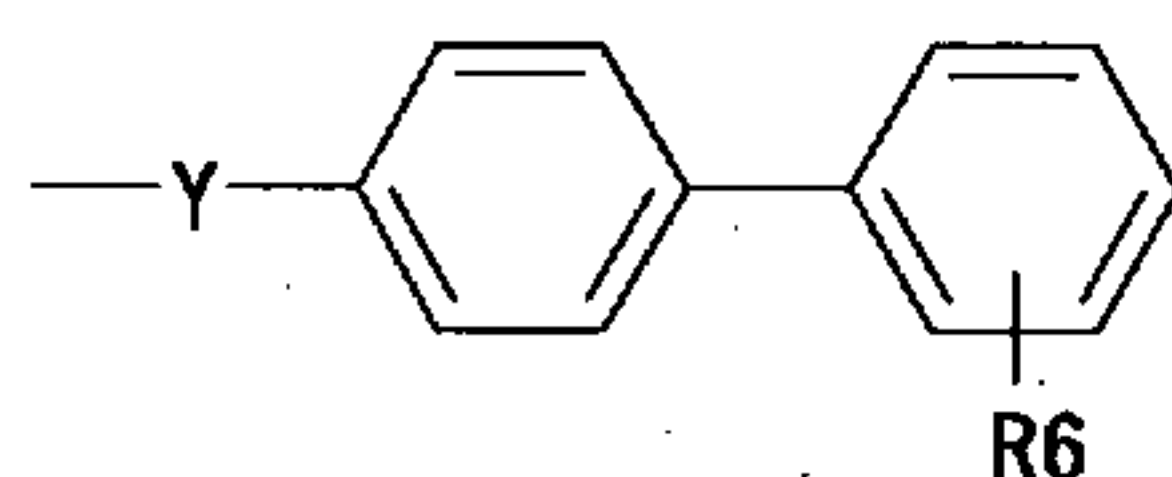
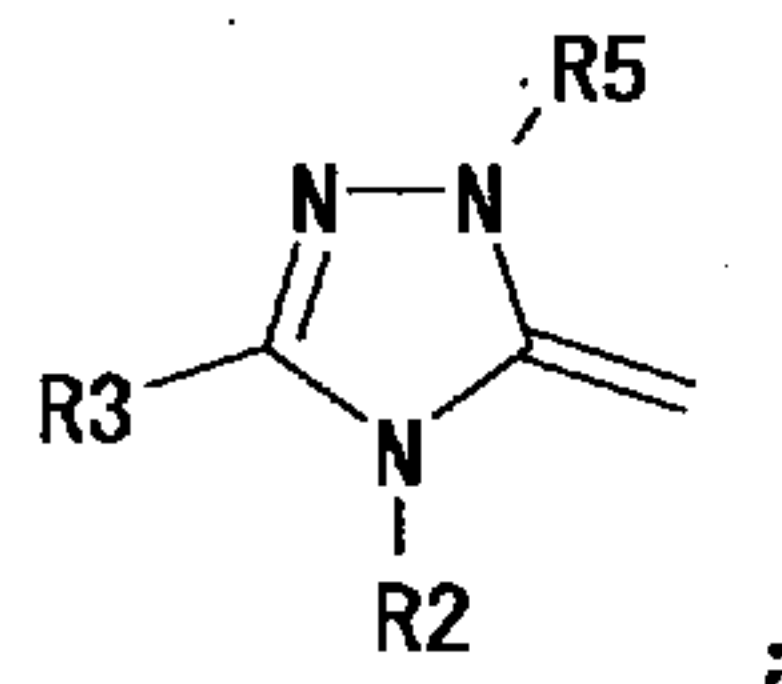
(54) Title: HETEROMONOCYCLIC COMPOUND AND USE THEREOF



(I)



or



(57) Abstract: A compound represented by the formula (I): wherein R1 is an oxo group, =N-R or the like; a group represented by the formula: is a group represented by the formula:; R2 is a group represented by the formula: or a salt thereof. The compound of the present invention is useful as a drug for the prophylaxis or treatment of circulatory diseases, metabolic diseases and/or central nervous system diseases.

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CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 372

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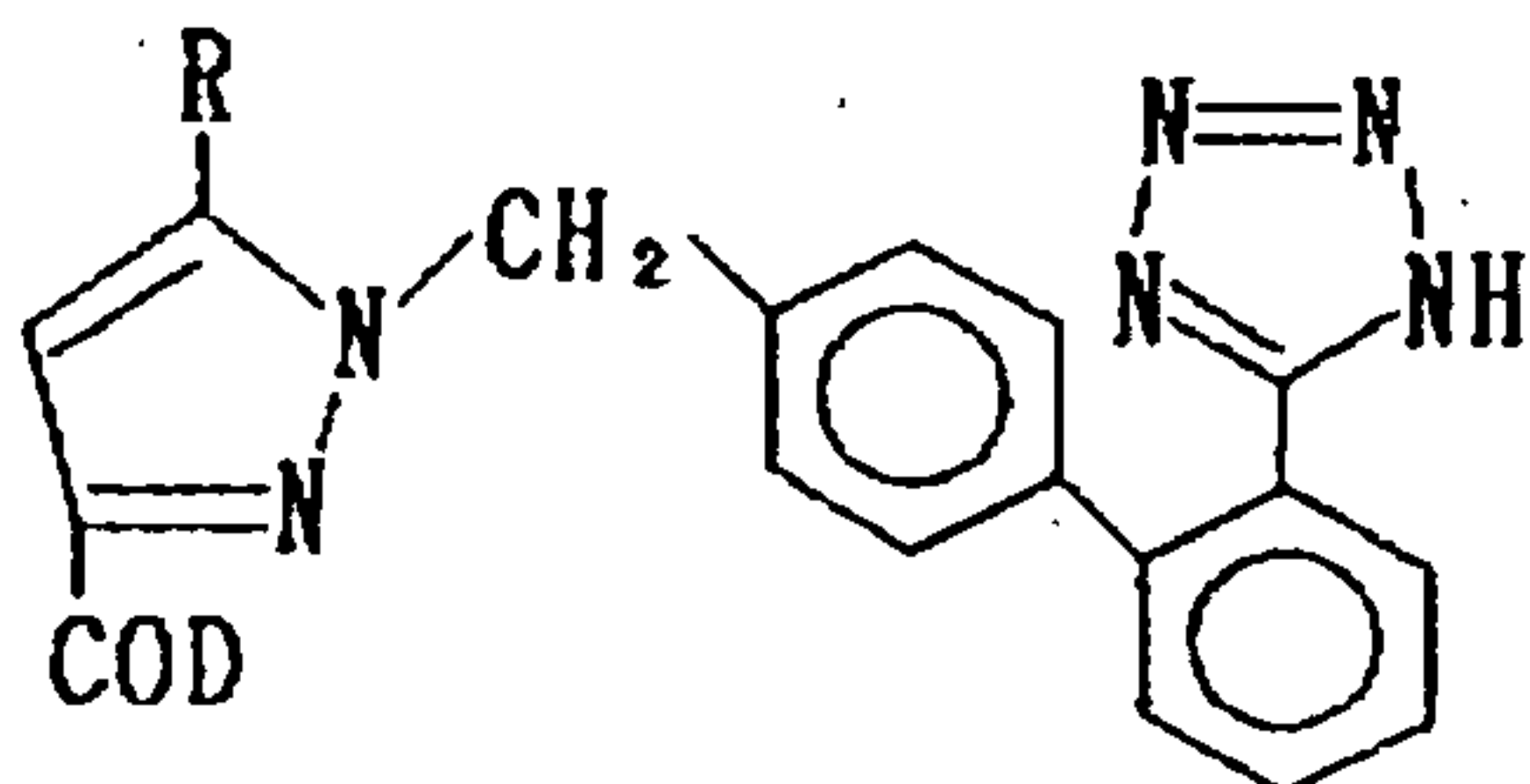
NOTE POUR LE TOME / VOLUME NOTE:

DESCRIPTION**HETEROMONOCYCLIC COMPOUND AND USE THEREOF****Technical Field**

The present invention relates to a novel heteromonocyclic
 5 compound having superior properties as a pharmaceutical agent,
 a production method thereof and use thereof. More particularly,
 the present invention relates to a heteromonocyclic compound
 having a particular structure and superior pharmacological
 action such as strong and sustained hypotensive action,
 10 insulin sensitizing activity and the like, and superior
 property such as crystallinity and stability and the like,
 which is useful as an agent for the prophylaxis or treatment
 of circulatory diseases such as hypertension, cardiac disease
 (cardiac hypertrophy, cardiac failure, myocardial infarction
 15 and the like), arteriosclerosis, kidney disease (diabetic
 nephropathy, chronic glomerulonephritis and the like),
 cerebral apoplexy and the like; metabolic diseases such as
 hyperlipidemia, obesity, diabetes and the like; and/or central
 nervous system diseases such as depression, dementia,
 20 Alzheimer's disease and the like, or a salt thereof, or a
 prodrug thereof, a production method thereof, and use thereof
 and the like.

Background of the Invention

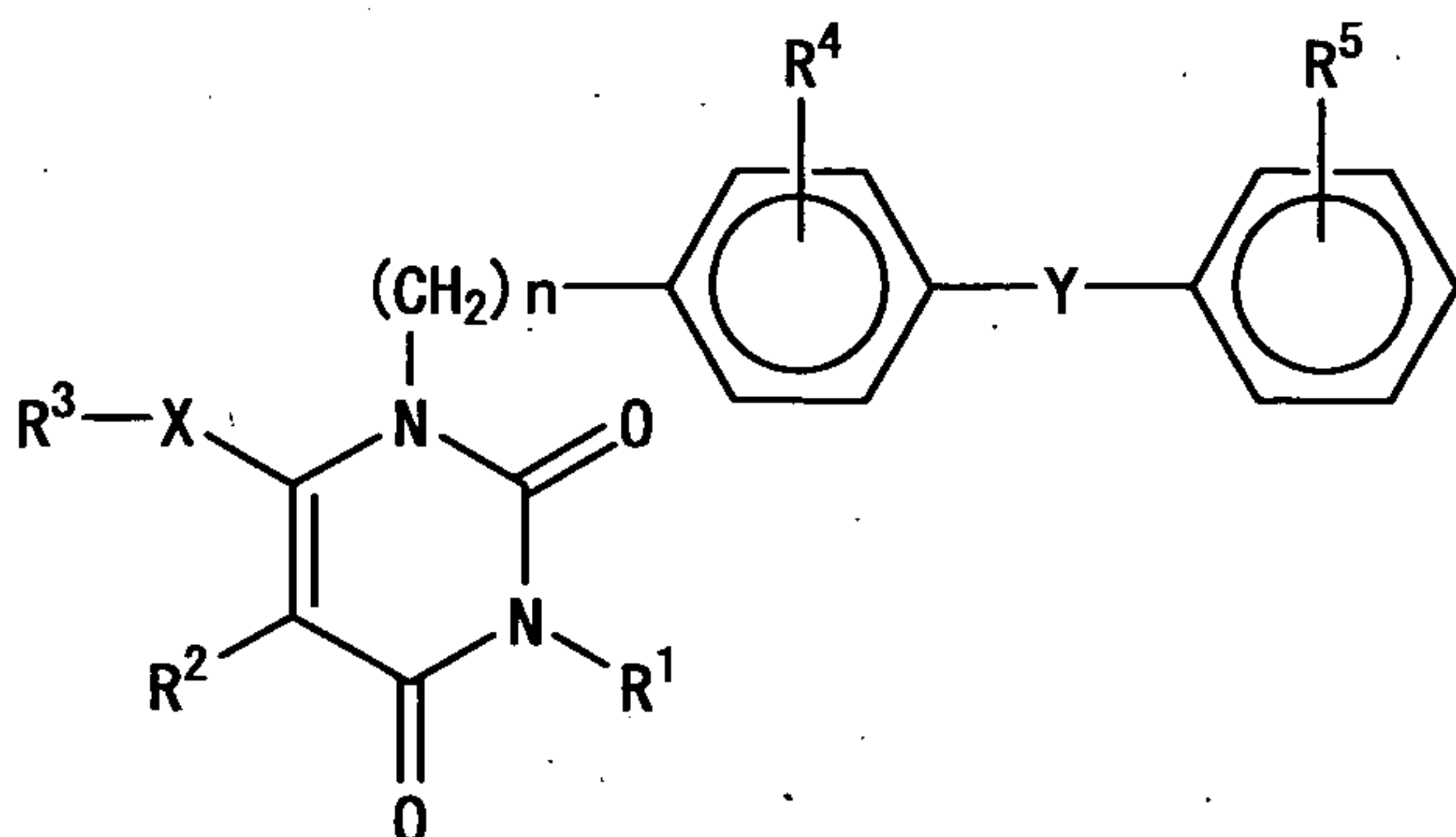
US Patent No. 5,183,899 (JP-A-3-218371) describes a
 25 compound represented by the formula



wherein R is an alkyl group and D is an alkoxy group, a
 hydroxyl group, a halogen atom or an amino group which may be
 substituted, or a salt thereof, and that the compound has an
 30 angiotensin II receptor antagonistic action and a hypotensive

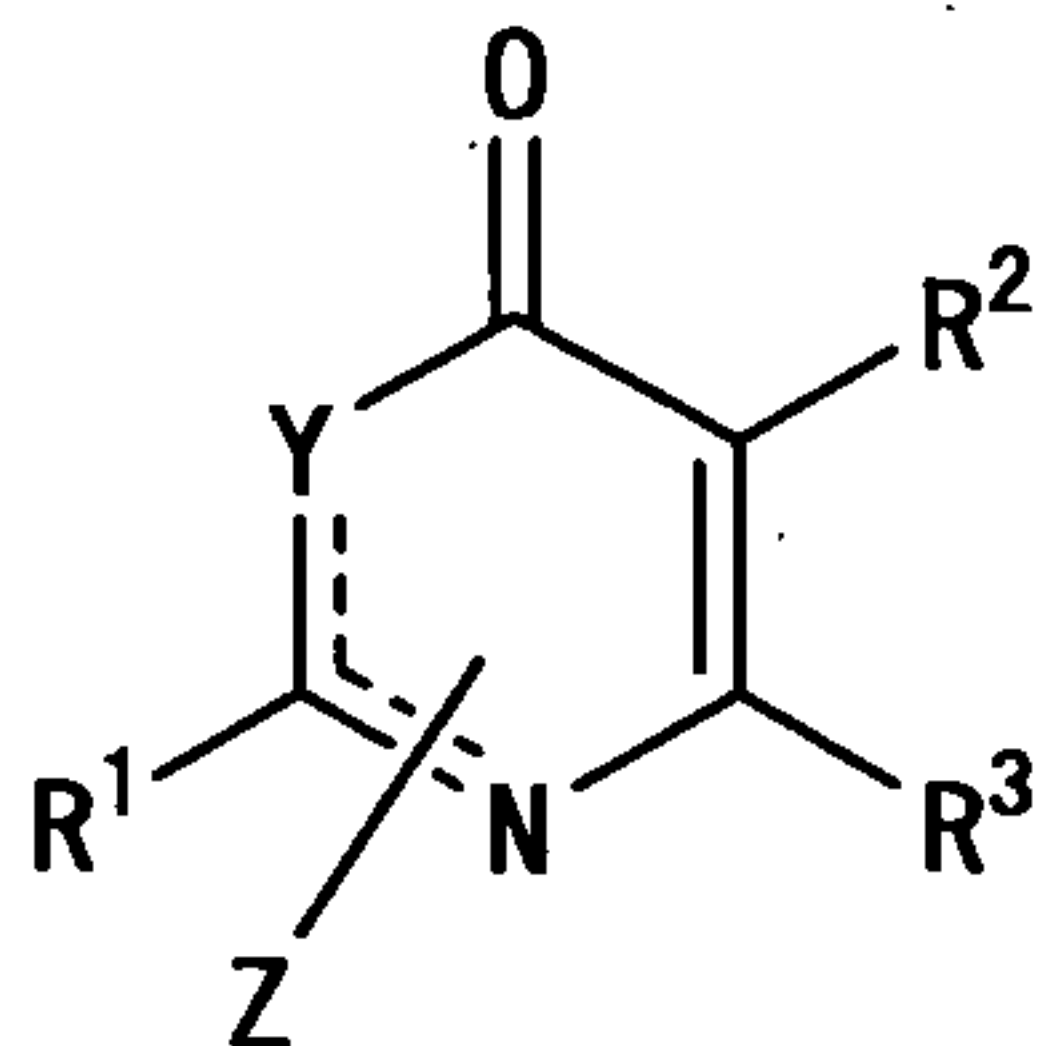
action and is useful as a therapeutic agent for circulatory diseases such as hypertension, cardiac disease, cerebral apoplexy and the like.

US Patent No. 5,162,326 (JP-A-4-330072) describes a
5 compound represented by the formula



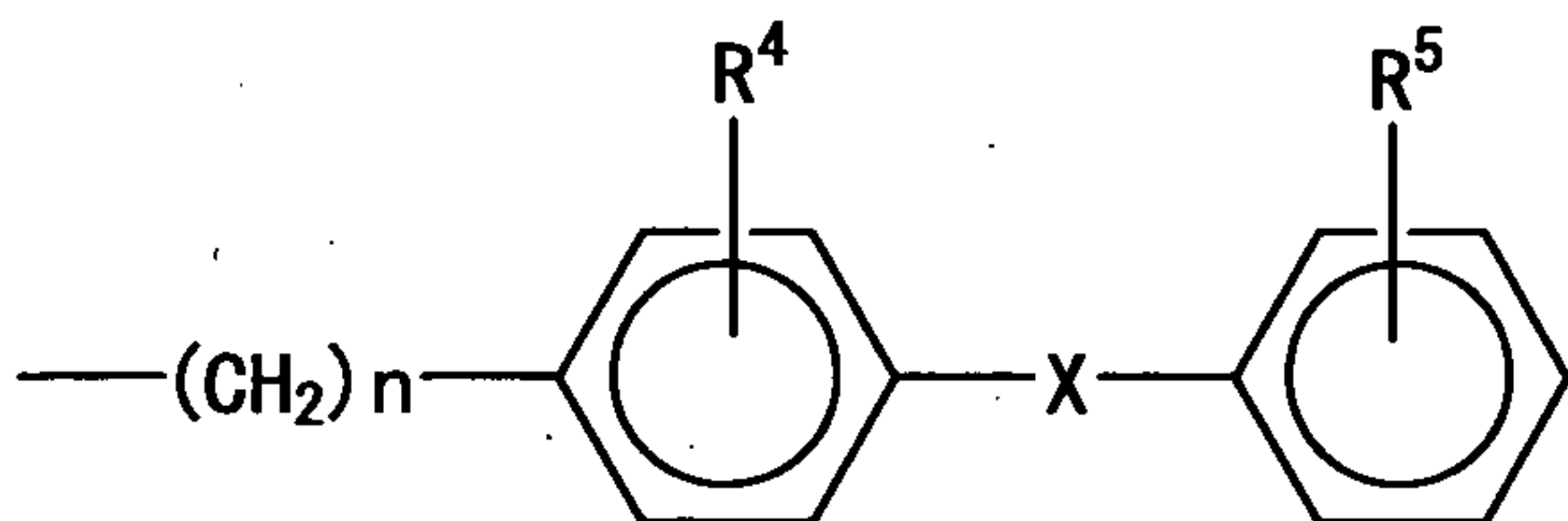
wherein R¹ is hydrogen or a hydrocarbon residue which may be substituted; R² is hydrogen, halogen, nitro, optionally substituted amino, formyl or a hydrocarbon residue which may
10 be substituted; R³ is a hydrocarbon residue which may be substituted; R⁴ is hydrogen, halogen or nitro; R⁵ is a residue capable of forming an anion or a residue convertible into an anion; X is a direct bond or a spacer having one atomic length and containing an oxygen, nitrogen or sulfur atom; Y is a
15 direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; n is an integer of 1 or 2; or a salt thereof, and that the compound has an angiotensin II receptor antagonistic action and a hypotensive action and is useful as a therapeutic agent for
20 circulatory diseases such as hypertension, cardiac disease, cerebral apoplexy and the like.

US Patent No. 5,304,565 (JP-A-5-155862) describes a compound represented by the formula



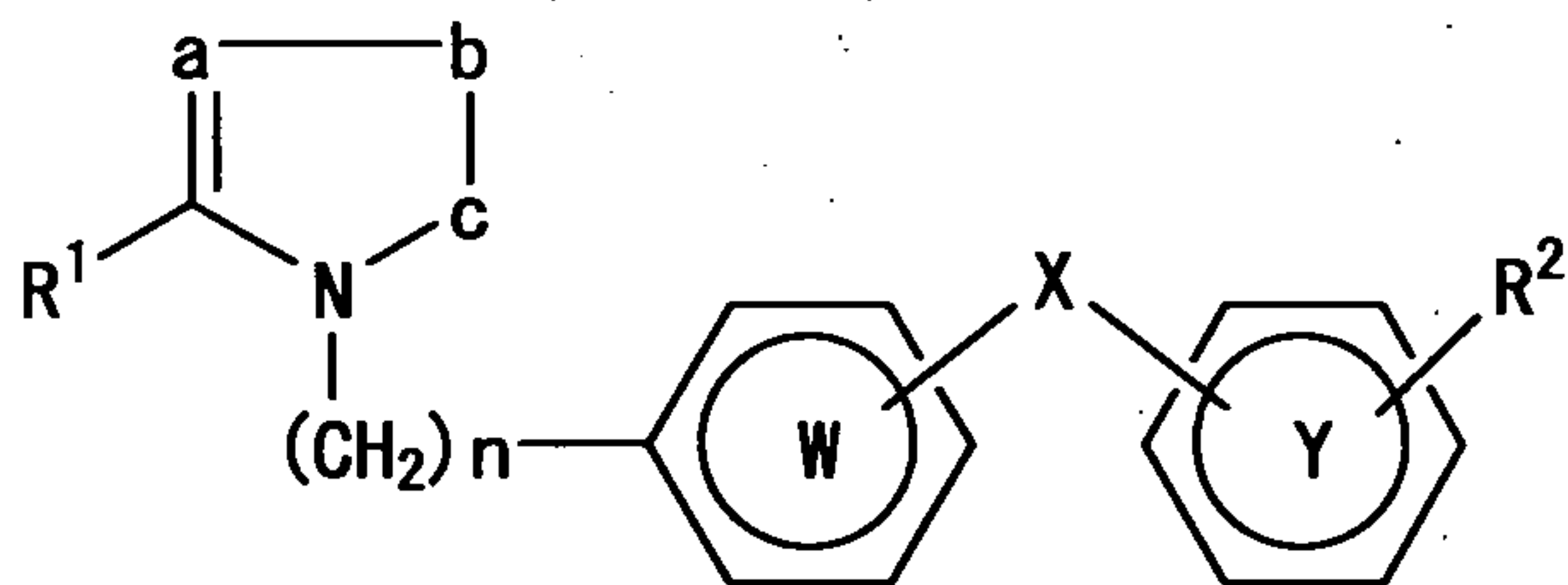
25 wherein R¹, which may be optionally bound through a hetero atom,

is a hydrocarbon residue which may be substituted; R^2 and R^3 which may be same or different, are each independently hydrogen, cyano, nitro, optionally substituted lower alkyl, or a group of the formula $-COD$ wherein D is alkoxy, hydroxy, halogen, or optionally substituted amino, or R^2 and R^3 are taken together to form a benzene ring which may be substituted; Y is N or CH; Z is bound to a ring nitrogen atom and is a group having the formula



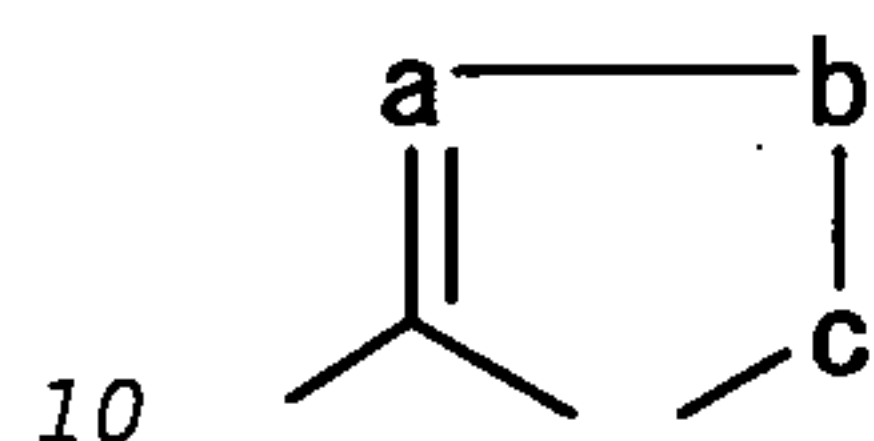
wherein R^4 is hydrogen, halogen or nitro, and R^5 is a residue capable of forming an anion or a residue convertible into an anion; X is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; n is an integer of 1 or 2; and the dotted line shows that one double bond exists; or a salt thereof, and the compound has an angiotensin II receptor antagonistic action and a hypotensive action and is useful as a therapeutic agent for circulatory diseases such as hypertension, cardiac disease, cerebral apoplexy and the like.

US Patent No. 5,243,054 (JP-A-5-271228) describes a compound represented by the formula



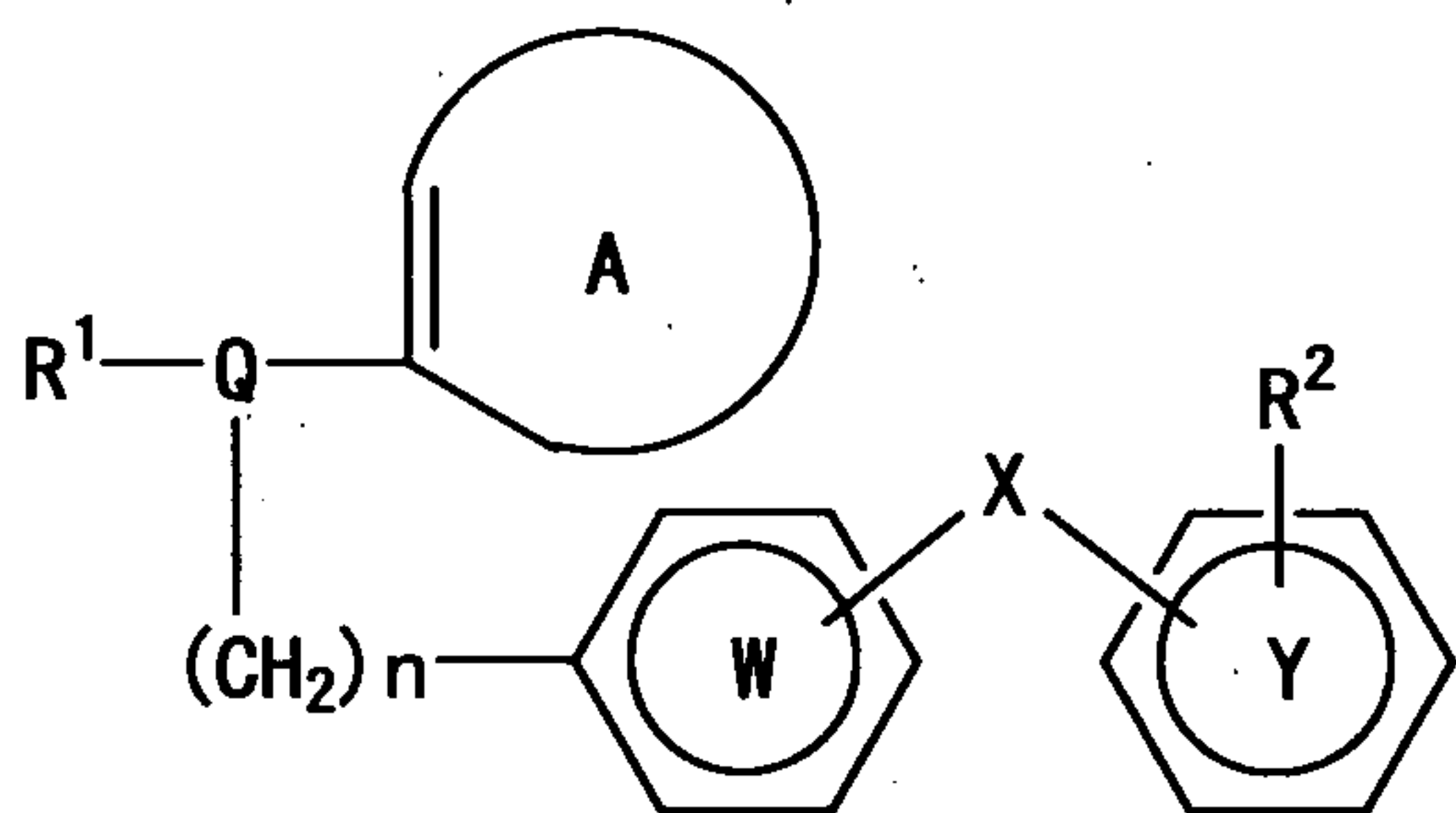
wherein R^1 is an optionally substituted hydrocarbon residue which is optionally bonded through a hetero atom; R^2 is an optionally substituted 5-7 membered heterocyclic residue having, as a group capable of constituting the ring, a carbonyl group, a thiocarbonyl group, an optionally oxidized sulfur atom or a group convertible into them; X is a direct

bond or a spacer having an atomic length of two or less between the ring Y and the ring W; W and Y are independently an optionally substituted aromatic hydrocarbon residue optionally containing a hetero atom or an optionally substituted heterocyclic residue; n is an integer of 1 or 2; a and b forming the heterocyclic residue are independently one or two optionally substituted carbon or hetero atoms; c is an optionally substituted carbon or hetero atom; and, in the group of the formula



substituents on adjacent two atoms forming the ring are optionally bonded to each other to form a 5-6 membered ring together with the two atoms forming the ring, or a salt thereof, and that the compound has an angiotensin II receptor antagonistic action, a hypotensive action and a central nervous system action and is useful as a therapeutic agent for circulatory diseases such as hypertension, cardiac disease, cerebral apoplexy, nephritis, arteriosclerosis and the like, or Alzheimer's disease or senile dementia.

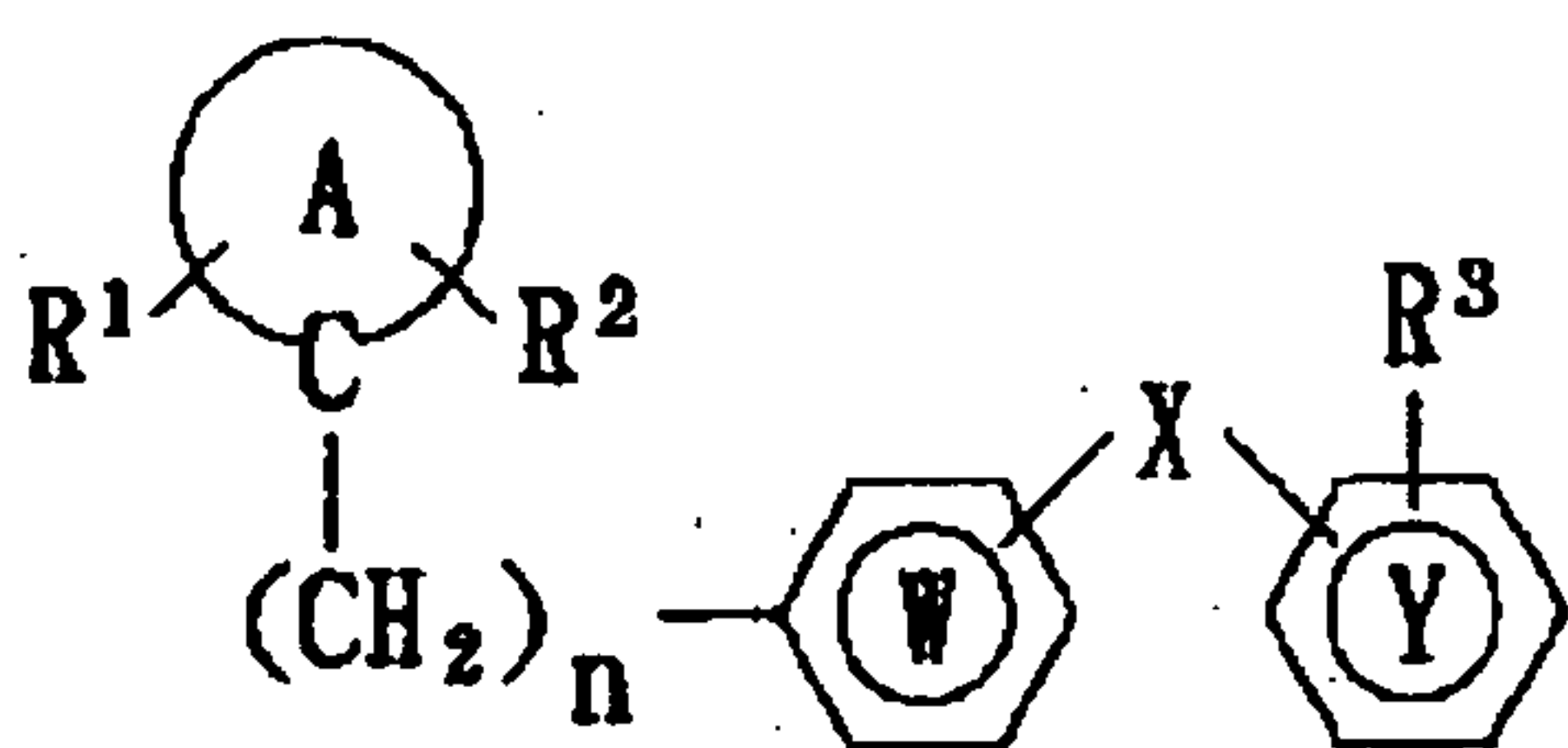
20 US Patent No. 5,500,427 (JP-A-6-239859) describes a compound represented by the formula



wherein R^1 is an optionally substituted hydrocarbon residue which is optionally bound through a hetero atom or an optionally substituted acyl group; R^2 is an optionally substituted 5-7 membered heterocyclic residue having, as a group capable of constituting the ring, carbonyl group, thiocarbonyl group, an optionally oxidized sulfur atom or a

group convertible into them; Q is CH or N; X is a direct bond or a spacer having an atomic length of two or less between the ring Y and the ring W; rings W and Y are each an optionally substituted aromatic hydrocarbon residue optionally containing
 5 a hetero atom or an optionally substituted heterocyclic residue; n is an integer of 1 or 2; the ring A is an optionally substituted 5-8 membered cyclic group, and two of the substituents are optionally bound to each other to form a ring, or a salt thereof, and that the compound has an
 10 angiotensin II receptor antagonistic action and a hypotensive action, and is useful as a therapeutic agent for circulatory diseases such as hypertension, cardiac disease, nephritis, cerebral apoplexy and the like, or an agent for improving cerebral function.

15 US Patent No. 5,496,835 (JP-A-7-070118) describes a compound represented by the formula



wherein the ring A is a 5-10 membered aromatic heterocyclic group optionally having, besides R¹ and R², further
 20 substituents; R¹ is an optionally substituted hydrocarbon residue which is optionally bonded through a hetero atom; R² is a group capable of liberating proton in a living body or a group convertible thereinto; R³ is an 5-7 membered optionally substituted heterocyclic residue having, as a group capable of
 25 constituting the ring, carbonyl group, thiocarbonyl group, an optionally oxidized sulfur atom or a group convertible into them; X shows that the ring Y and the ring W are bonded to each other directly or through a spacer having an atomic length of two or less; the ring W and the ring Y are each an
 30 optionally substituted aromatic hydrocarbon or aromatic heterocyclic residue; and n is an integer of 1 to 3, or a salt thereof, and that compound has an angiotensin II receptor

antagonistic action and a hypotensive action and is useful as a therapeutic agent for circulatory diseases such as hypertension, cardiac disease, cerebral apoplexy and the like, or an agent for improving cerebral function.

- 5 However, there is no report that the above-mentioned compounds have an angiotensin II receptor antagonistic action and a peroxisome proliferator-activated receptor (PPAR) agonistic action.

10

Disclosure of the Invention

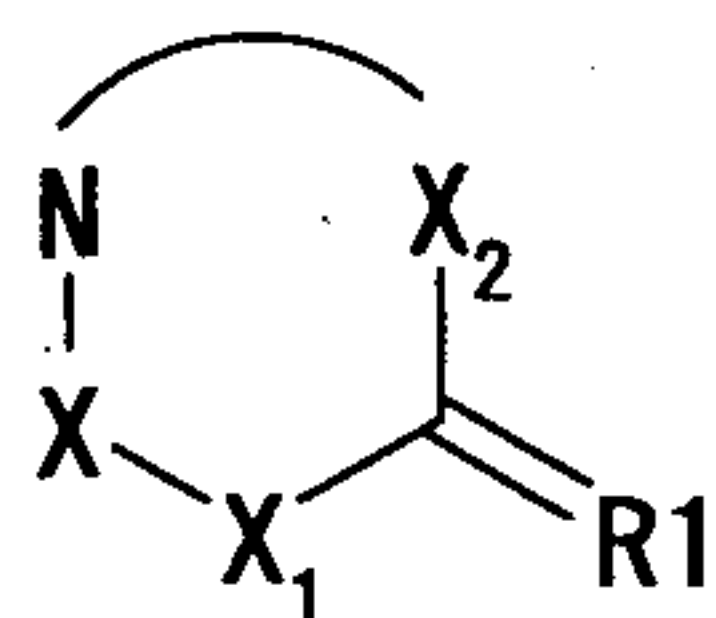
 An object of the present invention is to provide a novel compound superior as a pharmaceutical agent for the prophylaxis or treatment of circulatory diseases such as hypertension and the like; metabolic diseases such as diabetes
15 and the like; central nervous system diseases such as dementia and the like; and the like.

 The present inventors have conducted intensive studies in an attempt to find a new compound having a superior pharmacological action and superior physicochemical properties
20 so as to provide a pharmaceutical agent more useful as a prophylactic or therapeutic drug for circulatory diseases, metabolic diseases, central nervous system diseases, and the like. As a result, they have found that a compound represented by the following formula (I) or a salt thereof (to be referred
25 to as "compound (I)" in the present specification) has an angiotensin II receptor antagonistic action and a peroxisome proliferator-activated receptor (PPAR) agonistic action (including a partial agonistic action) and is useful as an agent for the prophylaxis or treatment for circulatory
30 diseases such as hypertension, cardiac disease (cardiac hypertrophy, cardiac failure, myocardial infarction and the like), arteriosclerosis, kidney disease (diabetic nephropathy, chronic glomerulonephritis and the like), cerebral apoplexy and the like; metabolic diseases such as hyperlipidemia,
35 obesity, diabetes and the like; and/or central nervous system

diseases such as depression, dementia, Alzheimer's disease and the like, which resulted in the completion of the present invention.

Accordingly, the present invention relates to

- 5 [1] a compound represented by the following formula (I):



(I)

wherein

R1 is

- (1) an oxo group;
 10 (2) a thioxo group;
 (3) a group represented by the formula: =N-R

wherein

R is

- (i) an optionally substituted C1-C6 alkyl group;
 15 (ii) an optionally substituted C3-C6 cycloalkyl group;
 (iii) a group represented by the formula: -O-Ra

wherein Ra is hydrogen, an optionally substituted C1-C6 alkyl group or an optionally substituted C3-C6 cycloalkyl group; or

- 20 (iv) a group represented by the formula: -N(Rb)-Rc
 wherein Rb and Rc are each independently hydrogen, an optionally substituted C1-C6 alkyl group or an optionally substituted C3-C6 cycloalkyl group, or Rb and Rc are bonded to each other to form, together with the nitrogen atom
 25 bonded thereto, an optionally substituted nitrogen-containing heterocyclic group;

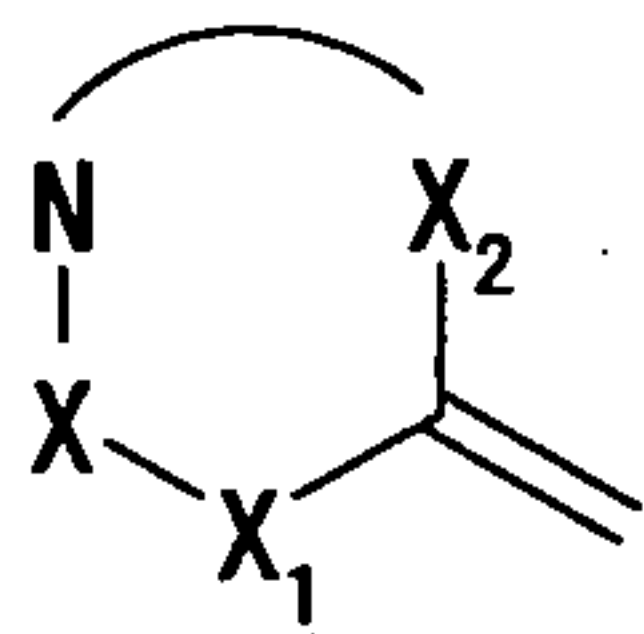
- (4) a group represented by the formula: =N-CO-R'

wherein R' is an optionally substituted C1-C6 alkyl group or an optionally substituted cyclic group;

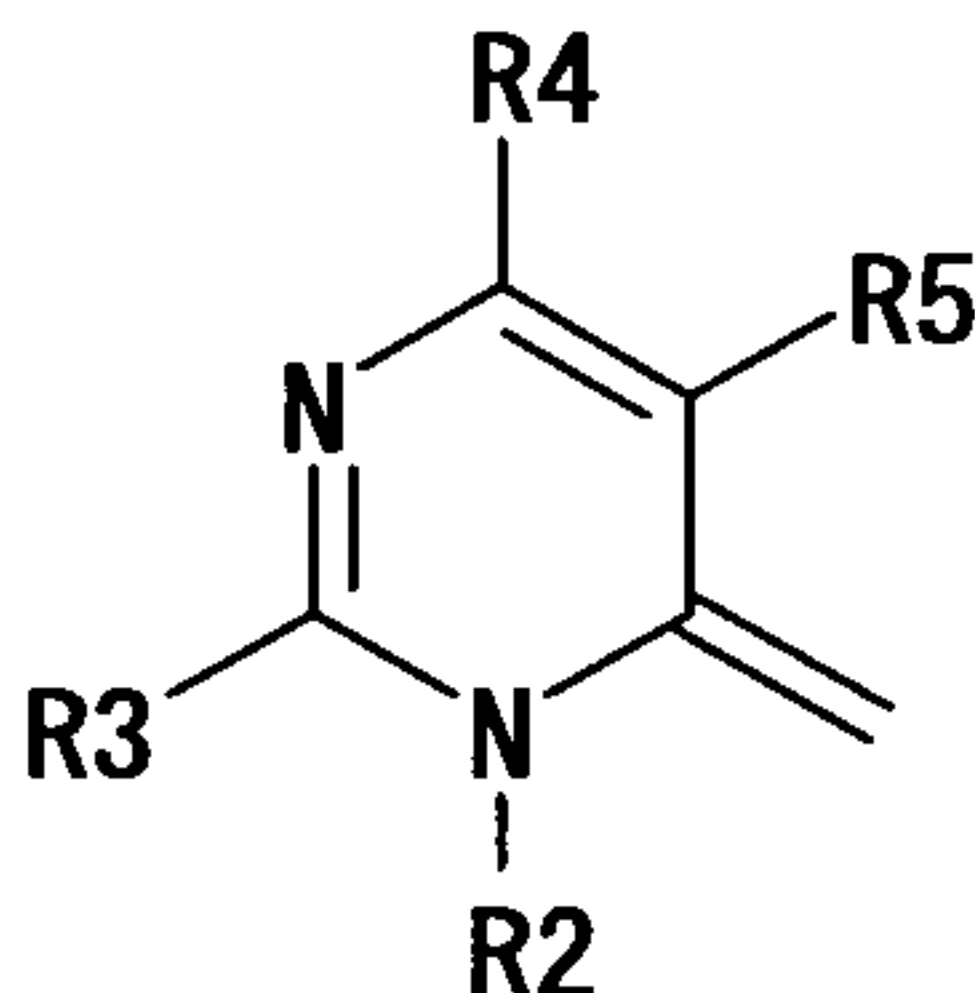
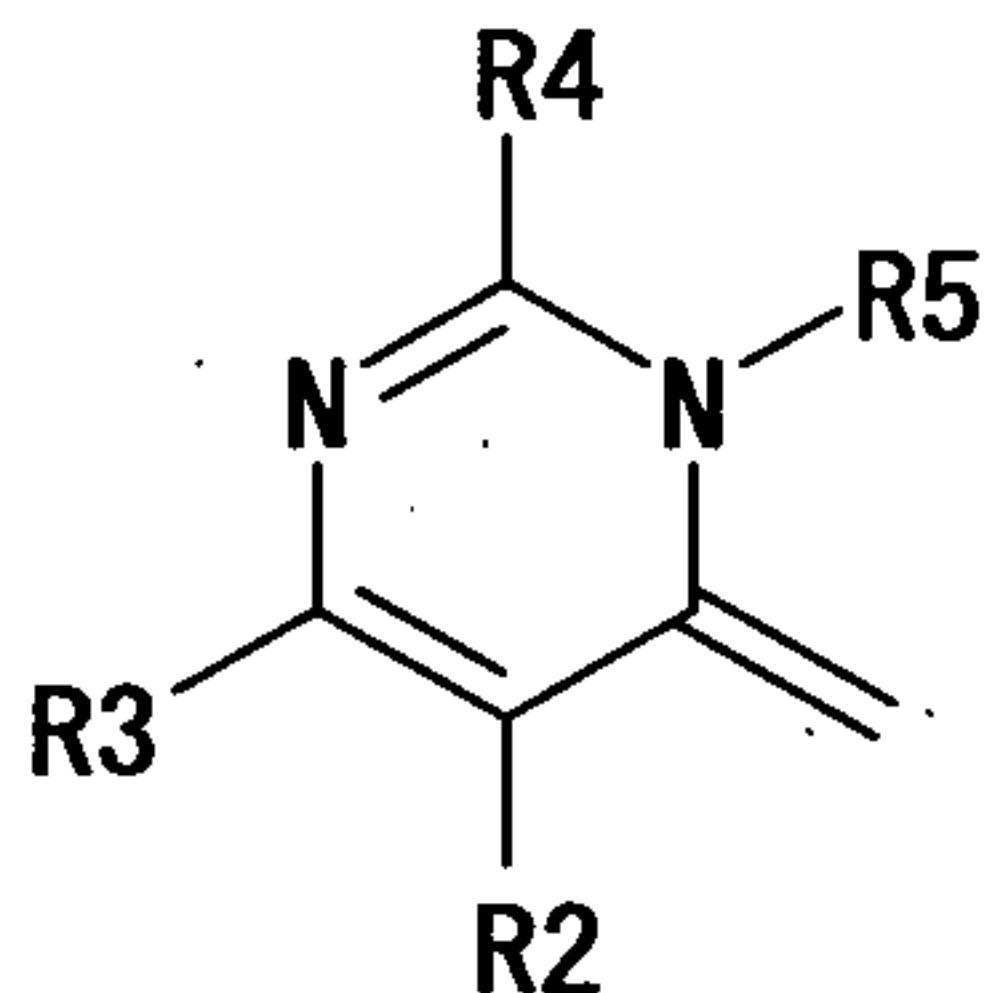
- 30 (5) a group represented by the formula: =N-CO-OR'

wherein R' is as defined above; or

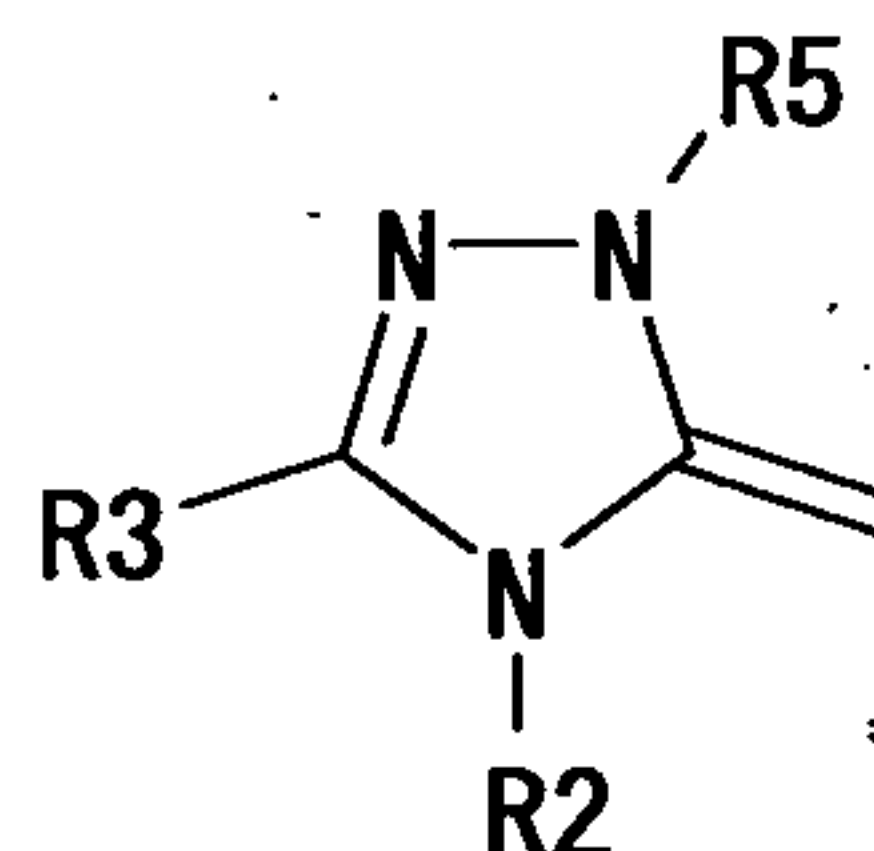
(6) a group represented by the formula: $=N-SO_2-R'$
 wherein R' is as defined above; and
 a group represented by the formula:



5 is

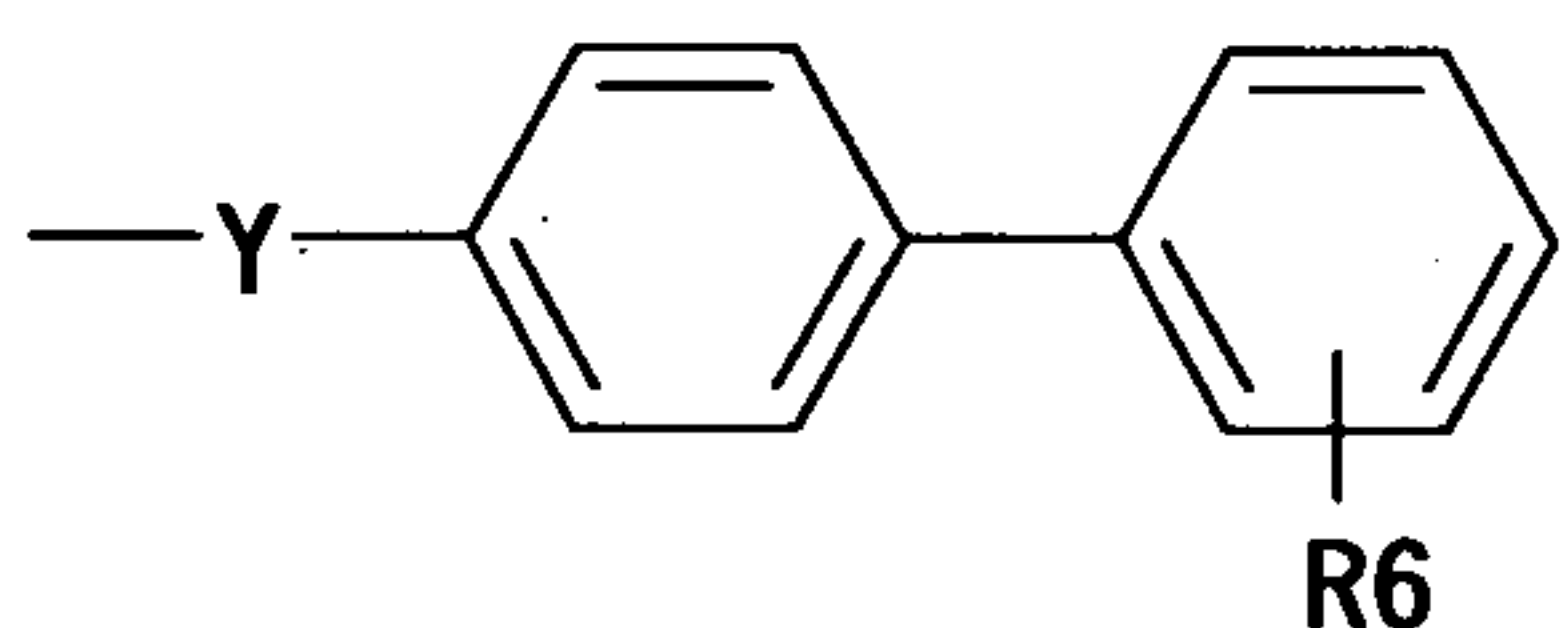


or

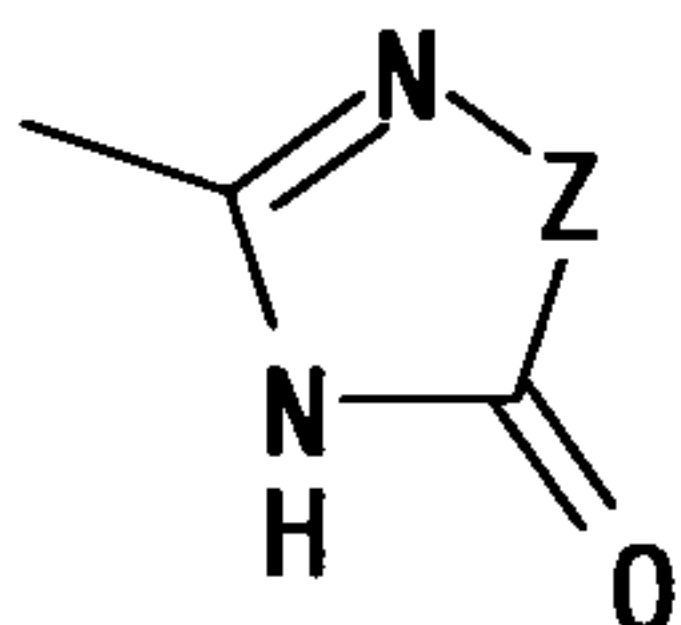


wherein

R_2 is a group represented by the formula:



10 wherein R_6 is a group represented by the formula:



wherein Z is O or $S(O)_n$ (n is an integer of 0 to 2), and
 Y is an optionally substituted C_1 - C_4 alkylene group or
 a group represented by the formula: $-O-W-$, $-W-O-$, $-N(R_d)-W-$ or
 15 $-W-N(R_d)-$

wherein W is a bond or an optionally substituted C_1 - C_4
 alkylene group, and R_d is an optionally substituted C_1 - C_6
 alkyl group or an optionally substituted C_3 - C_6 cycloalkyl
 group (the biphenyl group is optionally further substituted);

20 R_3 and R_4 are each independently

(1) hydrogen,

(2) an optionally substituted C_1 - C_6 alkyl group,

- (3) an optionally substituted C3-C6 cycloalkyl group,
 (4) an optionally substituted C1-C6 alkoxy group,
 (5) an optionally substituted C3-C6 cycloalkyloxy group,
 (6) an optionally substituted C1-C6 alkylamino group,
 5 (7) an optionally substituted di(C1-C6)alkylamino group or
 (8) an optionally substituted C1-C6 alkylthio group; and
 R5 is

- (1) hydrogen,
 (2) an optionally substituted C1-C6 alkyl group,
 10 (3) an optionally substituted C2-C6 alkenyl group,
 (4) an optionally substituted cyclic group,
 (5) a group represented by the formula: -CO-R8

wherein R8 is an optionally substituted C1-C6 alkyl group or
 an optionally substituted cyclic group, or

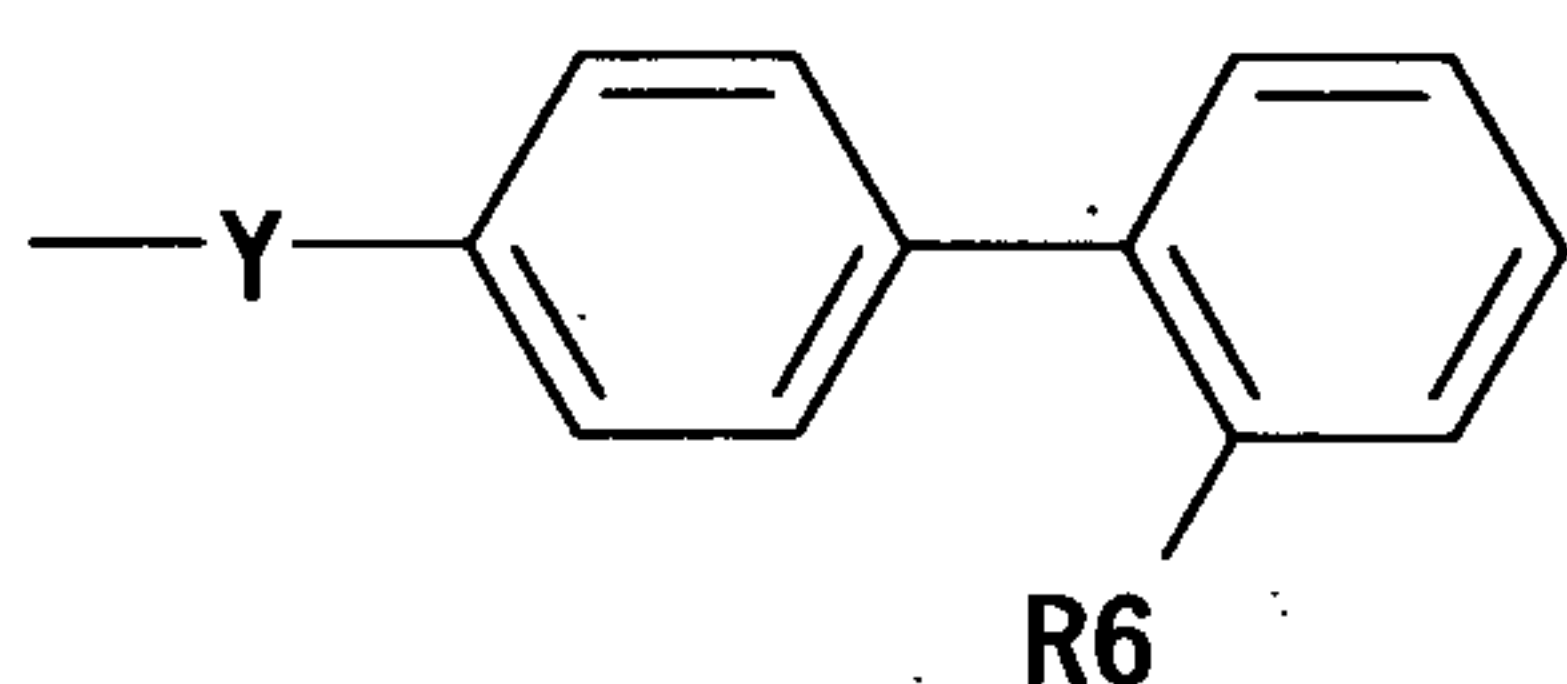
- 15 (6) a group represented by the formula: -O-R8'

wherein R8' is an optionally substituted C1-C6 alkyl group or
 an optionally substituted cyclic group,

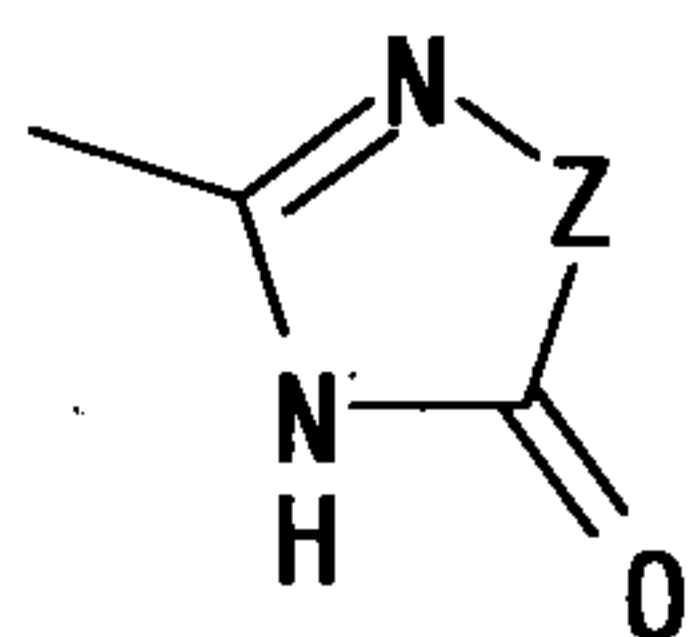
or a salt thereof;

- [2] the compound of aforementioned [1], wherein R1 is an oxo
 20 group;

- [3] the compound of aforementioned [1], wherein R2 is a group
 represented by the formula:



wherein R6 is a group represented by the formula:



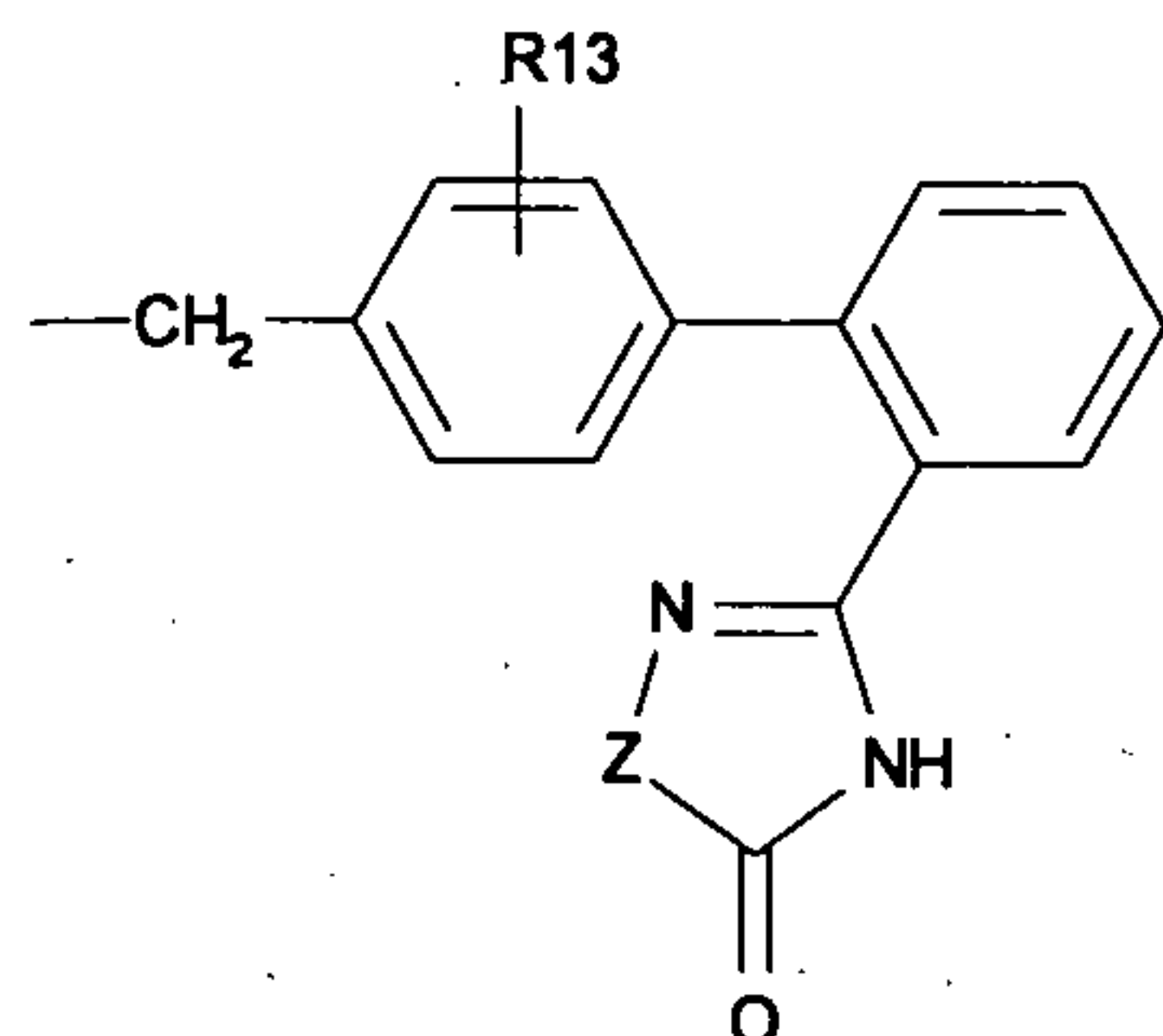
25

wherein Z is O or S(O)_n (n is an integer of 0 to 2), and
 Y is a C1-C4 alkylene group,

(the biphenyl group is optionally further substituted);

- [4] the compound of aforementioned [3], wherein R2 is a group

represented by the formula:

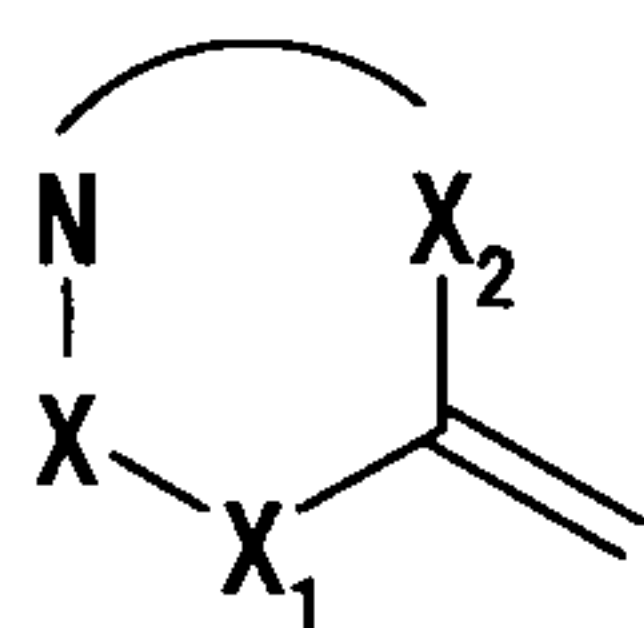


wherein R13 is

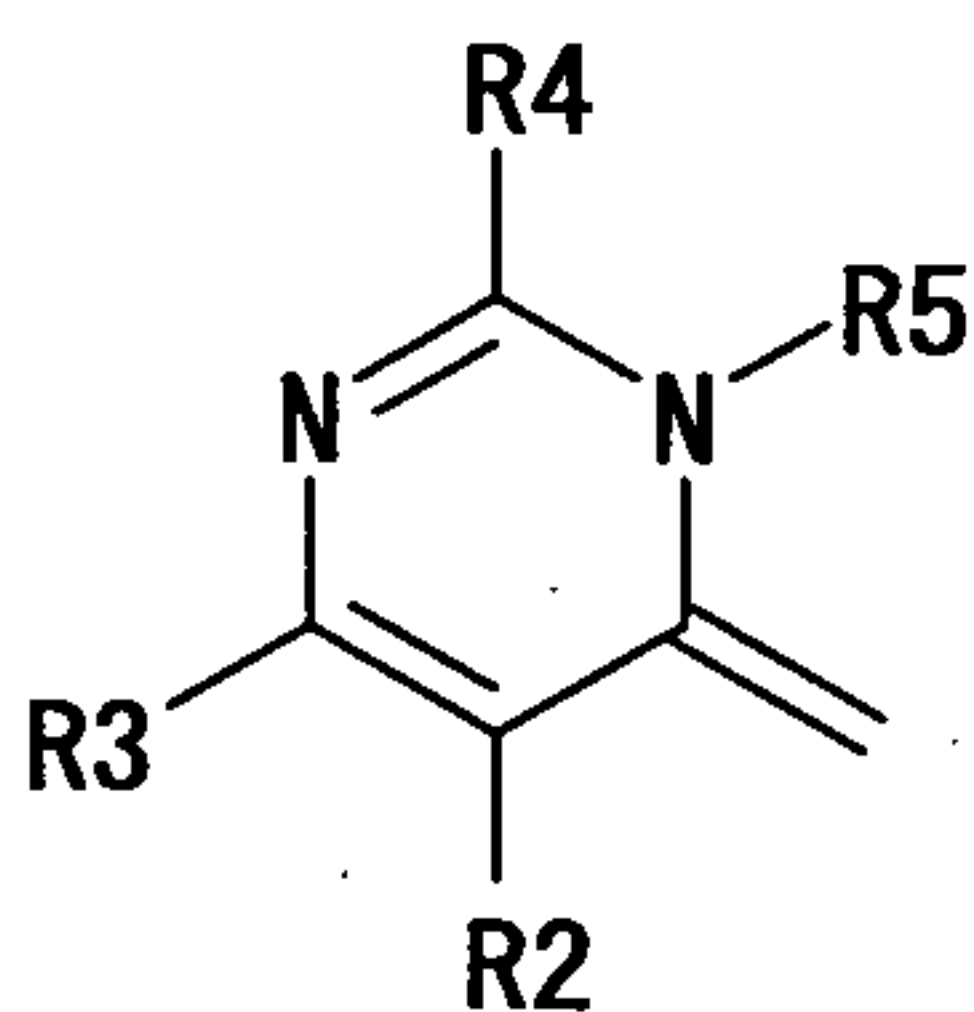
- (1) hydrogen,
- 5 (2) halogen,
- (3) a C1-C6 alkoxy group, or
- (4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group, and

10 Z is O or S;

[5] the compound of aforementioned [1], wherein a group represented by the formula:



is



15

wherein R2, R3, R4 and R5 are as defined in aforementioned [1];

[6] the compound of aforementioned [5], wherein R3 is

- (1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;
- (2) a C3-C6 cycloalkyl group;

- (3) a C1-C6 alkoxy group; or
(4) a C1-C6 alkylthio group;
[7] the compound of aforementioned [5], wherein R4 is
(1) hydrogen;
5 (2) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of a C1-C6
alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon
group and a heterocyclic group;
(3) a C3-C6 cycloalkyl group;
10 (4) a C1-C6 alkoxy group; or
(5) a di(C1-C6)alkylamino group;
[8] the compound of aforementioned [5], wherein R5 is an
optionally substituted C1-C6 alkyl group or an optionally
substituted cyclic group;
15 [9] the compound of aforementioned [8], wherein R5 is an
optionally substituted C6-C14 aryl group;
[10] the compound of aforementioned [9], wherein R5 is a C6-
C14 aryl group optionally substituted by 1 to 3 substituents
selected from the group consisting of
20 (i) halogen;
(ii) a hydroxy group;
(iii) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of halogen, a
hydroxy group, a C1-C6 alkoxy group and a C1-C6 alkyl-carbonyl
25 group;
(iv) a C2-C6 alkenyl group optionally substituted by 1 to 3
substituents selected from the group consisting of halogen and
a hydroxy group;
(v) a C1-C6 alkoxy group optionally substituted by 1 to 3
30 substituents selected from the group consisting of a C2-C6
alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a
hydroxy group, a C3-C6 cycloalkyl group, a C1-C6 alkoxy-
carbonyl group and a carbamoyl group;
(vi) a C2-C6 alkenyloxy group;
35 (vii) a C2-C6 alkynyloxy group;

(viii) a C1-C6 alkyl-carbonylamino group;

(ix) a C1-C6 alkylthio group;

(x) a C1-C6 alkylsulfinyl group;

(xi) a C1-C6 alkylsulfonyl group;

5 (xii) a C1-C6 alkyl-carbonyl group;

(xiii) a C1-C6 alkyl-carbamoyl group; and

(xiv) a di(C1-C6)alkyl-carbamoyl group;

[11] 3-(4-isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;
 10 6-butyl-2-methoxy-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-phenylpyrimidin-4(3H)-one;
 6-butyl-3-(3,4-dimethylphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
 15 4(3H)-one;
 6-butyl-3-[3-(1-hydroxy-1-methylethyl)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 6-butyl-3-(4-ethoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-
 20 1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 3-[4-(1-ethylpropoxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;
 3-(4-tert-butoxyphenyl)-2-ethyl-5-{[2'-(5-oxo-4,5-dihydro-
 25 1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;
 2-ethyl-3-[4-(2-hydroxy-1,1-dimethylethoxy)phenyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one; or
 30 2-ethyl-3-[4-(2-hydroxy-1,1-dimethylpropoxy)phenyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;
 or a salt thereof;

[12] the compound of aforementioned [9], wherein R5 is a C6-C14 aryl group optionally substituted by 1 to 3 substituents
 35

selected from the group consisting of

- (i) a C3-C6 cycloalkyl group;
 - (ii) a C3-C10 cycloalkyloxy group optionally substituted by 1 to 3 substituents selected from the group consisting of
5 halogen, an oxo group, a hydroxy group, a C1-C6 alkyl group, a C1-C6 alkoxy group optionally substituted by 1 to 3 halogens, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-C1-C6 alkyl group;
 - (iii) a C6-C14 aryloxy group;
 - 10 (iv) a heterocyclyl-oxy group optionally substituted by 1 to 3 C1-C6 alkyl groups;
 - (v) a heterocyclyl-C1-C6 alkyloxy group; and
 - (vi) a heterocyclic group;
- [13] 3-[4-(cyclobutyloxy)phenyl]-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propylpyrimidin-4(3H)-one;
- 3-[4-(cyclopropyloxy)phenyl]-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propylpyrimidin-4(3H)-one;
- 20 3-[4-(cyclopentyloxy)phenyl]-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propylpyrimidin-4(3H)-one;
- 2-ethyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propyl-3-[4-(tetrahydro-2H-pyran-4-yloxy)phenyl]pyrimidin-4(3H)-one;
- 25 2-ethyl-3-(4-{{(2R)-2-hydroxycyclopentyl}oxy}phenyl)-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propylpyrimidin-4(3H)-one;
- 2-ethyl-3-{4-[(trans-4-hydroxycyclohexyl)oxy]phenyl}-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propylpyrimidin-4(3H)-one;
- 30 2-ethyl-3-{4-[(cis-4-hydroxycyclohexyl)oxy]phenyl}-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propylpyrimidin-4(3H)-one;
- 35 2-ethyl-3-{4-[(4-oxocyclohexyl)oxy]phenyl}-5-{{2'-(5-oxo-4,5-

dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-6-propylpyrimidin-4(3H)-one;

3-(4-{[(2R,4s,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl]oxy}phenyl)-2-ethyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]-6-propylpyrimidin-4(3H)-one; or

2-ethyl-3-{4-[(3-hydroxycyclohexyl)oxy]phenyl}-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]-6-propylpyrimidin-4(3H)-one;

10 or a salt thereof;

[14] the compound of aforementioned [8], wherein R5 is an optionally substituted heterocyclic group;

[15] the compound of aforementioned [14], wherein R5 is a heterocyclic group optionally substituted by 1 to 3
15 substituents selected from the group consisting of

(i) halogen;

(ii) an oxo group;

(iii) a hydroxy group;

(iv) an amino group;

20 (v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group;

(vi) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a
25 hydroxy group and a C3-C6 cycloalkyl group;

(vii) a heterocycl-yl-oxy group;

(viii) a C1-C6 alkyl-carbonylamino group; and

(ix) a C1-C6 alkoxy-carbonyl group;

[16] 6-butyl-2-cyclopropyl-3-(2,3-dihydro-1-benzofuran-5-yl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one;

6-butyl-3-(2,3-dihydro-1-benzofuran-5-yl)-2-isopropyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one;

35 6-butyl-3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-

methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one;
 3-(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-
 5 6-propylpyrimidin-4(3H)-one;
 3-(4-hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one;
 6-butyl-3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-
 10 methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one;
 2-methyl-3-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one;
 15 3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one; or
 3-(7-fluoro-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one;
 20 or a salt thereof;

[17] the compound of aforementioned [8], wherein R5 is an optionally substituted C1-C6 alkyl group;

[18] the compound of aforementioned [17], wherein R5 is a C1-
 25 C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of

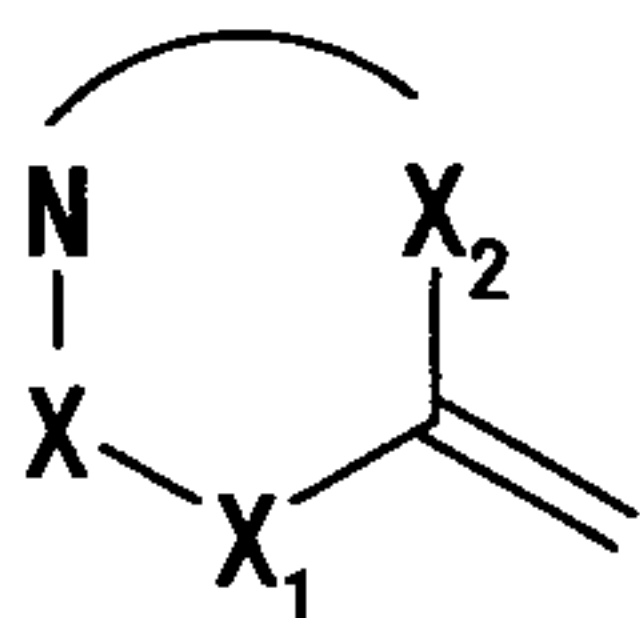
- (i) a hydroxy group;
- (ii) a carboxy group;
- (iii) a C1-C6 alkoxy-carbonyl group;
- 30 (iv) a C1-C6 alkyl-carbonyl group;
- (v) a C3-C10 cycloalkyl-carbonyl group;
- (vi) a C6-C14 aryl-carbonyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group;
- 35 (vii) a heterocyclyl-carbonyl group;

- (viii) a C1-C6 alkyl-carbamoyl group;
- (ix) a C3-C6 cycloalkyl group;
- (x) an adamantyl group;
- (xi) a C6-C14 aryl group optionally substituted by 1 to 3
 5 substituents selected from the group consisting of halogen; a
 C1-C6 alkyl group optionally substituted by 1 to 3
 substituents selected from the group consisting of halogen, a
 hydroxy group and a C1-C6 alkoxy group; a C1-C6 alkoxy group
 optionally substituted by 1 to 3 substituents selected from
 10 the group consisting of halogen and a hydroxy group; a C1-C6
 alkylsulfonyl group; a carboxy group; a C1-C6 alkoxy-carbonyl
 group; a C1-C6 alkyl-carbonyl group; and a heterocyclyl-
 carbonyl group;
- (xii) a heterocyclic group optionally substituted by 1 to 3
 15 substituents selected from the group consisting of halogen; a
 hydroxy group; a C1-C6 alkyl group optionally substituted by 1
 to 3 substituents selected from the group consisting of
 halogen, a hydroxy group and a C1-C6 alkoxy group; a C6-C14
 aryl group; a C7-C16 aralkyl group; a heterocyclic group; and
 20 a C1-C6 alkoxy group optionally substituted by 1 to 3
 substituents selected from the group consisting of halogen and
 a hydroxy group; and
- (xiii) a C1-C6 alkoxyimino group;
- [19] 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-
 25 oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-
 thienylmethyl)pyrimidin-4(3H)-one;
 6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-
 4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
 yl]methyl}pyrimidin-4(3H)-one;
 30 3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-
 oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-
 dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
 4(3H)-one;
 35 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-

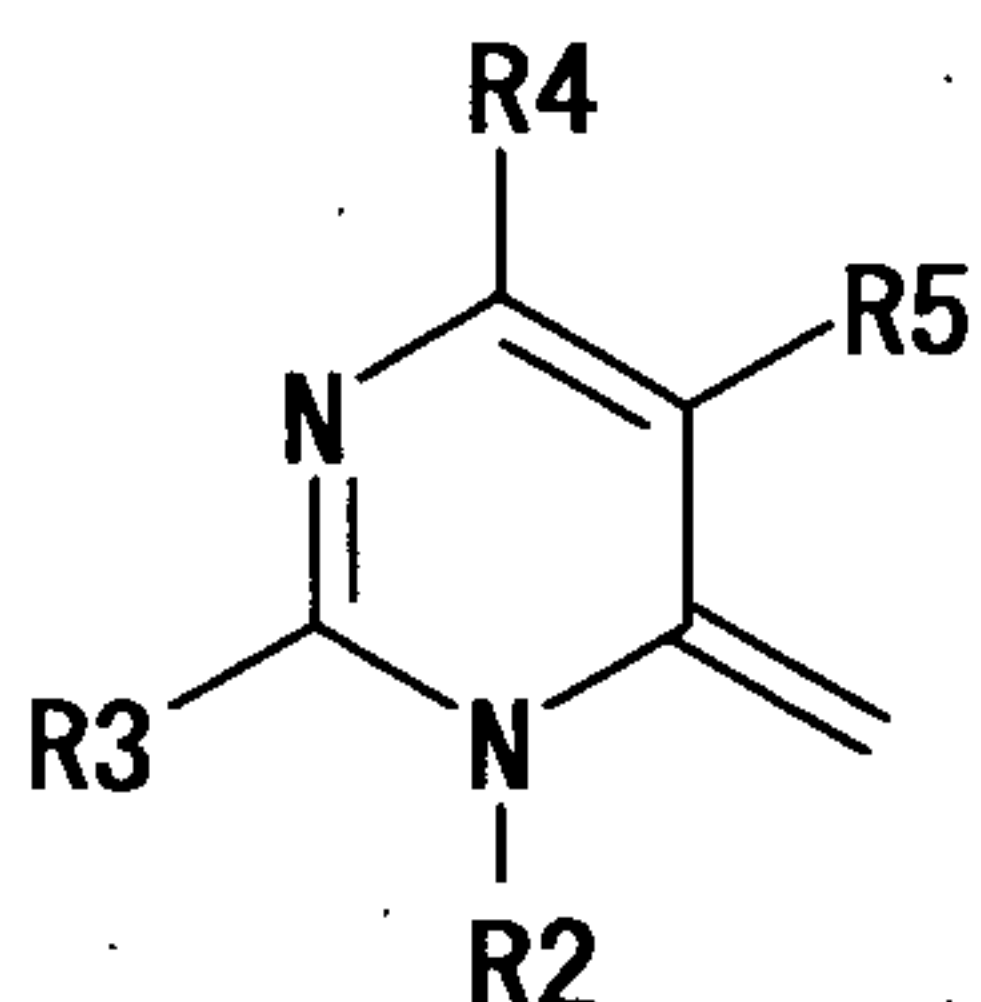
yl)biphenyl-4-yl]methyl}-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one;
 6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one;
 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]pyrimidin-4(3H)-one; or
 6-butyl-3-(2,6-difluorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;

or a salt thereof;

[20] the compound of aforementioned [1], wherein the group represented by the formula:



is a group represented by the formula:



wherein R2, R3, R4 and R5 are as defined in aforementioned [1];

[21] the compound of aforementioned [20], wherein R3 is (1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6

alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;

(2) a C3-C6 cycloalkyl group;

(3) a C1-C6 alkoxy group; or

5 (4) a C1-C6 alkylthio group;

[22] the compound of aforementioned [20], wherein R4 is

(1) hydrogen;

(2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6
10 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group and a heterocyclic group;

(3) a C3-C6 cycloalkyl group;

(4) a C1-C6 alkoxy group; or

(5) a di(C1-C6)alkylamino group;

15 [23] the compound of aforementioned [20], wherein R5 is an optionally substituted C1-C6 alkyl group or an optionally substituted cyclic group;

[24] 5-benzyl-2-ethoxy-6-methyl-3-{{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
20 6-methyl-3-{{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one;

5-(4-isopropoxyphenyl)-6-methyl-3-{{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-
25 4(3H)-one;

5-benzyl-6-methyl-3-{{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one;

2-butyl-5-[hydroxy(phenyl)methyl]-6-methyl-3-{{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
30 4(3H)-one;

5-benzoyl-2-butyl-6-methyl-3-{{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;

6-ethyl-5-(morpholin-4-ylmethyl)-3-{{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-
35 4(3H)-one;

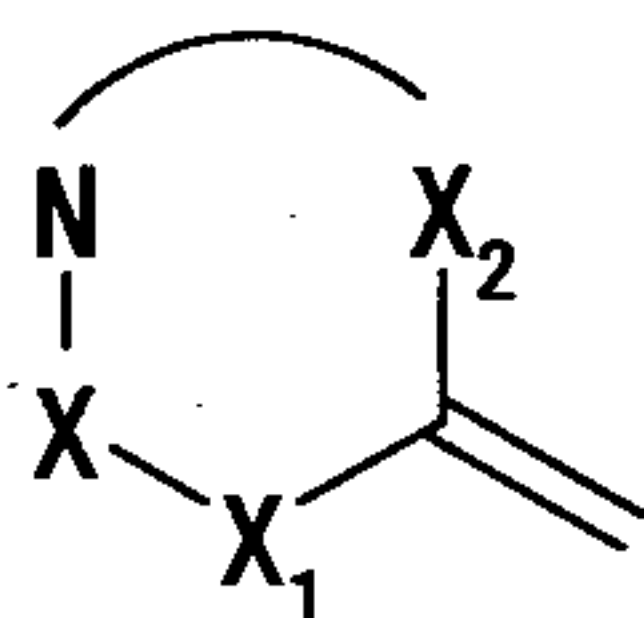
6-ethyl-5-(1-hydroxy-2-methylpropyl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one;

6-ethyl-5-(6-isopropoxy-pyridin-3-yl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one; or

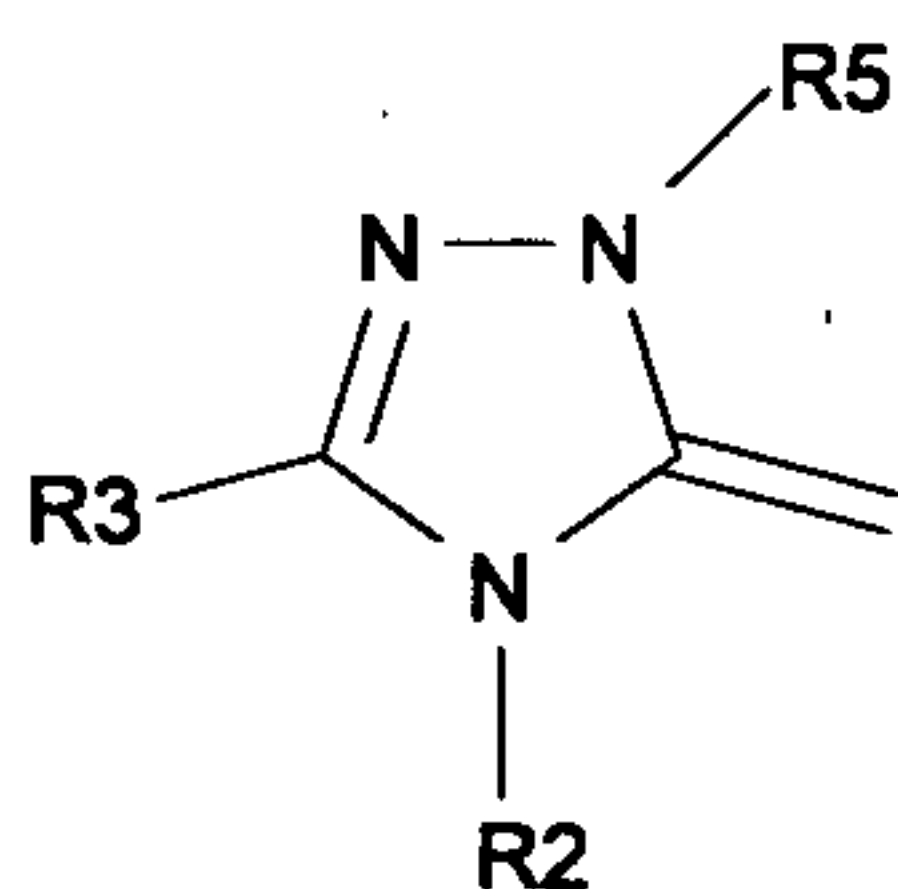
6-ethyl-5-[4-(2-hydroxy-1,1-dimethylethoxy)phenyl]-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one;

10 or a salt thereof;

[25] the compound of aforementioned [1], wherein the group represented by the formula:



is a group represented by the formula:



15

wherein R2, R3 and R5 are as defined in aforementioned [1];

[26] the compound of aforementioned [25], wherein R3 is a C1-C6 alkyl group;

[27] the compound of aforementioned [25], wherein R5 is an optionally substituted C1-C6 alkyl group or an optionally substituted cyclic group;

[28] 3-(4'-{[3-butyl-1-(2,2-dimethylpropyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one;

3-(4'-{[3-butyl-1-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one;

3-(4'-{[3-butyl-5-oxo-1-(2-phenylethyl)-1,5-dihydro-4H-1,2,4-

triazol-4-yl)methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one;
 3-{4'-[(3-butyl-1-sec-butyl-5-oxo-1,5-dihydro-4H-1,2,4-
 triazol-4-yl)methyl}biphenyl-2-yl]-1,2,4-oxadiazol-5(4H)-one;
 3-{4'-[(3-butyl-5-oxo-1-phenyl-1,5-dihydro-4H-1,2,4-triazol-4-
 5 yl)methyl}biphenyl-2-yl]-1,2,4-oxadiazol-5(4H)-one;
 3-(4'-{[3-butyl-5-oxo-1-(tetrahydro-2H-pyran-2-yl)methyl)-1,5-
 dihydro-4H-1,2,4-triazol-4-yl)methyl}biphenyl-2-yl)-1,2,4-
 oxadiazol-5(4H)-one;
 3-[4'-({3-butyl-1-[2-(4-fluorophenyl)-2-oxoethyl]-5-oxo-1,5-
 10 dihydro-4H-1,2,4-triazol-4-yl)methyl}biphenyl-2-yl]-1,2,4-
 oxadiazol-5(4H)-one;
 3-[4'-({3-butyl-1-[2-(4-methoxyphenyl)-2-oxoethyl]-5-oxo-1,5-
 dihydro-4H-1,2,4-triazol-4-yl)methyl}biphenyl-2-yl]-1,2,4-
 oxadiazol-5(4H)-one; or
 15 3-(4'-{[3-butyl-1-(3,3-dimethyl-2-oxobutyl)-5-oxo-1,5-dihydro-
 4H-1,2,4-triazol-4-yl)methyl}biphenyl-2-yl)-1,2,4-oxadiazol-
 5(4H)-one;

or a salt thereof;

[29] a prodrug of the compound of aforementioned [1];

20 [30] a pharmaceutical agent comprising the compound of
 aforementioned [1] or a prodrug thereof as an active
 ingredient;

[31] the pharmaceutical agent of aforementioned [30], which
 has an angiotensin II receptor inhibitory activity and/or a
 25 peroxisome proliferator-activated receptor agonistic activity;

[32] the pharmaceutical agent of aforementioned [30], which is
 an agent for the prophylaxis or treatment of circulatory
 diseases, metabolic diseases and/or central nervous system
 diseases;

30 [33] the pharmaceutical agent of aforementioned [30], which is
 an agent for the prophylaxis or treatment of hypertension,
 cardiac disease, arteriosclerosis, kidney disease, cerebral
 apoplexy, hyperlipidemia, obesity, diabetes, dementia and/or
 Alzheimer's disease;

35 [34] a method for inhibiting an angiotensin II receptor and/or

activating a peroxisome proliferator-activated receptor in a mammal, which comprises administering the compound of aforementioned [1] or a prodrug thereof to said mammal;

[35] a method for preventing or treating circulatory diseases, metabolic diseases and/or central nervous system diseases in a mammal, which comprises administering the compound of aforementioned [1] or a prodrug thereof to said mammal;

[36] a method for preventing or treating hypertension, cardiac disease, arteriosclerosis, kidney disease, cerebral apoplexy, hyperlipidemia, obesity, diabetes, dementia and/or Alzheimer's disease in a mammal, which comprises administering the compound of aforementioned [1] or a prodrug thereof to said mammal;

[37] use of the compound of aforementioned [1] or a prodrug thereof for the production of an agent which has an angiotensin II receptor inhibitory activity and/or a peroxisome proliferator-activated receptor agonistic activity;

[38] use of the compound of aforementioned [1] or a prodrug thereof for the production of an agent for the prophylaxis or treatment of circulatory diseases, metabolic diseases and/or central nervous system diseases;

[39] use of the compound of aforementioned [1] or a prodrug thereof for the production of an agent for the prophylaxis or treatment of hypertension, cardiac disease, arteriosclerosis, kidney disease, cerebral apoplexy, hyperlipidemia, obesity, diabetes, dementia and/or Alzheimer's disease; and the like.

Detailed Description of the Invention

The definition of each symbol used in the present specification is described in detail in the following.

In the present specification, the "halogen" is fluorine, chlorine, bromine or iodine.

In the present specification, the "C1-C6 alkyl group" is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3$ or the like.

In the present specification, the "C2-C6 alkenyl group" is, for example, vinyl, allyl, propenyl, isopropenyl, but-3-en-1-yl, pent-4-en-1-yl, hex-5-en-1-yl, 2-methylprop-1-en-1-yl or the like.

5 In the present specification, the "C2-C6 alkynyl group" is, for example, ethynyl, prop-2-yn-1-yl, but-3-yn-1-yl, pent-4-yn-1-yl, hex-5-yn-1-yl or the like.

In the present specification, the "C3-C6 cycloalkyl group" is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

10 In the present specification, the "C6-C14 aryl group" is, for example, phenyl, naphthyl (e.g., 1-naphthyl, 2-naphthyl), anthryl, phenanthryl or the like, preferably phenyl or naphthyl, more preferably phenyl.

In the present specification, the "C7-C16 aralkyl group" is, for example, benzyl, 1-phenylethyl, 2-phenylethyl, naphthylmethyl (1-naphthylmethyl, 2-naphthylmethyl); 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl or the like.

In the present specification, the "C1-C6 alkoxy group" is, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, $-OCH(CH_2CH_3)_2$ or the like.

In the present specification, the "optionally halogenated C1-C6 alkyl group" is the above-mentioned "C1-C6 alkyl group" optionally substituted by 1 to 5 of the above-mentioned "halogen". For example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, trifluoromethyl and the like can be mentioned.

In the present specification, the "optionally halogenated C1-C6 alkoxy group" is the above-mentioned "C1-C6 alkoxy group" optionally substituted by 1 to 5 of the above-mentioned "halogen". For example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, trifluoromethoxy, 2-fluoroethoxy and the like can be mentioned.

35 In the present specification, the "heterocyclic group" is,

unless otherwise specified, for example, a 4- to 14-membered (preferably 5- to 10-membered) (monocyclic, bicyclic or tricyclic) heterocyclic group, preferably (i) a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group, (ii) a 4- to 10-membered (preferably 5- to 10-membered) non-aromatic heterocyclic group, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom or the like.

The "aromatic heterocyclic group" is, for example, a monocyclic aromatic heterocyclic group such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or the like; or an aromatic fused heterocyclic group such as benzofuryl, isobenzofuryl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, benzo[d]isoxazolyl, benzothiazolyl, benzo[d]isothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-a]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl or the like.

The "non-aromatic heterocyclic group" is, for example, a monocyclic non-aromatic heterocyclic group such as azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl,

piperazinyl or the like; or a non-aromatic fused heterocyclic group such as isochromanyl, dihydrobenzopyranyl, isochromenyl, chromenyl (2H-chromenyl, 4H-chromenyl), 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinolyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl or the like.

In the present specification, the "C2-C6 alkenyloxy group" is, for example, vinyloxy, allyloxy, propenyloxy, isopropenyloxy, but-3-en-1-yloxy, pent-4-en-1-yloxy, hex-5-en-1-yloxy or the like.

10 In the present specification, the "C2-C6 alkynyloxy group" is, for example, ethynyloxy, prop-2-yn-1-yloxy, but-3-yn-1-yloxy, pent-4-yn-1-yloxy, hex-5-yn-1-yloxy, 1-methylbut-3-yn-1-yloxy or the like.

In the present specification, the "C3-C6 cycloalkyloxy group" is cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy.

In the present specification, the "C3-C10 cycloalkyloxy group" is cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, cyclooctyloxy or the like.

20 In the present specification, the "C6-C14 aryloxy group" is, for example, phenoxy, 1-naphthyloxy, 2-naphthyloxy or the like.

In the present specification, the "C7-C16 aralkyloxy group" is, for example, benzyloxy, phenethyloxy or the like.

25 In the present specification, the "heterocyclyl-oxy group" is, for example, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds
30 selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom. Preferable examples of the "heterocyclyl-oxy group" include tetrahydrofuranyloxy (e.g., tetrahydrofuran-3-yloxy), tetrahydropyranyloxy (e.g., tetrahydropyran-4-yloxy), piperidinyloxy (e.g., piperidin-4-yloxy) and the like.
35

In the present specification, the "heterocyclyl-C1-C6 alkyloxy group" is, for example, a heterocyclyl-(C1-C6)alkyloxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom. Preferable examples of the "heterocyclyl-C1-C6 alkyloxy group" include tetrahydrofuranylmethoxy (e.g., tetrahydrofuran-3-ylmethoxy), tetrahydropyranylmethoxy (e.g., tetrahydropyran-4-ylmethoxy), piperidinylmethoxy (e.g., piperidin-4-ylmethoxy) and the like.

In the present specification, the "C1-C6 alkylamino group" is, for example, an amino group monosubstituted by the above-mentioned "C1-C6 alkyl group". For example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, tert-butylamino, pentylamino, isopentylamino, neopentylamino, tert-pentylamino, hexylamino and the like can be mentioned.

In the present specification, the "di(C1-C6)alkylamino group" is, for example, an amino group disubstituted by the above-mentioned "C1-C6 alkyl group". For example, dimethylamino, diethylamino, N-ethyl-N-methylamino and the like can be mentioned.

In the present specification, the "C6-C14 arylamino group" is, for example, an amino group monosubstituted by the above-mentioned "C6-C14 aryl group". For example, phenylamino, 1-naphthylamino, 2-naphthylamino and the like can be mentioned.

In the present specification, the "di(C6-C14)aryl amino group" is, for example, an amino group disubstituted by the above-mentioned "C6-C14 aryl group". For example, diphenylamino, dinaphthylamino and the like can be mentioned.

In the present specification, the "C7-C16 aralkylamino group" is, for example, an amino group monosubstituted by the above-mentioned "C7-C16 aralkyl group". For example, benzylamino, phenethylamino and the like can be mentioned.

In the present specification, the "di(C7-C16)aralkylamino group" is, for example, an amino group disubstituted by the above-mentioned "C7-C16 aralkyl group". For example, dibenzylamino, diphenethylamino and the like can be mentioned.

5 In the present specification, the "N-(C1-C6)alkyl-N-(C6-C14)arylamino group" is, for example, an amino group substituted by the above-mentioned "C1-C6 alkyl group" and the above-mentioned "C6-C14 aryl group". For example, N-methyl-N-phenylamino, N-ethyl-N-phenylamino and the like can be
10 mentioned.

In the present specification, the "N-(C1-C6)alkyl-N-(C7-C16)aralkylamino group" is, for example, an amino group substituted by the above-mentioned "C1-C6 alkyl group" and the above-mentioned "C7-C16 aralkyl group". For example, N-methyl-
15 N-benzylamino, N-ethyl-N-benzylamino and the like can be mentioned.

In the present specification, the "C1-C6 alkyl-carbonylamino group" is, for example, acetylamino, propanoylamino, butanoylamino, 2-methylpropanoylamino,
20 pentanoylamino, 3-methylbutanoylamino, 2,2-dimethylpropanoylamino or the like.

In the present specification, the "C1-C6 alkylthio group" is, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio or the
25 like.

In the present specification, the "C1-C6 alkylsulfinyl group" is, for example, methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, sec-butylsulfinyl, tert-butylsulfinyl or the like.

30 In the present specification, the "C1-C6 alkylsulfonyl group" is, for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl or the like.

In the present specification, the "optionally esterified
35 carboxy group" is, for example, carboxy group, C1-C6 alkoxy-

carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like), C6-C14 aryloxy-carbonyl group (e.g., phenoxycarbonyl and the like), C7-C16 aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl and the like) or the like.

In the present specification, the "C1-C6 alkyl-carbonyl group" is, for example, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 3-methylbutanoyl, 2,2-dimethylpropanoyl or the like.

10 In the present specification, the "C3-C10 cycloalkyl-carbonyl group" is, for example, cyclopentylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl or the like.

In the present specification, the "C6-C14 aryl-carbonyl group" is, for example, benzoyl, 1-naphthoyl, 2-naphthoyl or
15 the like.

In the present specification, the "C7-C16 aralkyl-carbonyl group" is, for example, phenylacetyl, 3-phenylpropanoyl or the like.

In the present specification, the "C1-C6 alkoxy-carbonyl group" is, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl or the like.

In the present specification, the "C6-C14 aryloxy-carbonyl group" is, for example, phenoxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl or the like.

25 In the present specification, the "C7-C16 aralkyloxy-carbonyl group" is, for example, benzyloxycarbonyl, phenethyloxycarbonyl or the like.

In the present specification, the "heterocyclyl-carbonyl group" is, for example, a heterocyclyl-carbonyl group wherein
30 the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom. Preferable examples of the
35 "heterocyclyl-carbonyl group" include 1-pyrrolidinylcarbonyl,

piperidinocarbonyl, 1-piperazinylcarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl and the like.

In the present specification, the "C1-C6 alkyl-carbamoyl group" is, for example, a carbamoyl group monosubstituted by
5 the above-mentioned "C1-C6 alkyl group". For example, methylcarbamoyl, ethylcarbamoyl and the like can be mentioned.

In the present specification, the "di(C1-C6)alkyl-carbamoyl group" is, for example, a carbamoyl group disubstituted by the above-mentioned "C1-C6 alkyl group". For
10 example, dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-methylcarbamoyl and the like can be mentioned.

In the present specification, the "C6-C14 aryl-carbamoyl group" is, for example, a carbamoyl group monosubstituted by the above-mentioned "C6-C14 aryl group". For example,
15 phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl and the like can be mentioned.

In the present specification, the "di(C6-C14)aryl-carbamoyl group" is, for example, a carbamoyl group disubstituted by the above-mentioned "C6-C14 aryl group". For
20 example, diphenylcarbamoyl, dinaphthylcarbamoyl and the like can be mentioned.

In the present specification, the "C1-C6 alkylsulfamoyl group" is, for example, a sulfamoyl group monosubstituted by the above-mentioned "C1-C6 alkyl group". For example,
25 methylsulfamoyl, ethylsulfamoyl and the like can be mentioned.

In the present specification, the "di(C1-C6)alkylsulfamoyl group" is, for example, a sulfamoyl group disubstituted by the above-mentioned "C1-C6 alkyl group". For
example, dimethylsulfamoyl, diethylsulfamoyl, N-ethyl-N-
30 methylsulfamoyl and the like can be mentioned.

In the present specification, the "C6-C14 arylsulfamoyl group" is, for example, a sulfamoyl group monosubstituted by the above-mentioned "C6-C14 aryl group". For example,
phenylsulfamoyl, 1-naphthylsulfamoyl, 2-naphthylsulfamoyl and
35 the like can be mentioned.

In the present specification, the "di(C6-C14)arylsulfamoyl group" is, for example, a sulfamoyl group disubstituted by the above-mentioned "C6-C14 aryl group". For example, diphenylsulfamoyl, dinaphthylsulfamoyl and the like
5 can be mentioned.

In the present specification, the "C1-C6 alkoxyimino group" is, for example, methoxyimino, ethoxyimino, propoxyimino, isopropoxyimino, butoxy imino, isobutoxyimino, sec-butoxy imino, tert-butoxy imino, pentyloxyimino,
10 hexyloxyimino or the like.

In the present specification, the "hydroxy-C1-C6 alkyl group" is, for example, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxy-1-methylethyl or the like.

15 In the present specification, the "C1-C6 alkoxy-C1-C6 alkyl group" is, for example, methoxymethyl, 2-methoxyethyl, 1-methoxyethyl, ethoxymethyl, 2-ethoxyethyl or the like.

In the present specification, the "optionally substituted C1-C6 alkyl group", "optionally substituted C2-C6 alkenyl
20 group", "optionally substituted C2-C6 alkynyl group", "optionally substituted C1-C6 alkoxy group" or "optionally substituted C1-C6 alkylthio group" is, for example, "C1-C6 alkyl group", "C2-C6 alkenyl group", "C2-C6 alkynyl group", "C1-C6 alkoxy group" or "C1-C6 alkylthio group", each
25 optionally substituted by 1 to 5, preferably 1 to 3, substituents selected from the group consisting of

- (1) halogen,
- (2) a hydroxy group,
- (3) an amino group,
- 30 (4) a nitro group,
- (5) a cyano group,
- (6) an optionally halogenated C1-C6 alkoxy group,
- (7) a C3-C6 cycloalkyloxy group,
- (8) a C6-C14 aryloxy group,
- 35 (9) a C7-C16 aralkyloxy group,

- (10) a C1-C6 alkylamino group,
(11) a di(C1-C6)alkylamino group,
(12) a C6-C14 arylamino group,
(13) a di(C6-C14)arylaminogroup,
5 (14) a C7-C16 aralkylamino group,
(15) a di(C7-C16)aralkylamino group,
(16) a N-(C1-C6)alkyl-N-(C6-C14)arylaminogroup,
(17) an N-(C1-C6)alkyl-N-(C7-C16)aralkylaminogroup,
(18) a C1-C6 alkyl-carbonylamino group,
10 (19) a C1-C6 alkylthio group,
(20) a C1-C6 alkylsulfinyl group,
(21) a C1-C6 alkylsulfonyl group,
(22) an optionally esterified carboxy group,
(23) a C1-C6 alkyl-carbonyl group,
15 (24) a C3-C10 cycloalkyl-carbonyl group,
(25) an optionally substituted C6-C14 aryl-carbonyl group,
(26) a C7-C16 aralkyl-carbonyl group,
(27) a heterocyclyl-carbonyl group,
(28) a carbamoyl group,
20 (29) a thiocarbamoyl group,
(30) a C1-C6 alkyl-carbamoyl group,
(31) a di(C1-C6)alkyl-carbamoyl group,
(32) a C6-C14 aryl-carbamoyl group,
(33) a di(C6-C14)aryl-carbamoyl group,
25 (34) a sulfamoyl group,
(35) a C1-C6 alkylsulfamoyl group,
(36) a di(C1-C6)alkylsulfamoyl group,
(37) a C6-C14 arylsulfamoyl group,
(38) a di(C6-C14)aryl-sulfamoyl group,
30 (39) an optionally substituted cyclic group,
(40) a C1-C6 alkoxyimino group,

and the like. Here, the "optionally substituted cyclic group" includes, for example, those similar to the below-mentioned "optionally substituted cyclic group" for R5.

35 In the present specification, the "C6-C14 aryl-carbonyl

group" of the "optionally substituted C6-C14 aryl-carbonyl group" optionally has 1 to 5, preferably 1 to 3, substituents at substitutable position(s). Examples of such substituent include halogen, a hydroxy group, an optionally halogenated C1-C6 alkyl group, an optionally halogenated C1-C6 alkoxy group, an amino group, a C1-C6 alkylamino group, a di(C1-C6)alkylamino group, a C1-C6 alkylthio group, a C1-C6 alkylsulfonyl group, a carboxy group, a C1-C6 alkoxy-carbonyl group, a C1-C6 alkyl-carbonyl group and the like.

10 In the present specification, the "optionally substituted C1-C6 alkylamino group" is, for example, an amino group monosubstituted by the above-mentioned "optionally substituted C1-C6 alkyl group".

In the present specification, the "optionally substituted 15 di(C1-C6)alkylamino group" is, for example, an amino group disubstituted by the above-mentioned "optionally substituted C1-C6 alkyl group".

In the aforementioned formulas, R5 is hydrogen, an optionally substituted C1-C6 alkyl group, an optionally substituted C2-C6 alkenyl group, an optionally substituted 20 cyclic group, a group represented by the formula: -CO-R8 wherein R8 is an optionally substituted C1-C6 alkyl group or an optionally substituted cyclic group, or a group represented by the formula: -O-R8' wherein R8' is an optionally substituted C1-C6 alkyl group or an optionally substituted 25 cyclic group.

Preferably, R5 is an optionally substituted C1-C6 alkyl group or an optionally substituted cyclic group, more preferably an optionally substituted cyclic group.

30 The "cyclic group" of the "optionally substituted cyclic group" for R5 is, for example, a cyclic hydrocarbon group or a heterocyclic group.

The "cyclic hydrocarbon group" is, for example, an alicyclic hydrocarbon group constituted by 3 to 14 carbon 35 atoms, an aromatic hydrocarbon group constituted by 6 to 14

carbon atoms, or the like.

The "alicyclic hydrocarbon group" is, for example, a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like), a C3-C6 cycloalkenyl group (e.g., cyclopentenyl, cyclohexenyl and the like), a C5-C14 cycloalkadienyl group (e.g., 2,4-cyclopentadienyl, 1,3-cyclohexadienyl and the like), an indanyl group, an adamantyl group or the like.

The "aromatic hydrocarbon group" is, for example, a C6-C14 aryl group (e.g., phenyl, naphthyl, anthryl, phenanthryl and the like) or the like.

The "heterocyclic group" is, for example, a 4- to 14-membered (preferably 5- to 10-membered) (monocyclic, bicyclic or tricyclic) heterocyclic group, preferably (i) a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group or (ii) a 4- to 10-membered (preferably 5- to 10-membered) non-aromatic heterocyclic group, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or the like.

The "aromatic heterocyclic group" is, for example, a monocyclic aromatic heterocyclic group such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or the like; or an aromatic fused heterocyclic group such as benzofuryl, isobenzofuryl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, benzo[d]isoxazolyl, benzothiazolyl, benzo[d]isothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, acridinyl,

phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-a]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl or the like.

The "non-aromatic heterocyclic group" is, for example, a monocyclic non-aromatic heterocyclic group such as oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl or the like; or a non-aromatic fused heterocyclic group such as isochromanyl, dihydrobenzopyranyl, isochromenyl, chromenyl (2H-chromenyl, 4H-chromenyl), 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinolyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl or the like.

The "cyclic group" of the "optionally substituted cyclic group" for R5 is preferably a C3-C6 cycloalkyl group, a C3-C6 cycloalkenyl group, an indanyl group, a C6-C14 aryl group, a heterocyclic group or the like, more preferably a C6-C14 aryl group or a heterocyclic group.

The "cyclic group" of the "optionally substituted cyclic group" for R5 optionally has 1 to 5, preferably 1 to 3, substituents at substitutable position(s). Such substituent includes, for example,

- (1) halogen,
- (2) an oxo group,
- (3) a hydroxy group,
- (4) an amino group,
- (5) a nitro group,
- (6) a cyano group,
- (7) a C1-C6 alkyl group,
- (8) a C2-C6 alkenyl group,
- (9) a C2-C6 alkynyl group,

- (10) a C3-C6 cycloalkyl group,
- (11) a C6-C14 aryl group,
- (12) a C7-C16 aralkyl group,
- (13) a heterocyclic group,
- 5 (14) a C1-C6 alkoxy group,
- (15) a C2-C6 alkenyloxy group,
- (16) a C2-C6 alkynyloxy group,
- (17) an optionally substituted C3-C10 cycloalkyloxy group
(preferably, a C3-C10 cycloalkyloxy group optionally
10 substituted by 1 to 3 substituents selected from the group
consisting of halogen, an oxo group, a hydroxy group, a C1-C6
alkyl group, a C1-C6 alkoxy group optionally substituted by 1
to 3 halogens, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-
C1-C6 alkyl group),
- 15 (18) a C6-C14 aryloxy group,
- (19) a C7-C16 aralkyloxy group,
- (20) an optionally substituted heterocyclyl-oxy group
(preferably, a heterocyclyl-oxy group optionally substituted
by 1 to 3 C1-C6 alkyl groups),
- 20 (21) a heterocyclyl-C1-C6 alkyloxy group,
- (22) a C1-C6 alkylamino group,
- (23) a di(C1-C6)alkylamino group,
- (24) a C6-C14 arylamino group,
- (25) a di(C6-C14)arylamino group,
- 25 (26) a C7-C16 aralkylamino group,
- (27) a di(C7-C16)aralkylamino group,
- (28) an N-(C1-C6)alkyl-N-(C6-C14)arylamino group,
- (29) an N-(C1-C6)alkyl-N-(C7-C16)aralkylamino group,
- (30) a C1-C6 alkyl-carbonylamino group,
- 30 (31) a C1-C6 alkylthio group,
- (32) a C1-C6 alkylsulfinyl group,
- (33) a C1-C6 alkylsulfonyl group,
- (34) an optionally esterified carboxy group,
- (35) a C1-C6 alkyl-carbonyl group,
- 35 (36) a C3-C6 cycloalkyl-carbonyl group,

- (37) a C6-C14 aryl-carbonyl group,
(38) a C7-C16 aralkyl-carbonyl group,
(39) a heterocyclyl-carbonyl group,
(40) a carbamoyl group,
5 (41) a thiocarbamoyl group,
(42) a C1-C6 alkyl-carbamoyl group,
(43) a di(C1-C6)alkyl-carbamoyl group,
(44) a C6-C14 aryl-carbamoyl group,
(45) a di(C6-C14)aryl-carbamoyl group,
10 (46) a sulfamoyl group,
(47) a C1-C6 alkylsulfamoyl group,
(48) a di(C1-C6)alkylsulfamoyl group,
(49) a C6-C14 arylsulfamoyl group,
(50) a di(C6-C14)aryl-sulfamoyl group,
15 and the like. Here, the "C1-C6 alkyl group", "C2-C6 alkenyl group" and "C2-C6 alkynyl group" are each optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a C1-C6 alkylamino group, a di(C1-C6)alkylamino group, a C3-C6 cycloalkyl group, a C1-C6 alkyl-carbonyl group, a C1-C6 alkoxy-carbonyl group and a carbamoyl group. In addition, the "C1-C6 alkoxy group" is optionally substituted by 1 to 3 substituents selected from the group consisting of a C2-C6 alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a C1-C6 alkylamino group, a di(C1-C6)alkylamino group, a C3-C6 cycloalkyl group, a C1-C6 alkyl-carbonyl group, a C1-C6 alkoxy-carbonyl group and a carbamoyl group.
25 group.

The "optionally substituted cyclic group" for R5 is preferably a cyclic group optionally substituted by 1 to 3 substituents selected from the group consisting of

- (1) a C1-C6 alkyl group,
(2) a C2-C6 alkenyl group,
(3) a C3-C6 cycloalkyl group,
35 (4) an oxo group,

- (5) a hydroxy group,
 - (6) an amino group,
 - (7) a C1-C6 alkoxy group,
 - (8) a C2-C6 alkenyloxy group,
 - 5 (9) a C2-C6 alkynyloxy group,
 - (10) an optionally substituted C3-C10 cycloalkyloxy group
(preferably, a C3-C10 cycloalkyloxy group optionally
substituted by 1 to 3 substituents selected from the group
consisting of halogen, an oxo group, a hydroxy group, a C1-C6
10 alkyl group, a C1-C6 alkoxy group optionally substituted by 1
to 3 halogens, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-
C1-C6 alkyl group),
 - (11) a C6-C14 aryloxy group,
 - (12) an optionally substituted heterocyclyl-oxy group
15 (preferably, a heterocyclyl-oxy group optionally substituted
by 1 to 3 C1-C6 alkyl groups),
 - (13) a heterocyclyl-C1-C6 alkyloxy group,
 - (14) a C1-C6 alkylamino group,
 - (15) a di(C1-C6)alkylamino group,
 - 20 (16) a C1-C6 alkyl-carbonylamino group,
 - (17) a C1-C6 alkylthio group,
 - (18) a C1-C6 alkylsulfinyl group,
 - (19) a C1-C6 alkylsulfonyl group,
 - (20) a C1-C6 alkoxy-carbonyl group,
 - 25 (21) a C1-C6 alkyl-carbonyl group,
 - (22) a C1-C6 alkyl-carbamoyl group,
 - (23) a di(C1-C6)alkyl-carbamoyl group,
 - (24) a heterocyclic group,
 - (25) halogen
- 30 (wherein the "C1-C6 alkyl group" and "C2-C6 alkenyl group" are
each optionally substituted by 1 to 3 substituents selected
from the group consisting of a C1-C6 alkoxy group, halogen, a
cyano group, a hydroxy group, a C1-C6 alkylamino group, a
di(C1-C6)alkylamino group, a C3-C6 cycloalkyl group, a C1-C6
35 alkyl-carbonyl group, a C1-C6 alkoxy-carbonyl group and a

carbamoyl group, and the "C1-C6 alkoxy group" is optionally substituted by 1 to 3 substituents selected from the group consisting of a C2-C6 alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a C1-C6 alkylamino group, a di(C1-C6)alkylamino group, a C3-C6 cycloalkyl group, a C1-C6 alkyl-carbonyl group, a C1-C6 alkoxy-carbonyl group and a carbamoyl group) and the like.

The "optionally substituted cyclic group" for R5 is more preferably

- 10 (1) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like),
- (2) a C3-C6 cycloalkenyl group (e.g., cyclohexenyl and the like),
- (3) an indanyl group optionally substituted by an oxo group or a hydroxy group,
- 15 (4) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like, preferably phenyl) optionally substituted by 1 to 3 substituents selected from the group consisting of
 - (i) halogen (e.g., F, Cl, Br and the like);
 - (ii) a hydroxy group;
 - 20 (iii) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group, a C1-C6 alkoxy group and a C1-C6 alkyl-carbonyl group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
 - 25 (iv) a C2-C6 alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;
 - (v) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like);
 - (vi) a C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, neopentyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of a C2-C6 alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a C3-C6 cycloalkyl group, a C1-C6 alkoxy-carbonyl group and a
 - 35 carbamoyl group;

- (vii) a C2-C6 alkenyloxy group (e.g., vinyloxy and the like);
- (viii) a C2-C6 alkynyloxy group (e.g., 1-methylbut-3-yn-1-yloxy and the like);
- (ix) a C3-C10 cycloalkyloxy group (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, an oxo group, a hydroxy group, a C1-C6 alkyl group, a C1-C6 alkoxy group optionally substituted by 1 to 3 halogens, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-C1-C6 alkyl group;
- (x) a C6-C14 aryloxy group (e.g., phenoxy and the like);
- (xi) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydrofuranyloxy, tetrahydropyranyloxy, piperidinyloxy and the like) optionally substituted by 1 to 3 C1-C6 alkyl groups;
- (xii) a heterocyclyl-C1-C6 alkyloxy group (preferably, a heterocyclyl-C1-C6 alkyloxy group wherein the heterocyclyl moiety is 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranylmethoxy and the like);
- (xiii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
- (xiv) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio and the like);
- (xv) a C1-C6 alkylsulfinyl group (e.g., methylsulfinyl, isopropylsulfinyl and the like)
- (xvi) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl and the like);
- (xvii) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the

like);

(xviii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);

(xix) a di(C1-C6)alkyl-carbamoyl group (e.g.,

5 dimethylcarbamoyl and the like);

(xx) a heterocyclic group (preferably, 5- or 6-membered, aromatic or non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of
10 nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like), and the like,

(5) a heterocyclic group (preferably, 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds
15 selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., furyl, thienyl, isoxazolyl, pyrazolyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-

20 dihydrobenzofuranyl, 1,3-benzodioxolyl, tetrahydropyranyl, indolyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) halogen (e.g., F, Cl, Br and the like);

(ii) an oxo group;

25 (iii) a hydroxy group;

(iv) an amino group;

(v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl,
30 tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);

(vi) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C3-C6 cycloalkyl group (e.g., methoxy,
35 ethoxy, isopropoxy, neopentyloxy, trifluoromethoxy and the

like);

(vii) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-
5 constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyloxy and the like);

(viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino
10 and the like);

(ix) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like)
and the like,
or the like.

15 The "C1-C6 alkyl group" of the "optionally substituted C1-C6 alkyl group" or "C2-C6 alkenyl group" of the "optionally substituted C2-C6 alkenyl group" for R5 optionally has 1 to 5, preferably 1 to 3, substituents at substitutable position(s). Such substituent includes, for example,

- 20 (1) halogen,
(2) a hydroxy group,
(3) an amino group,
(4) a nitro group,
(5) a cyano group,
25 (6) an optionally halogenated C1-C6 alkoxy group,
(7) a C3-C6 cycloalkyloxy group,
(8) a C6-C14 aryloxy group,
(9) a C7-C16 aralkyloxy group,
(10) a C1-C6 alkylamino group,
30 (11) a di(C1-C6)alkylamino group,
(12) a C6-C14 arylamino group,
(13) a di(C6-C14)arylamino group,
(14) a C7-C16 aralkylamino group,
(15) a di(C7-C16)aralkylamino group,
35 (16) an N-(C1-C6)alkyl-N-(C6-C14)arylamino group,

- (17) an N-(C1-C6)alkyl-N-(C7-C16)aralkylamino group,
- (18) a C1-C6 alkyl-carbonylamino group,
- (19) a C1-C6 alkylthio group,
- (20) a C1-C6 alkylsulfinyl group,
- 5 (21) a C1-C6 alkylsulfonyl group,
- (22) an optionally esterified carboxy group,
- (23) a C1-C6 alkyl-carbonyl group,
- (24) a C3-C10 cycloalkyl-carbonyl group,
- (25) an optionally substituted C6-C14 aryl-carbonyl group,
- 10 (26) a C7-C16 aralkyl-carbonyl group,
- (27) a heterocyclyl-carbonyl group,
- (28) a carbamoyl group,
- (29) a thiocarbamoyl group,
- (30) a C1-C6 alkyl-carbamoyl group,
- 15 (31) a di(C1-C6)alkyl-carbamoyl group,
- (32) a C6-C14 aryl-carbamoyl group,
- (33) a di(C6-C14)aryl-carbamoyl group,
- (34) a sulfamoyl group,
- (35) a C1-C6 alkylsulfamoyl group,
- 20 (36) a di(C1-C6)alkylsulfamoyl group,
- (37) a C6-C14 arylsulfamoyl group,
- (38) a di(C6-C14)aryl-sulfamoyl group,
- (39) an optionally substituted cyclic group,
- (40) a C1-C6 alkoxyimino group,
- 25 and the like.

The "optionally substituted C6-C14 aryl-carbonyl group" as a substituent of the above-mentioned "optionally substituted C1-C6 alkyl group" or "optionally substituted C2-C6 alkenyl group" for R5 is preferably a C6-C14 aryl-carbonyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group.

Examples of the "optionally substituted cyclic group" as a substituent of the above-mentioned "optionally substituted C1-C6 alkyl group" or "optionally substituted C2-C6 alkenyl group" for R5 include those similar to the aforementioned

"optionally substituted cyclic group" for R5.

The "cyclic group" of the "optionally substituted cyclic group" is preferably C3-C6 cycloalkyl group, adamantyl group, C6-C14 aryl group, a heterocyclic group or the like.

5 The "cyclic group" of the "optionally substituted cyclic group" optionally has 1 to 5, preferably 1 to 3, substituents at substitutable position(s). Examples of such substituent preferably include

- (1) halogen,
- 10 (2) a hydroxy group,
- (3) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group,
- (4) a C6-C14 aryl group,
- 15 (5) a C7-C16 aralkyl group,
- (6) a heterocyclic group,
- (7) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group,
- 20 (8) a C1-C6 alkylsulfonyl group,
- (9) a carboxy group,
- (10) a C1-C6 alkoxy-carbonyl group,
- (11) a C1-C6 alkyl-carbonyl group,
- (12) a heterocyclyl-carbonyl group,
- 25 and the like.

The "optionally substituted C1-C6 alkyl group" for R5 is preferably a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a hydroxy group, a C1-C6 alkoxy group, a C1-C6 alkylamino group, a
30 carboxy group, a C1-C6 alkoxy-carbonyl group, a C1-C6 alkyl-carbonyl group, a C3-C10 cycloalkyl-carbonyl group, an optionally substituted C6-C14 aryl-carbonyl group, a heterocyclyl-carbonyl group, a C1-C6 alkyl-carbamoyl group, halogen, an optionally substituted cyclic group and a C1-C6
35 alkoxyimino group.

The "optionally substituted C1-C6 alkyl group" for R5 is more preferably a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of

- (1) a hydroxy group,
- 5 (2) a C1-C6 alkoxy group,
- (3) a C1-C6 alkylamino group,
- (4) a carboxy group,
- (5) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and the like),
- 10 (6) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
- (7) a C3-C10 cycloalkyl-carbonyl group (e.g., cyclohexylcarbonyl, adamantylcarbonyl and the like),
- (8) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from
- 15 the group consisting of halogen and a C1-C6 alkoxy group,
- (9) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
- (10) a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is
- 20 a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for example, morpholinocarbonyl and the like),
- 25 (11) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
- (12) an adamantyl group,
- (13) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from
- 30 the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and
- 35 the like); a C1-C6 alkoxy group optionally substituted by 1 to

3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like),
(14) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, thiazolyl, isoxazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic

group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like, (15) a C1-C6 alkoxyimino group (e.g., isopropoxyimino group), and the like.

10 The "optionally substituted C2-C6 alkenyl group" for R5 is preferably a C2-C6 alkenyl group (e.g., vinyl, allyl, propenyl, isopropenyl, but-3-en-1-yl, pent-4-en-1-yl, hex-5-en-1-yl, 2-methylprop-1-en-1-yl) optionally substituted by 1 to 3 substituents selected from the group consisting of a hydroxy group, a C1-C6 alkoxy group, a C1-C6 alkylamino group, 15 a carboxy group, a C1-C6 alkoxy-carbonyl group, a C1-C6 alkyl-carbonyl group, a C3-C10 cycloalkyl-carbonyl group, an optionally substituted C6-C14 aryl-carbonyl group, a heterocyclyl-carbonyl group, a C1-C6 alkyl-carbamoyl group, 20 halogen, an optionally substituted cyclic group and a C1-C6 alkoxyimino group.

Examples of the "optionally substituted C1-C6 alkyl group" for R8 or R8' include those similar to the aforementioned "optionally substituted C1-C6 alkyl" for R5.

25 Examples of the "optionally substituted cyclic group" for R8 or R8' include those similar to the aforementioned "optionally substituted cyclic group" for R5.

R8 and R8' are preferably optionally substituted cyclic groups.

30 The "cyclic group" of the "optionally substituted cyclic group" for R8 or R8' is preferably a C6-C14 aryl group, a heterocyclic group or the like.

The "cyclic group" of the "optionally substituted cyclic group" for R8 or R8' optionally has 1 to 5, preferably 1 to 3, 35 substituents at substitutable position(s). Examples of such

substituent include

- (1) halogen,
 - (2) a hydroxy group,
 - (3) an amino group,
 - 5 (4) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group,
 - (5) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and
 - 10 a hydroxy group,
 - (6) a C1-C6 alkylamino group,
 - (7) a di(C1-C6)alkylamino group,
 - (8) a C1-C6 alkylthio group,
 - (9) a C1-C6 alkylsulfonyl group,
 - 15 (10) a carboxy group,
 - (11) a C1-C6 alkoxy-carbonyl group,
 - (12) a C1-C6 alkyl-carbonyl group
- and the like.

Examples of the "optionally substituted cyclic group" for

20 R8 preferably include

- (1) a C6-C14 aryl group (e.g., phenyl),
- (2) a heterocyclic group (preferably a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds
- 25 selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., thienyl, thiazolyl, isoxazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl,
- 30 benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl, preferably, morpholinyl),
- 35 and the like.

Examples of the group represented by the formula: -CO-R8 preferably include

- (1) a C6-C14 aryl (e.g., phenyl)-carbonyl group,
 - (2) a heterocyclyl-carbonyl group (heterocyclyl moiety of the
- 5 heterocyclyl-carbonyl group is preferably a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein
- 10 said 5- or 6-membered heterocyclic group is condensed with benzene ring (e.g., thienyl, thiazolyl, isoxazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl,
- 15 quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl)),
- and the like.

Examples of the "optionally substituted cyclic group" for

20 R8' preferably include

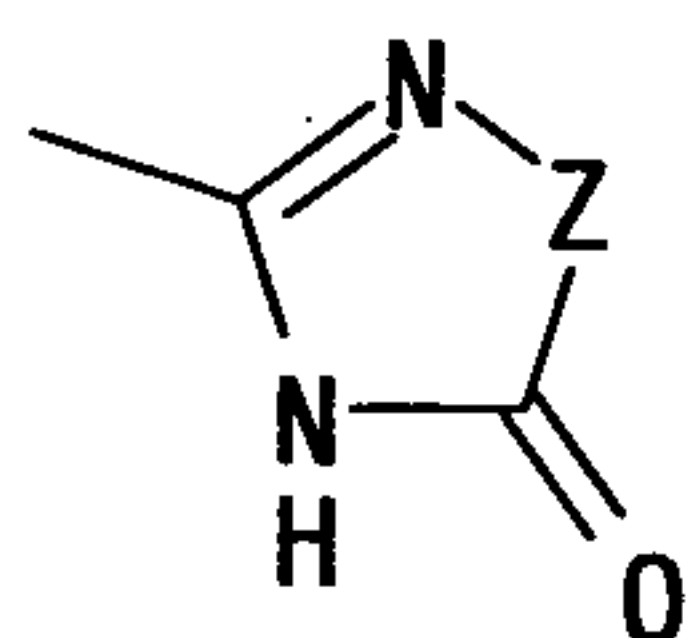
- (1) a C6-C14 aryl group (e.g., phenyl) optionally having 1 to 3 substituents selected from halogen; a C1-C6 alkyl group; and a C1-C6 alkoxy group optionally substituted by a hydroxy group,
 - (2) a heterocyclic group (preferably, a 5- or 6-membered
- 25 heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with
- 30 benzene ring (e.g., thienyl, thiazolyl, isoxazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl,
- 35 tetrahydropyranyl, 1,3-benzodioxolyl, 2,3-

dihydrobenzofuranyl)) optionally substituted by 1 to 3 C1-C6 alkyl groups, and the like.

Examples of the group represented by the formula: -O-R8' preferably include

- 5 (1) a C6-C14 aryl (e.g., phenyl)-oxy group optionally having 1 to 3 substituents selected from halogen; a C1-C6 alkyl group; and a C1-C6 alkoxy group optionally substituted by hydroxy group,
- (2) a heterocyclyl-oxy group (preferably, the heterocyclyl moiety of the heterocyclyl-oxy group is a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein
- 15 said 5- or 6-membered heterocyclic group is condensed with benzene ring (e.g., thienyl, thiazolyl, isoxazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl,
- 20 quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl)) optionally substituted by 1 to 3 C1-C6 alkyl groups, and the like.

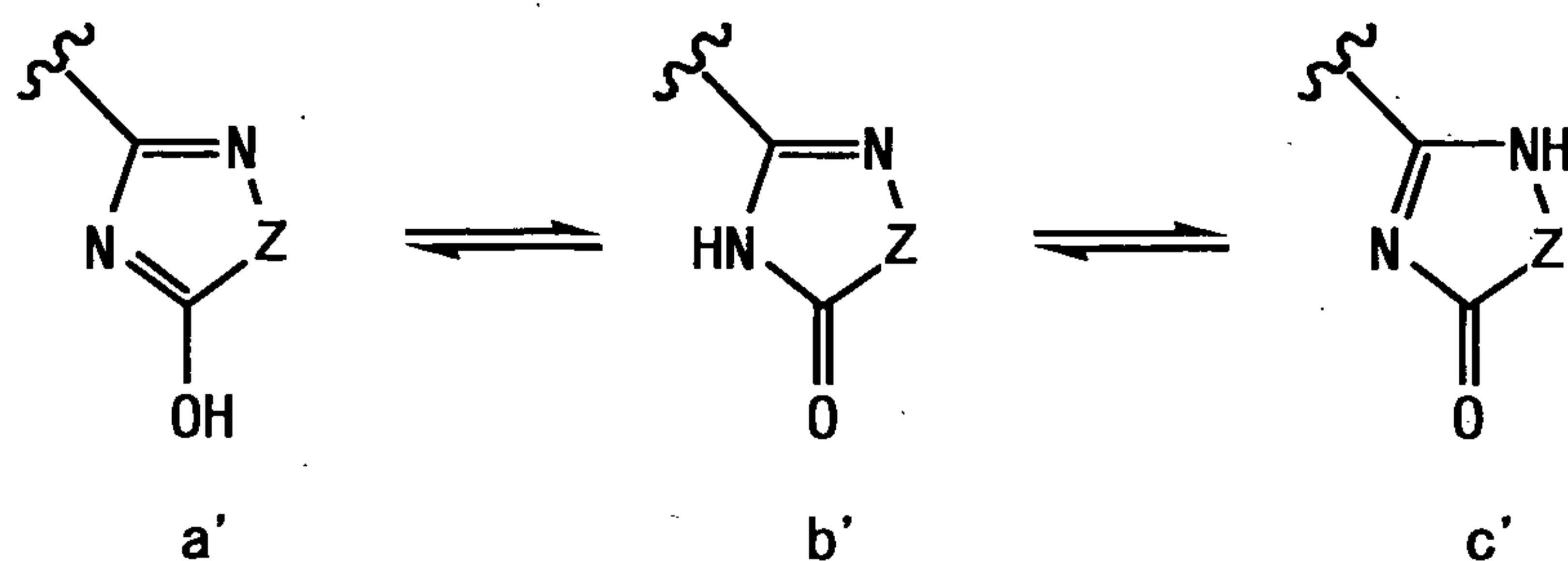
R6 is a monocycle heterocyclic group represented by the
25 formula



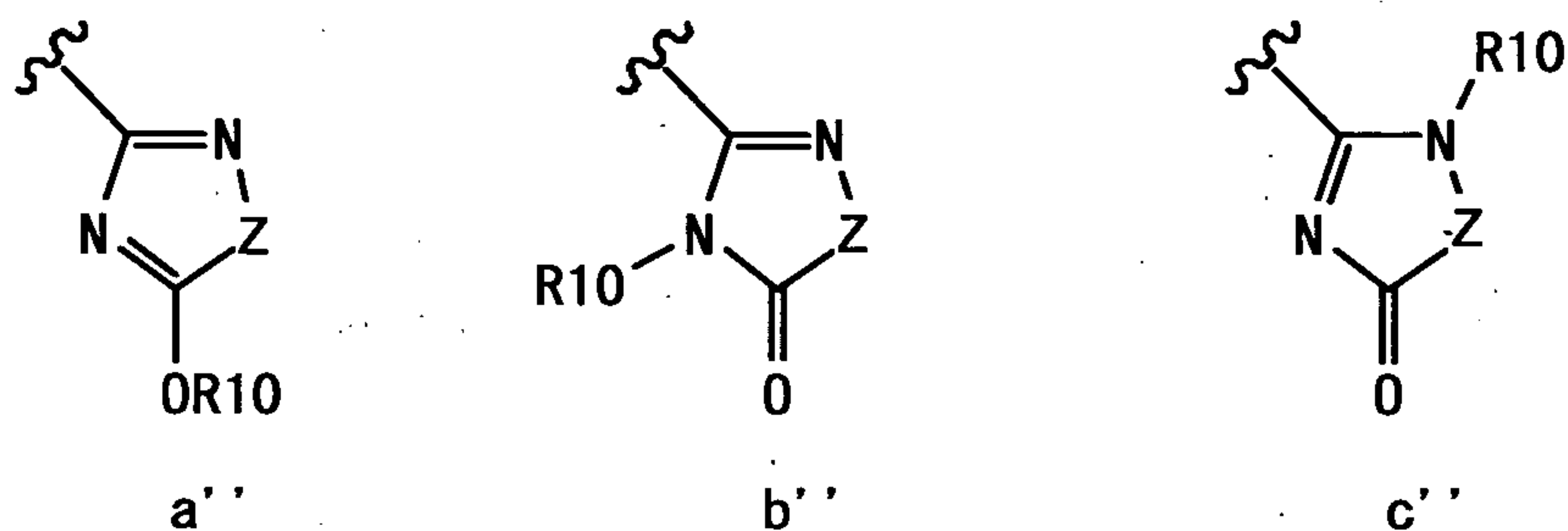
wherein Z is O or S(O)_n (n is an integer of 0 to 2). Z is preferably O or S.

While the substitutable position of R6 may be any of
30 ortho, meta and para, with preference given to ortho position.

The monocycle heterocyclic group for R6 includes the following three tautomers of a', b' and c'.



The above-mentioned heterocyclic group (R6) is optionally substituted by a group for R10, as shown below.



5 As the above-mentioned group for R10, a group represented by the formula $-\text{CH}(\text{R11})-\text{OCOR12}$ [wherein R11 is hydrogen, a straight chain or branched alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl and the like), a straight chain or a branched alkenyl group having 2 to 6 carbon atoms or a cycloalkyl group having 3 to 8 carbon atoms (e.g., cyclopentyl, cyclohexyl, cycloheptyl and the like), and R12 is a straight chain or a branched alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl and the like), a straight chain or a branched alkenyl group having 2 to 6 carbon atoms, a cycloalkyl group having 3 to 8 carbon atoms (e.g., cyclopentyl, cyclohexyl, cycloheptyl and the like), an alkyl group having 1 to 3 carbon atoms substituted by a cycloalkyl group having 3 to 8 carbon atoms (e.g., cyclopentyl, cyclohexyl, cycloheptyl and the like) or an optionally substituted aryl group having 6 to 14 carbon atoms such as phenyl (e.g., benzyl, p-chlorobenzyl, phenethyl, cyclopentylmethyl, cyclohexylmethyl and the like), an alkenyl group having 2 or 3 carbon atoms

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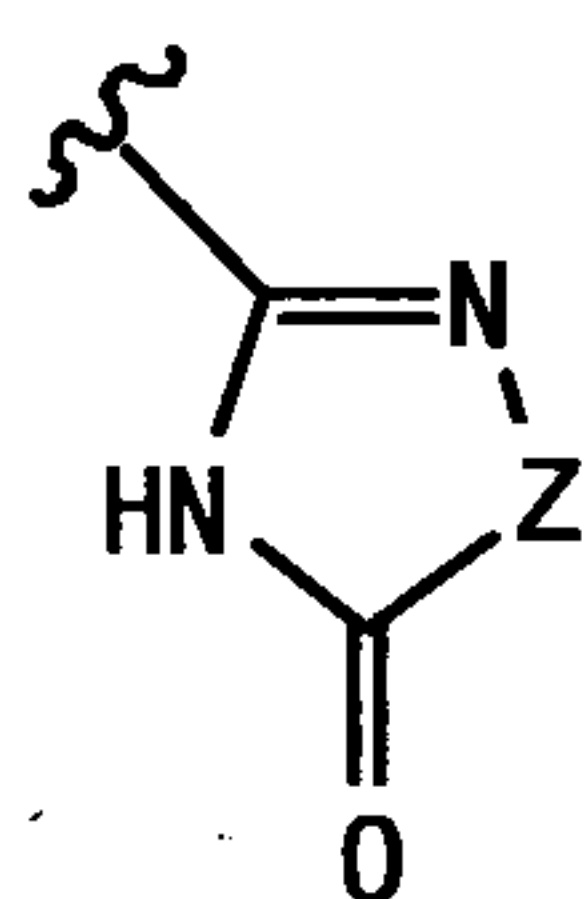
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substituted by a cycloalkyl group having 3 to 8 carbon atoms or an optionally substituted aryl group having 6 to 14 carbon atoms such as phenyl (e.g., those having alkenyl moiety such as vinyl, propenyl, allyl, isopropenyl and the like (e.g., cinnamyl and the like)), an optionally substituted aryl group having 6 to 14 carbon atoms such as phenyl (e.g., phenyl, p-tolyl, naphthyl and the like), a straight chain or a branched alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy and the like), a straight chain or a branched alkenyloxy group having 2 to 8 carbon atoms (e.g., allyloxy, isobutenyloxy and the like), a cycloalkyloxy group having 3 to 8 carbon atoms (e.g., cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like), an alkoxy group having 1 to 3 carbon atoms substituted by a cycloalkyl group having 3 to 8 carbon atoms (e.g., cyclopentyl, cyclohexyl, cycloheptyl and the like) or an optionally substituted aryl group having 6 to 14 carbon atoms such as phenyl (e.g., those having alkoxy moiety such as methoxy, ethoxy, propoxy, isopropoxy and the like (e.g., benzyloxy, phenethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy and the like)), an alkenyloxy group having 2 or 3 carbon atoms substituted by a cycloalkyl group having 3 to 8 carbon atoms (e.g., cyclopentyl, cyclohexyl, cycloheptyl and the like) or an optionally substituted aryl group having 6 to 14 carbon atoms such as phenyl (e.g., those having alkenyloxy moiety such as vinyloxy, propenyloxy, allyloxy, isopropenyloxy and the like (e.g., cinnamyloxy and the like)), or an optionally substituted aryloxy group having 6 to 14 carbon atoms such as phenoxy (e.g., phenoxy, p-nitrophenoxy, naphthoxy and the like)]; an optionally substituted alkyl group (e.g., C1-C6 alkyl group); or an acyl group (e.g., C2-C5 alkanoyl group, optionally substituted benzoyl group and the like); and the like can be mentioned. Examples of substituent R10 include methyl, ethyl, propyl, tert-butyl, methoxymethyl,

triphenylmethyl, cyanoethyl, acetyl, propionyl, pivaloyloxymethyl, 1-(cyclohexyloxycarbonyloxy)ethyl, 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, isobutyryloxymethyl, 1-(ethoxycarbonyloxy)ethyl, 1-(acetyloxy)ethyl, 1-(isobutyryloxy)ethyl, cyclohexylcarbonyloxymethyl, benzoyloxymethyl, cinnamyl, cyclopentylcarbonyloxymethyl and the like. Such group may be any as long as it is a substituent that is easily converted to the original heterocyclic group represented by the formula



biologically, or under physiological conditions (e.g., in vivo reaction such as oxidation, reduction or hydrolysis and the like by biological enzymes and the like), or chemically (what is called a prodrug).

In addition, substituent R6 may further have substituent(s) in addition to the above-mentioned groups for R10. Examples thereof include substituents such as an optionally substituted C1-C6 alkyl group (e.g., methyl, triphenylmethyl and the like), halogen (e.g., F, Cl, Br and the like), a nitro group, a cyano group, a C1-C6 alkoxy group, an amino group, a C1-C6 alkylamino group (e.g., methylamino and the like), a di(C1-C6)alkylamino group (e.g., dimethylamino and the like) and the like.

R1 is an oxo group; a thioxo group; or a group represented by the formula: =N-R, =N-CO-R', =N-CO-OR' or =N-SO₂-R'.

R is an optionally substituted C1-C6 alkyl group; an optionally substituted C3-C6 cycloalkyl group; a group represented by the formula: -O-Ra; or a group represented by the formula: -N(Rb)-Rc.

Ra is hydrogen, an optionally substituted C1-C6 alkyl group or an optionally substituted C3-C6 cycloalkyl group.

Rb and Rc are each independently hydrogen, an optionally substituted C1-C6 alkyl group or an optionally substituted C3-C6 cycloalkyl group, or Rb and Rc are bonded to each other to form, together with the nitrogen atom bonded thereto, an optionally substituted nitrogen-containing heterocyclic group.

Examples of the "optionally substituted C1-C6 alkyl group" for R, Ra, Rb or Rc include those similar to the "optionally substituted C1-C6 alkyl group" for R5. The "optionally substituted C1-C6 alkyl group" for R, Ra, Rb or Rc is preferably a C1-C6 alkyl group.

The "C3-C6 cycloalkyl group" of the "optionally substituted C3-C6 cycloalkyl group" for R, Ra, Rb or Rc optionally has 1 to 5, preferably 1 to 3, substituent(s) at substitutable position(s). Examples of such substituent include those recited as examples of the substituent of the "optionally substituted cyclic group" for R5. The "optionally substituted C3-C6 cycloalkyl group" for R, Ra, Rb or Rc is preferably a C3-C6 cycloalkyl group.

Rb and Rc may be bonded to each other to form, together with the nitrogen atom bonded thereto, an optionally substituted nitrogen containing heterocyclic group. The "nitrogen containing heterocyclic group" is, for example, a 4 to 8-membered (preferably 5- to 7-membered, more preferably 5- or 6-membered) nonaromatic heterocyclic group which contains, as a ring-constituting atom besides carbon atom, one nitrogen atom, and may further contain a hetero atom selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom. Preferable examples of the nitrogen-containing heterocyclic group include 1-azetidiny, 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 4-thiomorpholinyl, 3-thiazolidinyl, 3-oxazolidinyl, 1-azepanyl, 1-azocanyl, 1,4-diazepan-1-yl, 1,4-oxazepan-4-yl, 1,4-thiazepan-4-yl and the like. The "nitrogen-containing

heterocyclic group" optionally has 1 or 2 substituents at substitutable position(s). Examples of the substituent include a hydroxy group, an optionally halogenated C1-C6 alkyl group, a C6-C14 aryl group, a C7-C16 aralkyl group, a C1-C6 alkyl-carbonyl group, a C1-C6 alkoxy-carbonyl group and the like.

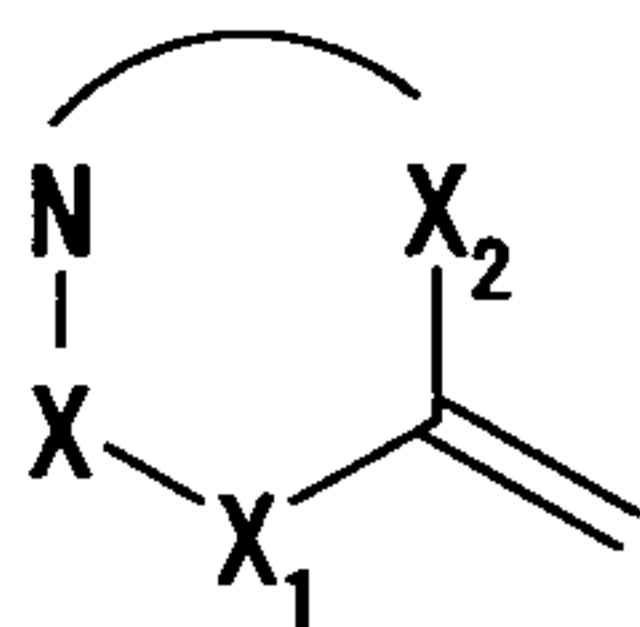
R' is an optionally substituted C1-C6 alkyl group or an optionally substituted cyclic group.

Examples of the "optionally substituted C1-C6 alkyl group" for R' include those similar to the "optionally substituted C1-C6 alkyl group" for R5. Preferable examples of the "optionally substituted C1-C6 alkyl group" for R' include a C1-C6 alkyl group.

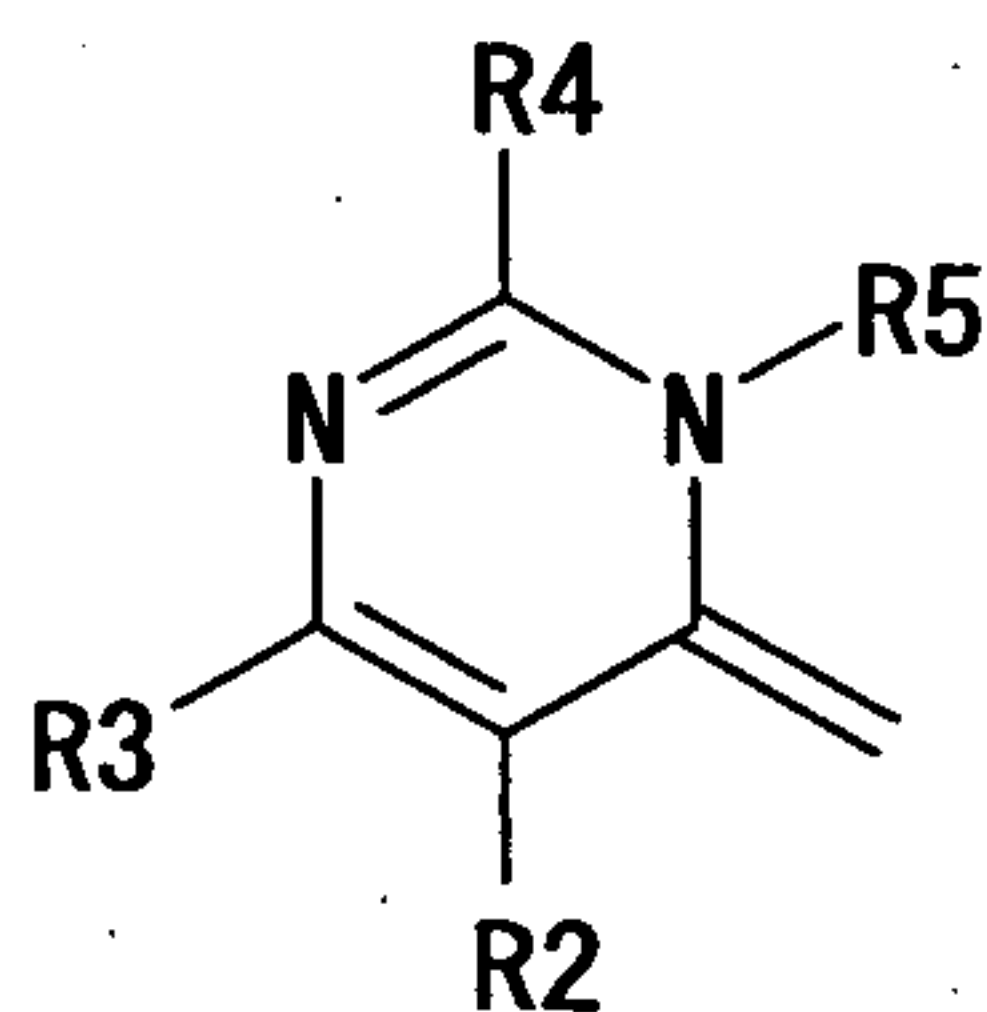
Examples of the "optionally substituted cyclic group" for R' include those similar to "optionally substituted cyclic group" for R5. Preferable examples of the "optionally substituted cyclic group" for R' include a C6-C14 aryl group.

R1 is preferably an oxo group or a group represented by the formula: $=N-SO_2-R'$ (R' is preferably a C1-C6 alkyl group or a C6-C14 aryl group), more preferably an oxo group.

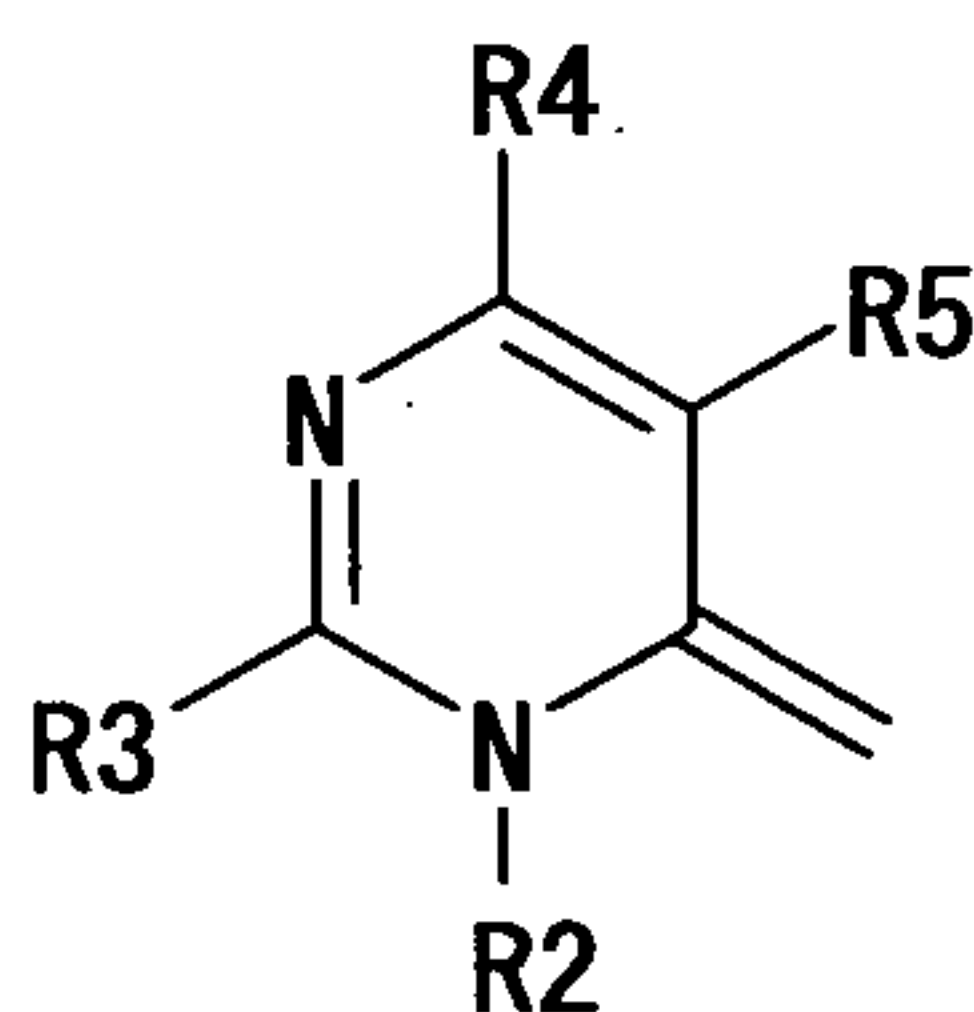
A group represented by the formula:



is preferably



or



Y is an optionally substituted C1-C4 alkylene group or a group represented by the formula: $-O-W-$, $-W-O-$, $-N(Rd)-W-$ or $-W-N(Rd)-$, wherein W is a bond or an optionally substituted C1-C4 alkylene group, and Rd is an optionally substituted C1-C6 alkyl group or an optionally substituted C3-C6 cycloalkyl

group.

The "C1-C4 alkylene group" for Y or W may be a straight chain or a branched chain, for example, methylene, ethylene, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-$, $CH(CH_3)-$, $-C(CH_3)_2-CH_2-$, $-CH_2-C(CH_3)_2-$ and the like can be mentioned.

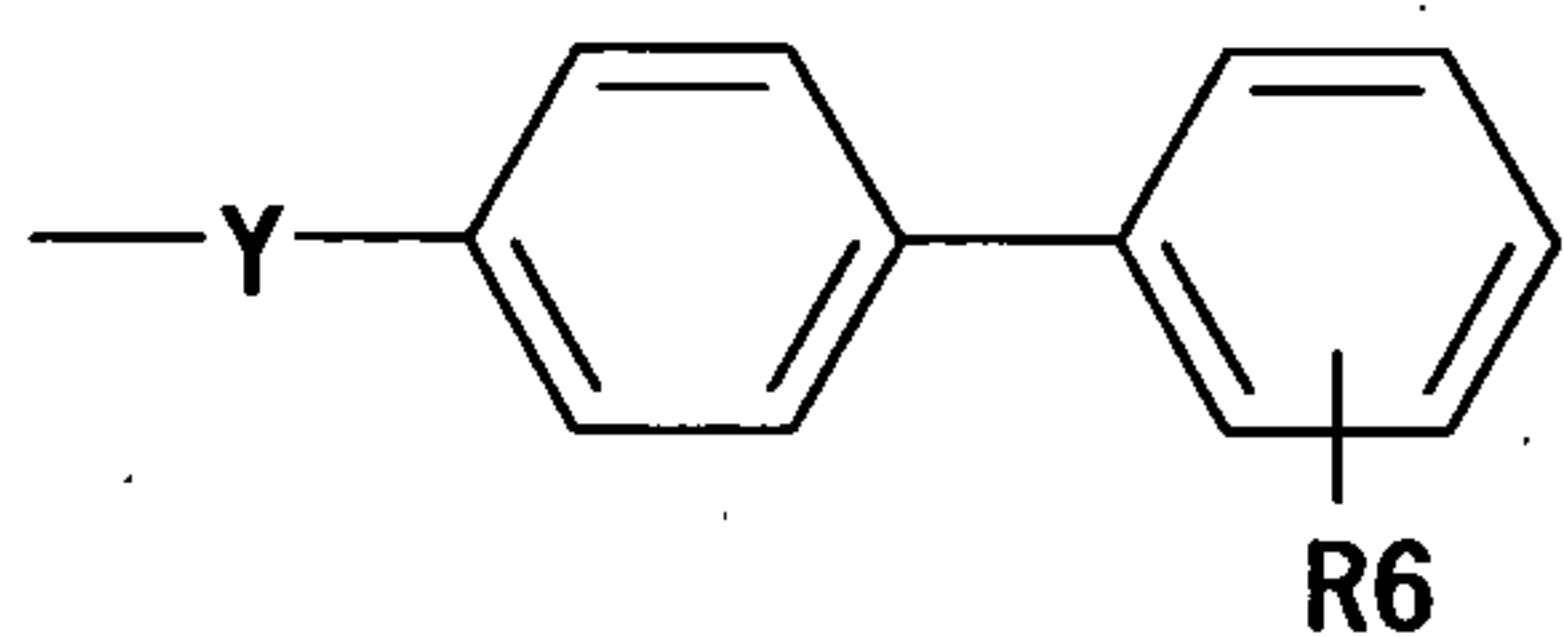
The "C1-C4 alkylene group" for Y or W optionally has 1 to 3 substituents at substitutable position(s). Examples of the substituent include halogen (e.g., F, Cl, Br and the like), an oxo group, a hydroxy group, a nitro group, a cyano group, an optionally halogenated C1-C6 alkoxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like), an amino group, a C1-C6 alkylamino group (e.g., methylamino and the like), a di(C1-C6)alkylamino group (e.g., dimethylamino and the like), a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like) and the like.

Examples of the "optionally substituted C1-C6 alkyl group" for Rd include those similar to the "optionally substituted C1-C6 alkyl group" for R5. The "optionally substituted C1-C6 alkyl group" for Rd is preferably a C1-C6 alkyl group.

Examples of the "optionally substituted C3-C6 cycloalkyl group" for Rd include those similar to the "optionally substituted C3-C6 cycloalkyl group" for R, Ra, Rb or Rc. The "optionally substituted C3-C6 cycloalkyl group" for Rd is preferably a C3-C6 cycloalkyl group.

Y is preferably a C1-C4 alkylene group, more preferably methylene or ethylene, and particularly preferably methylene.

In the group represented by the formula:



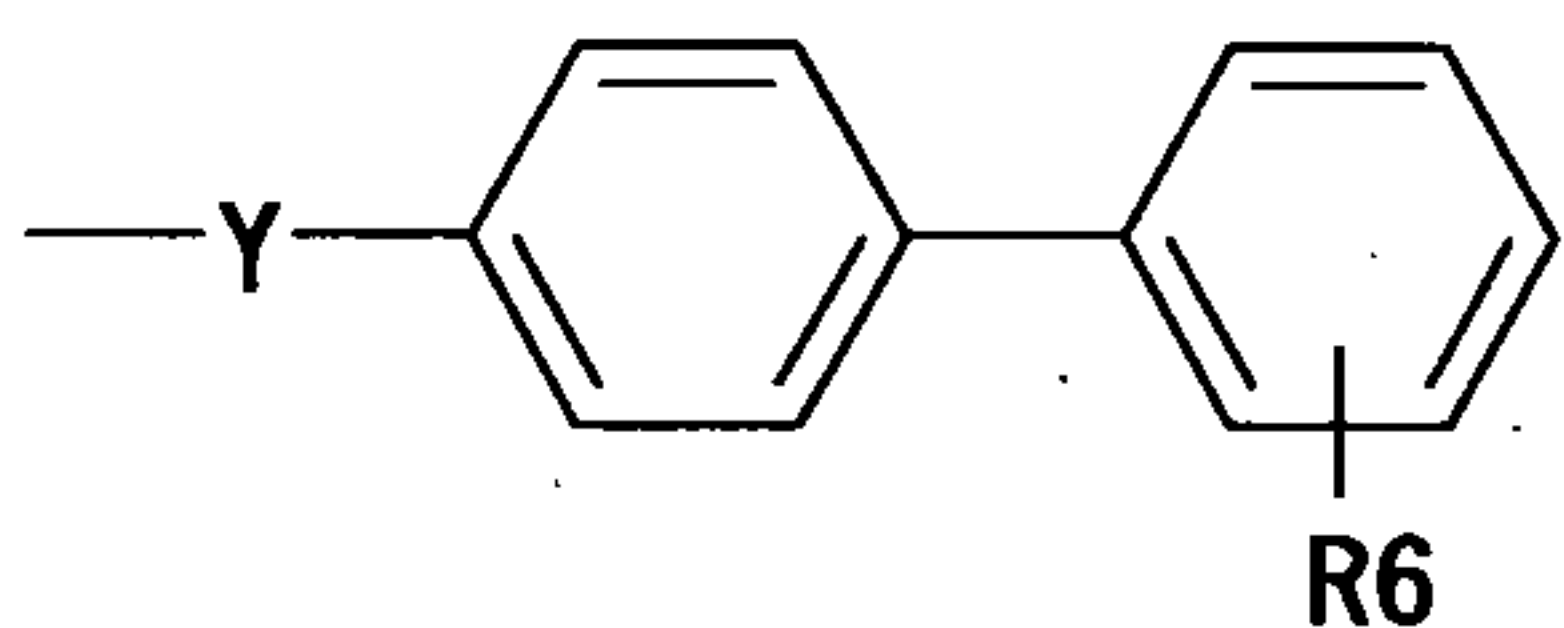
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the biphenyl group may be further optionally substituted. Examples of the substituent include 1 to 3 substituents

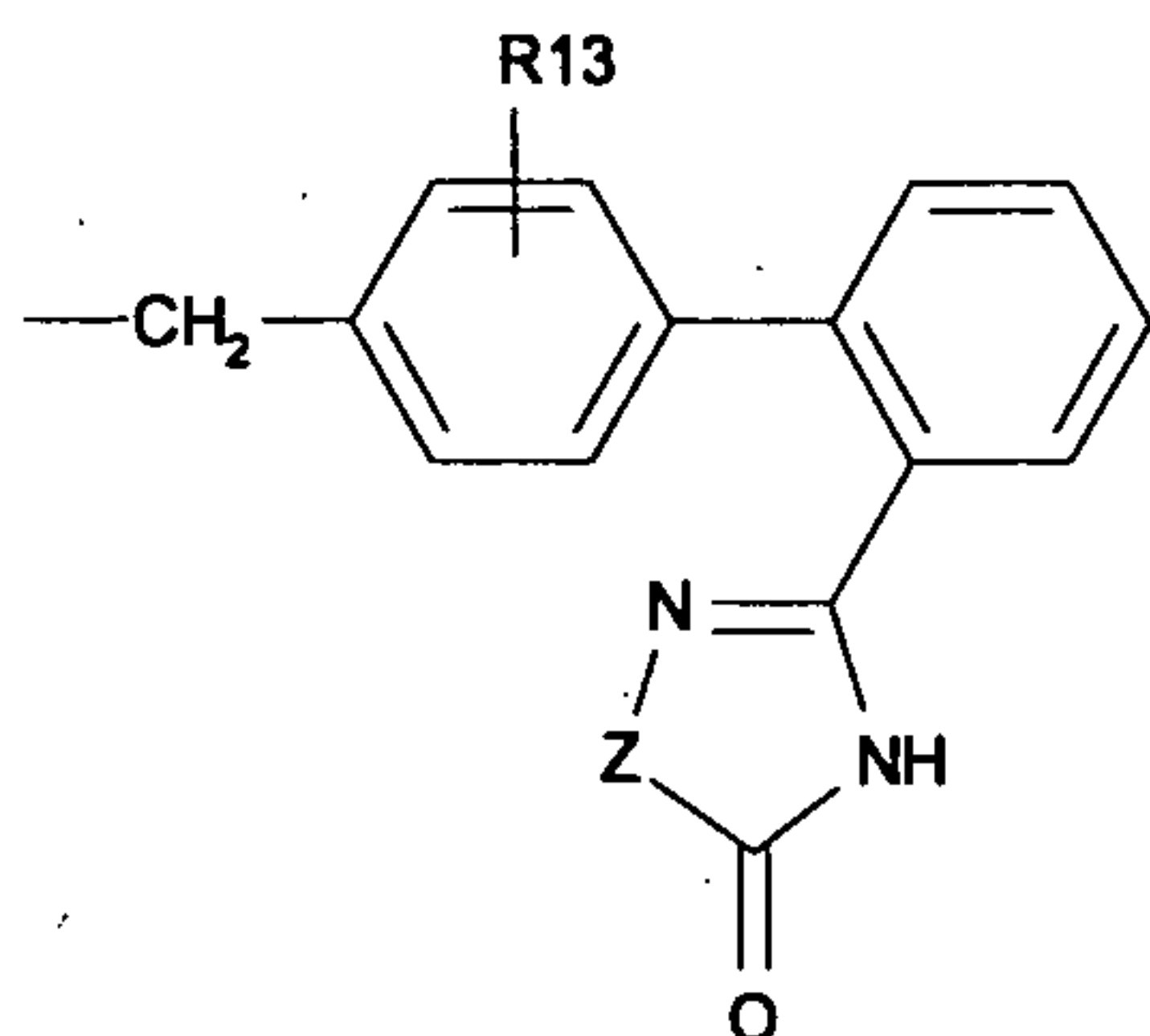
selected from the group consisting of halogen (e.g., F, Cl, Br and the like), a hydroxy group, a nitro group, a cyano group, an optionally halogenated C1-C6 alkyl group (e.g., methyl, ethyl, trifluoromethyl and the like), an optionally
 5 halogenated C1-C6 alkoxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like), an amino group, a C1-C6 alkylamino group (e.g., methylamino and the like), a di(C1-C6)alkylamino group (e.g., dimethylamino and the like), a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like)
 10 and the like.

Preferable examples of the substituent that the biphenyl group optionally further has include 1 to 3 substituents selected from the group consisting of
 (1) halogen (e.g., F, Cl, Br and the like);
 15 (2) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);
 and
 (3) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and C1-C6 alkoxy, and the like. More preferred is halogen (e.g., F, Cl, Br and
 20 the like), and still more preferred is fluorine.

Preferable examples of R2 represented by the formula



(each symbol is as defined above, and the biphenyl group may be further substituted) are, for example, a group represented
 25 by the formula



[wherein

R13 is

- (1) hydrogen,
- (2) halogen (e.g., F, Cl, Br and the like),
- (3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like),

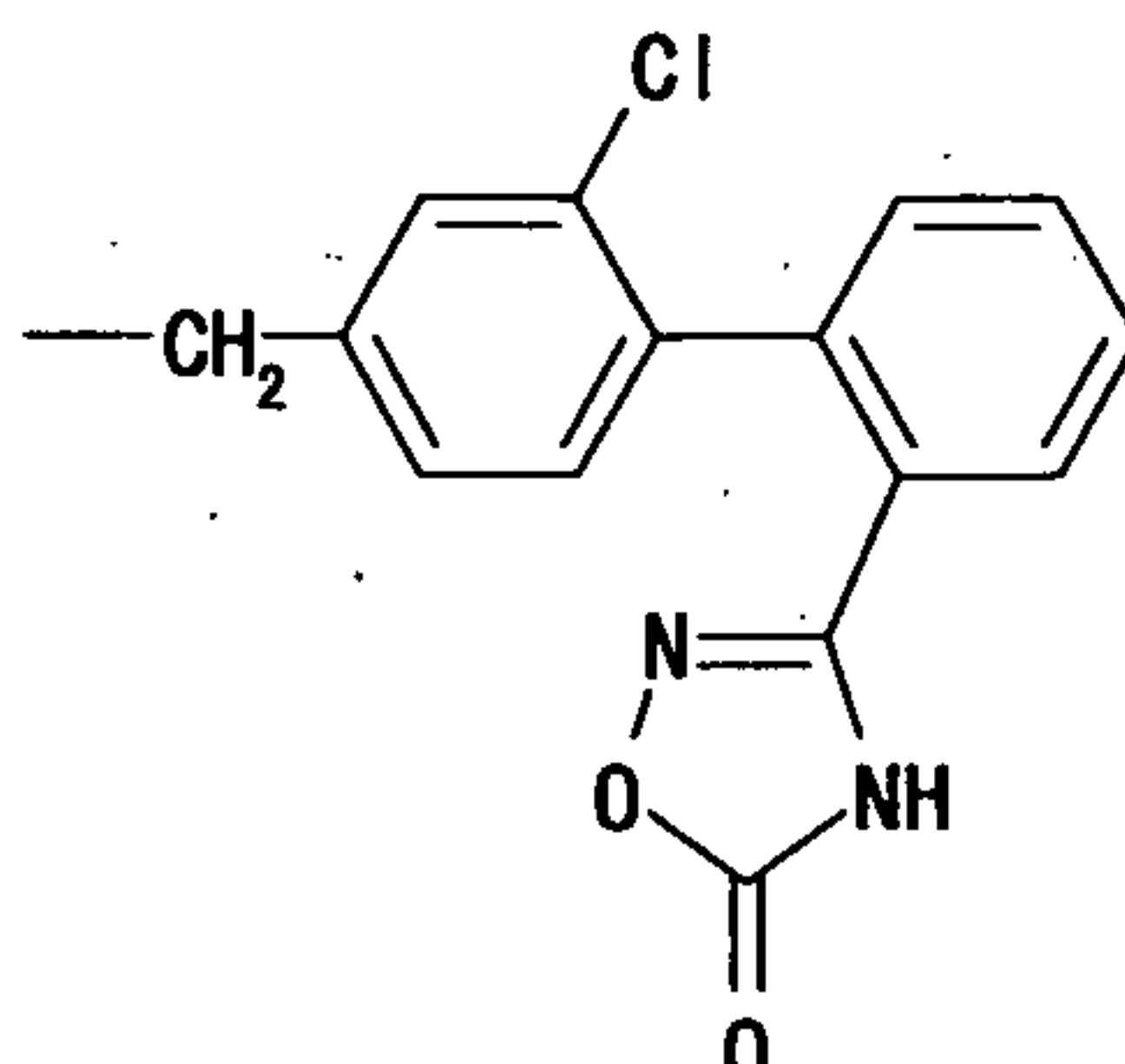
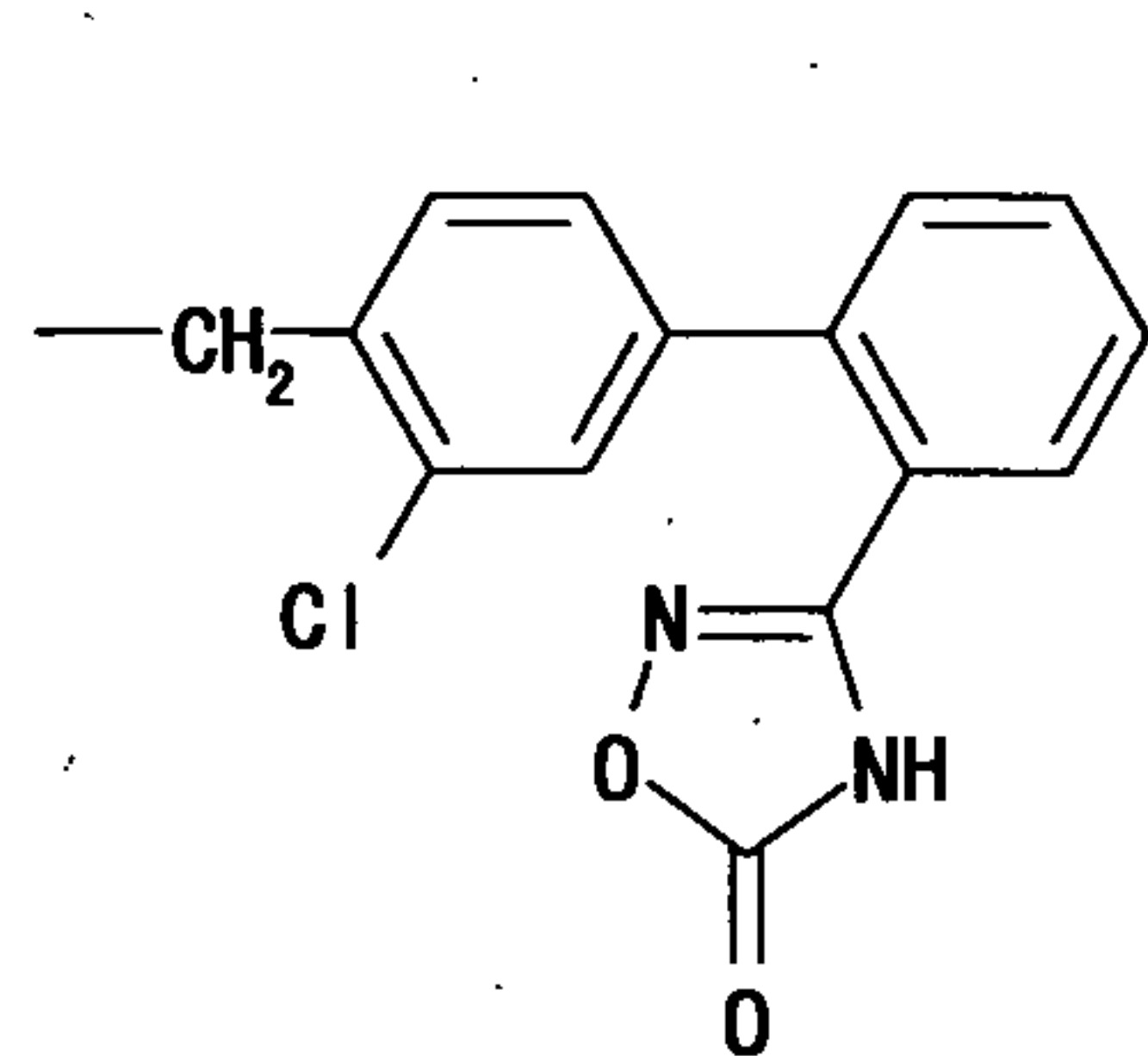
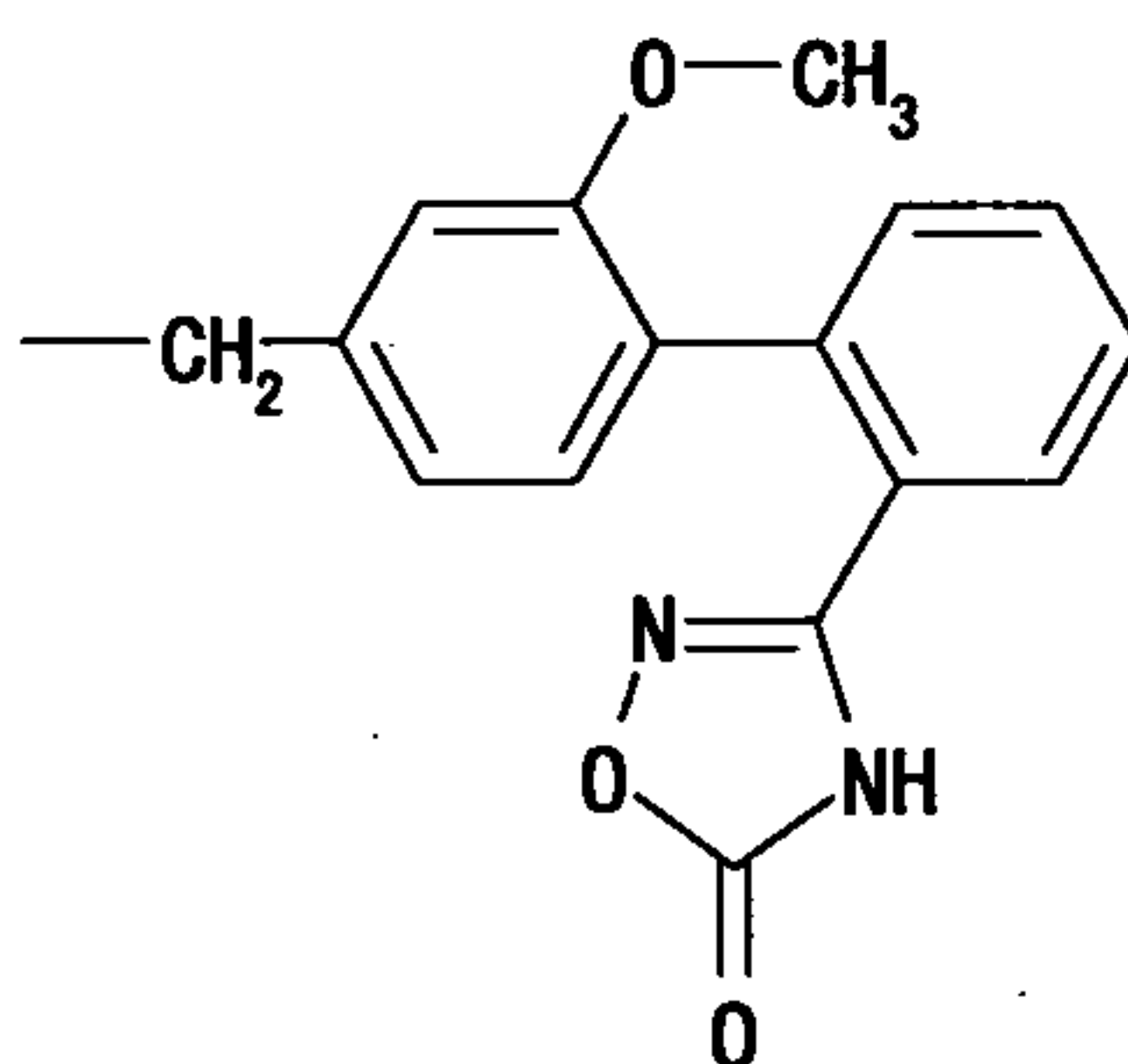
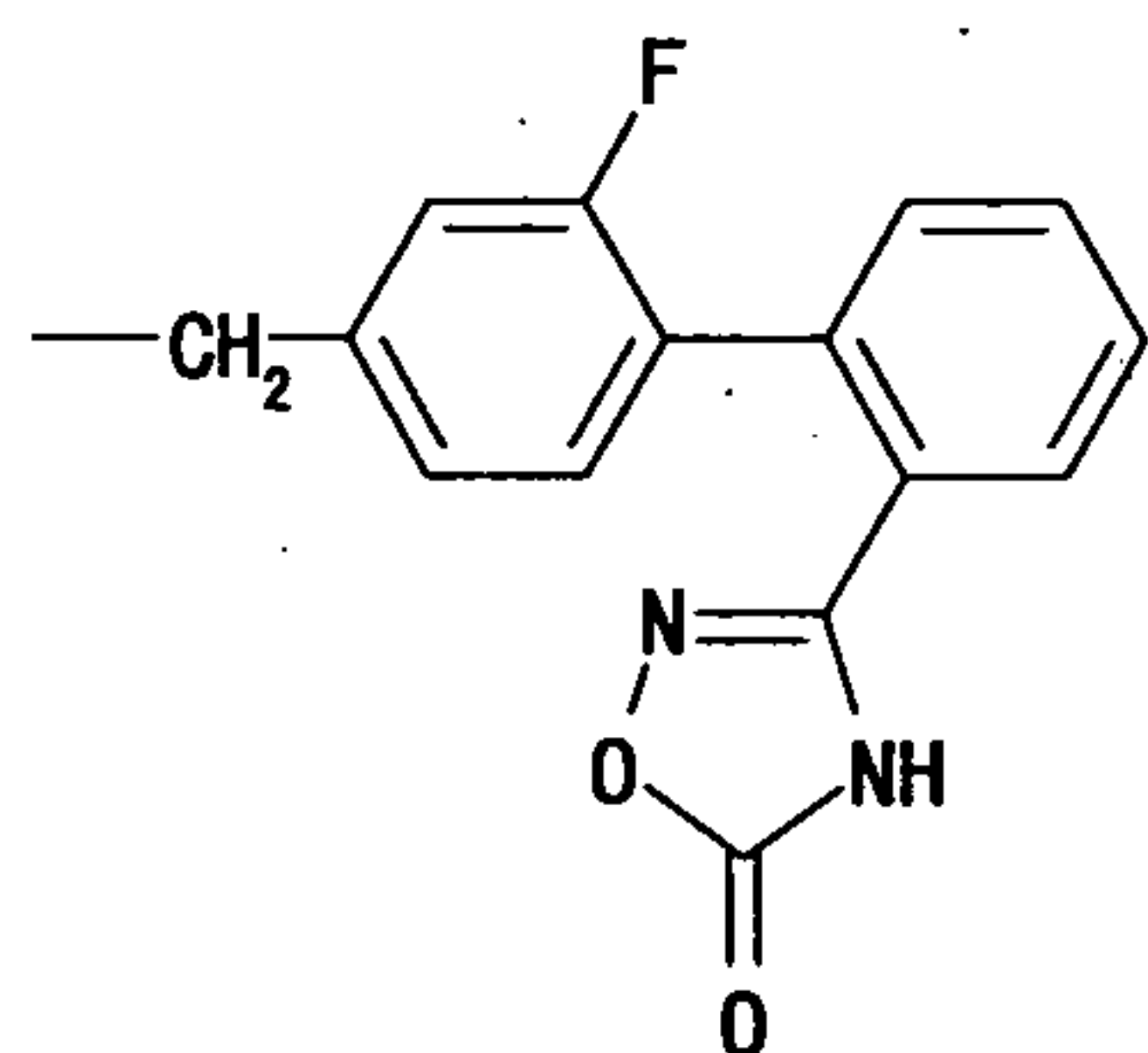
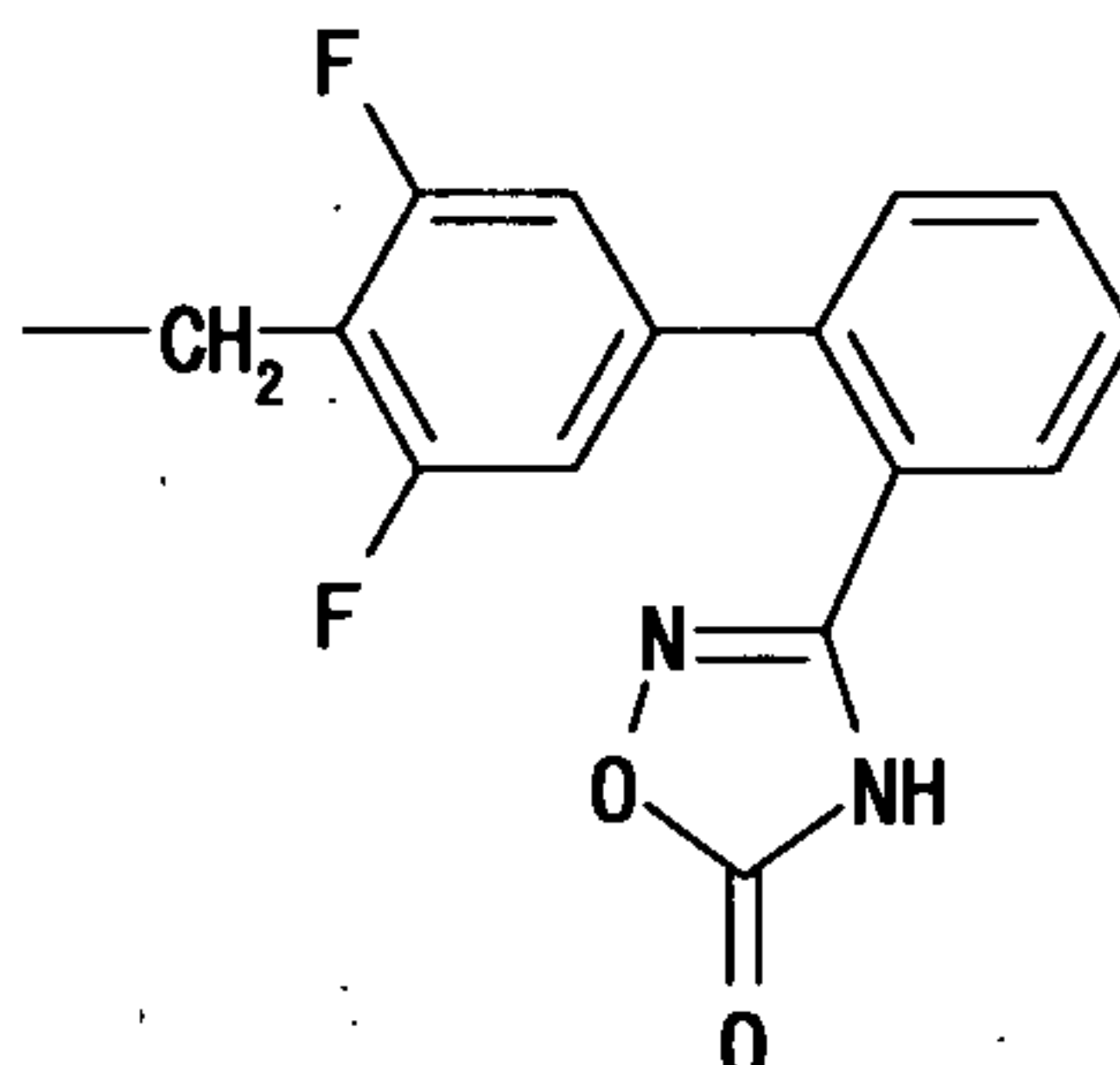
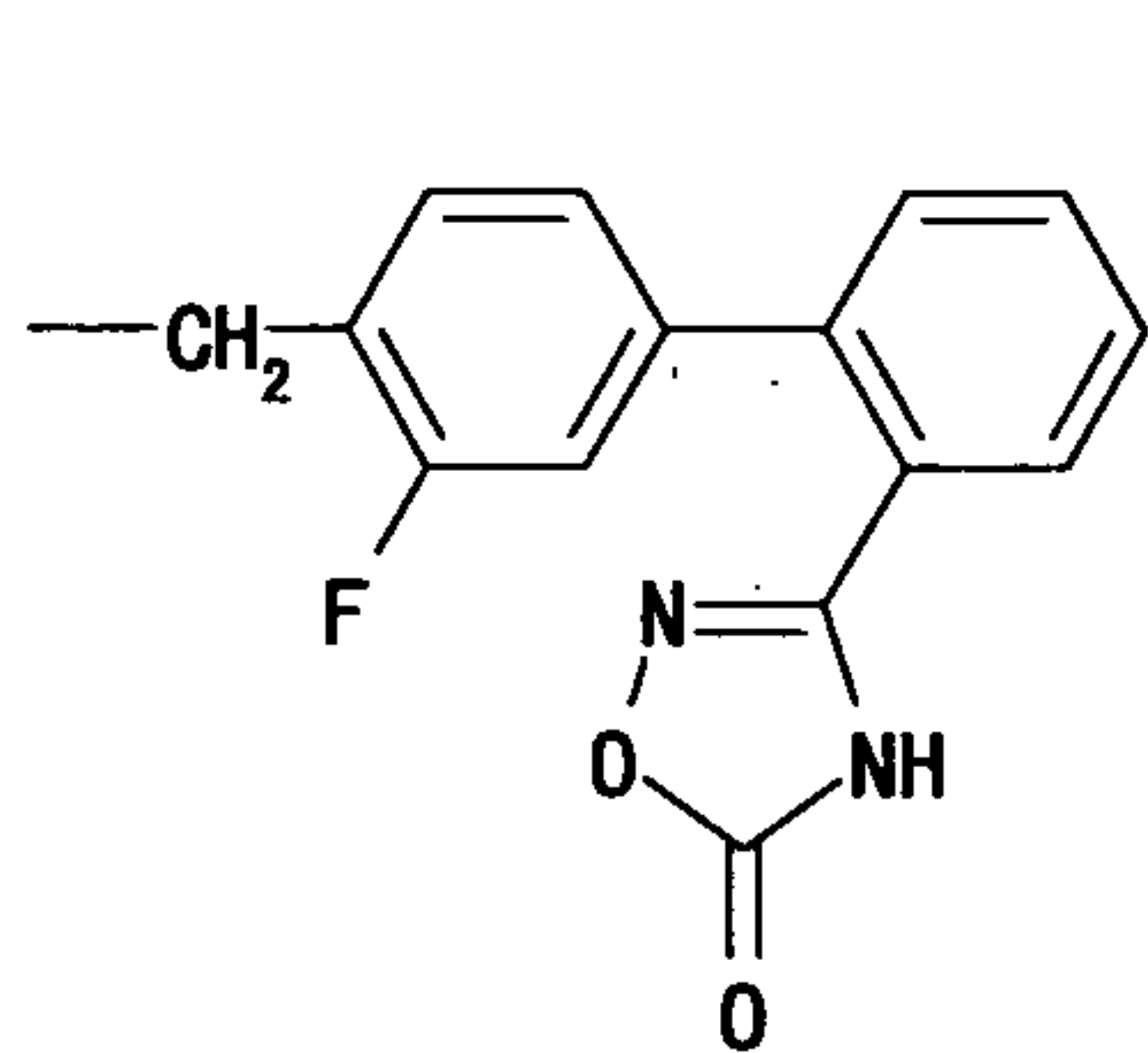
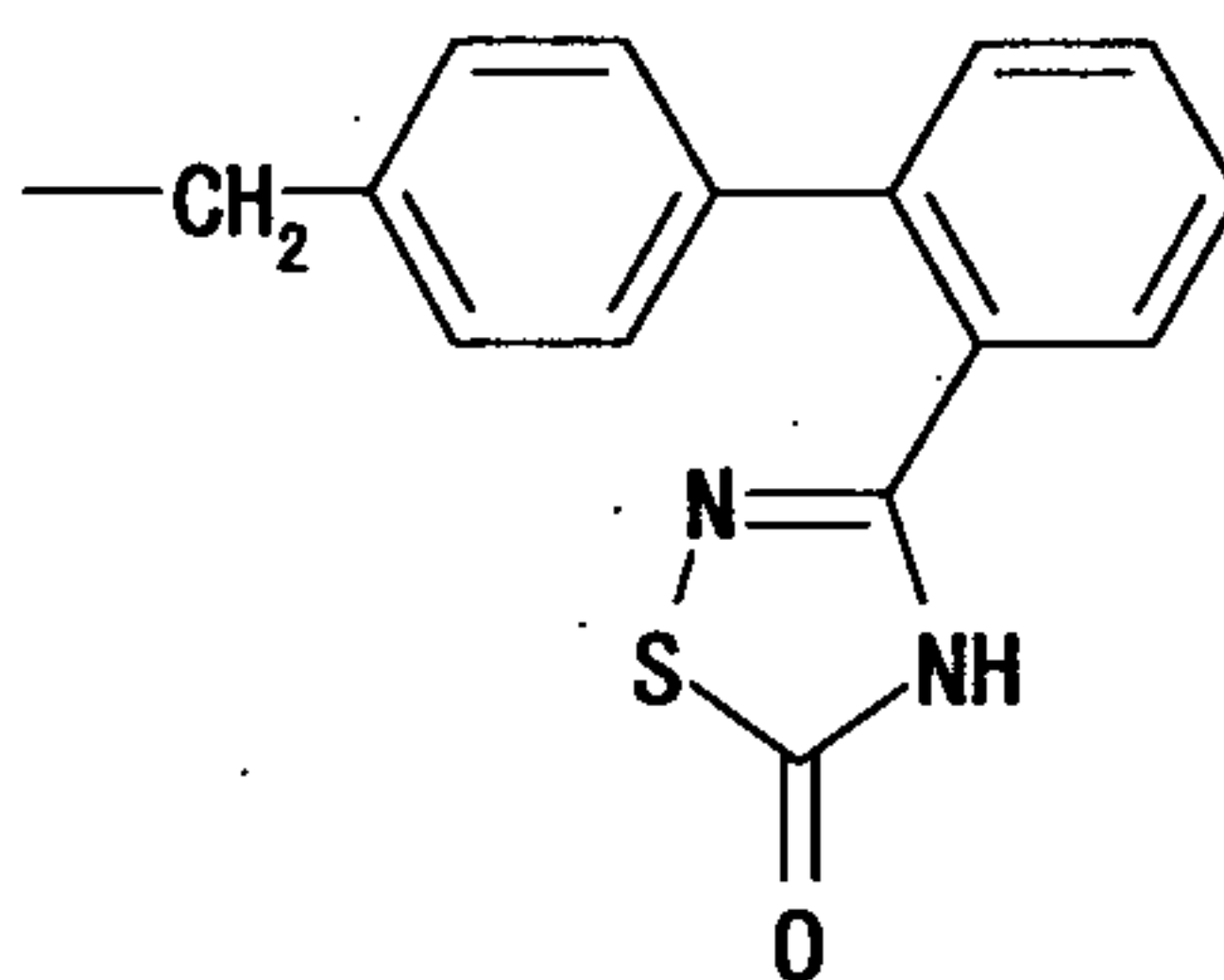
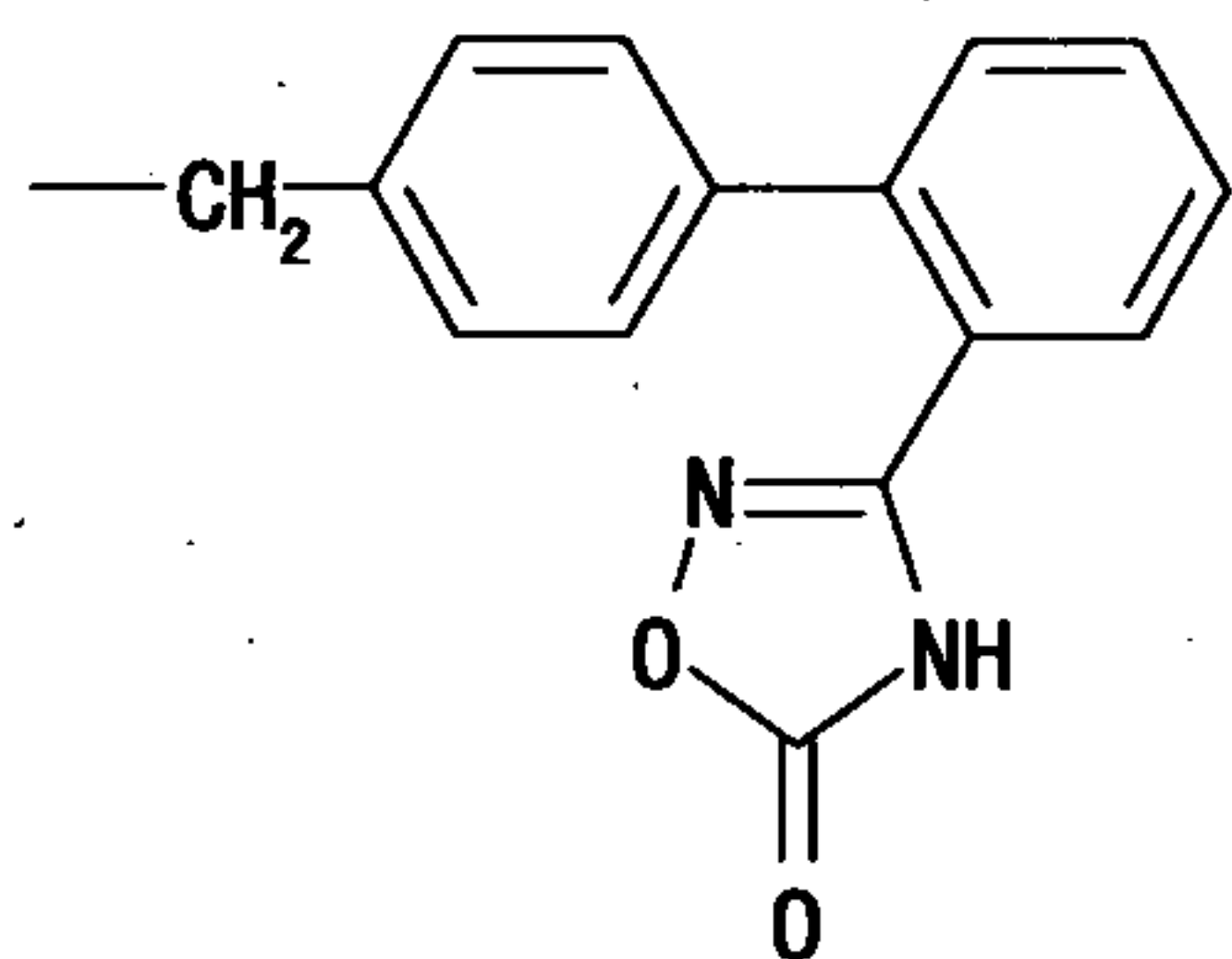
5. or

- (4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,

more preferably halogen (e.g., F, Cl, Br and the like),

10 and still more preferably fluorine; and

Z is O or S.], and specifically,



and the like are preferable.

Examples of the "optionally substituted C1-C6 alkyl group" for R3 or R4 include those similar to the "optionally substituted C1-C6 alkyl group" for R5.

5 As the "optionally substituted C1-C6 alkyl group" for R3 is preferably a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a C3-C6 cycloalkyloxy group, halogen, a hydroxy group, an oxo group and a C3-C6 cycloalkyl group, and
10 a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group is more preferable, and a C1-C6 alkyl group is further more preferable.

15 The "optionally substituted C1-C6 alkyl group" for R4 is preferably a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a C3-C6 cycloalkyloxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6
20 cycloalkyl group or a C6-C14 aryl group), a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur
25 atom and oxygen atom, for example, morpholinyl and the like) and a C1-C6 alkoxy-carbonyl group.

Examples of the "optionally substituted C3-C6 cycloalkyl group" for R3 or R4 include those similar to the "optionally substituted C3-C6 cycloalkyl group" for R, Ra, Rb or Rc. The
30 "optionally substituted C3-C6 cycloalkyl group" for R3 or R4 is preferably a C3-C6 cycloalkyl group.

The "optionally substituted C1-C6 alkoxy group" for R3 or R4 optionally has 1 to 5, preferably 1 to 3, substituents at substitutable position(s). Examples of the substituent include
35 those recited as the substituent of the "optionally

substituted C1-C6 alkyl group" for R5. The "optionally substituted C1-C6 alkoxy group" for R3 or R4 is preferably a C1-C6 alkoxy group.

Examples of the "optionally substituted C1-C6 alkylamino group" for R3 or R4 include an amino group monosubstituted by "optionally substituted C1-C6 alkyl group" can be mentioned. Examples of the "optionally substituted C1-C6 alkyl group" include those similar to the "optionally substituted C1-C6 alkyl group" for R5. The "optionally substituted C1-C6 alkylamino group" for R3 or R4 is preferably a C1-C6 alkylamino group.

Examples of the "optionally substituted di(C1-C6)alkylamino group" for R3 or R4 include an amino group disubstituted by "optionally substituted C1-C6 alkyl group". Examples of the "optionally substituted C1-C6 alkyl group" include those similar to the "optionally substituted C1-C6 alkyl group" for R5. The "optionally substituted di(C1-C6)alkylamino group" for R3 or R4 is preferably a di(C1-C6)alkylamino group.

The "optionally substituted alkylthio group" for R3 or R4 optionally has 1 to 5, preferably 1 to 3, substituents at substitutable position(s). Examples of the substituent include those similar to the substituents of the "optionally substituted C1-C6 alkyl group" for R5. The "optionally substituted alkylthio group" for R3 or R4 is preferably a C1-C6 alkylthio group.

As R3,

a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a C3-C6 cycloalkyloxy group, halogen, a hydroxy group, an oxo group and a C3-C6 cycloalkyl group;

a C3-C6 cycloalkyl group;

a C1-C6 alkoxy group;

a C3-C6 cycloalkyloxy group; or

a C1-C6 alkylthio group is preferable,

a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;

5. a C3-C6 cycloalkyl group;
 a C1-C6 alkoxy group; or
 a C1-C6 alkylthio group is more preferable, and
 a C1-C6 alkyl group is further more preferable.

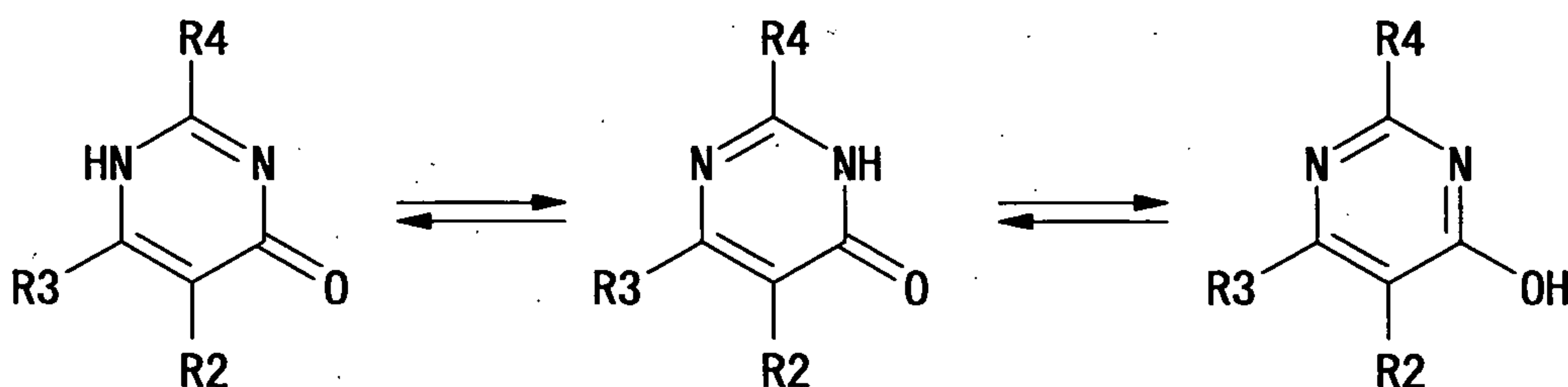
As R4,

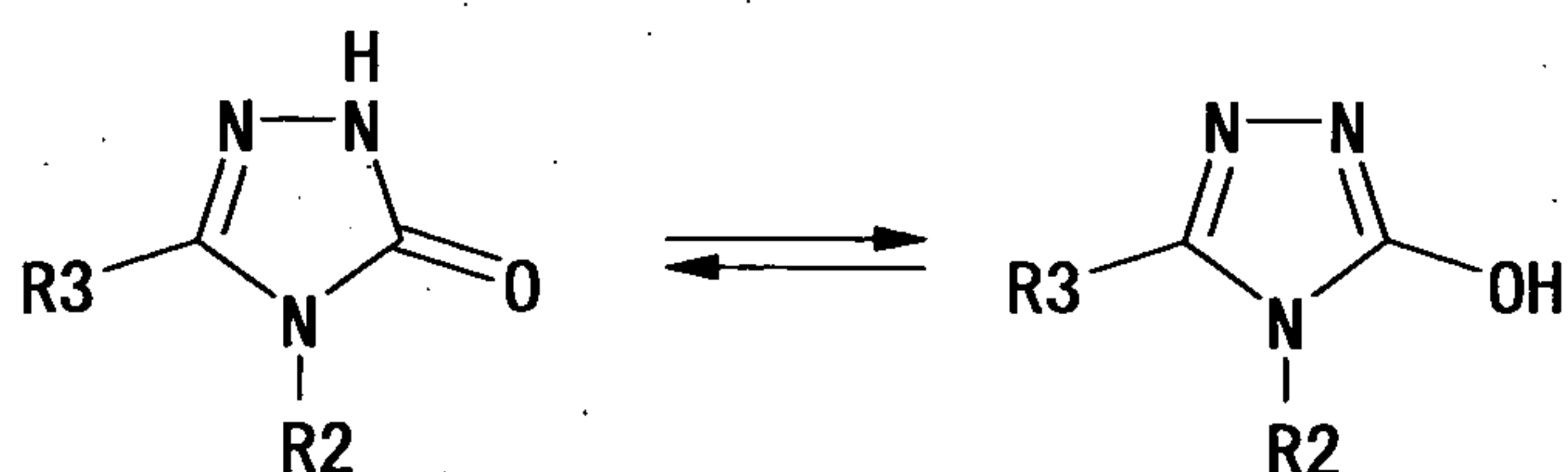
- 10 hydrogen;

a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a C3-C6 cycloalkyloxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl group), a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for example, morpholinyl and the like) and a C1-C6 alkoxy-carbonyl group;

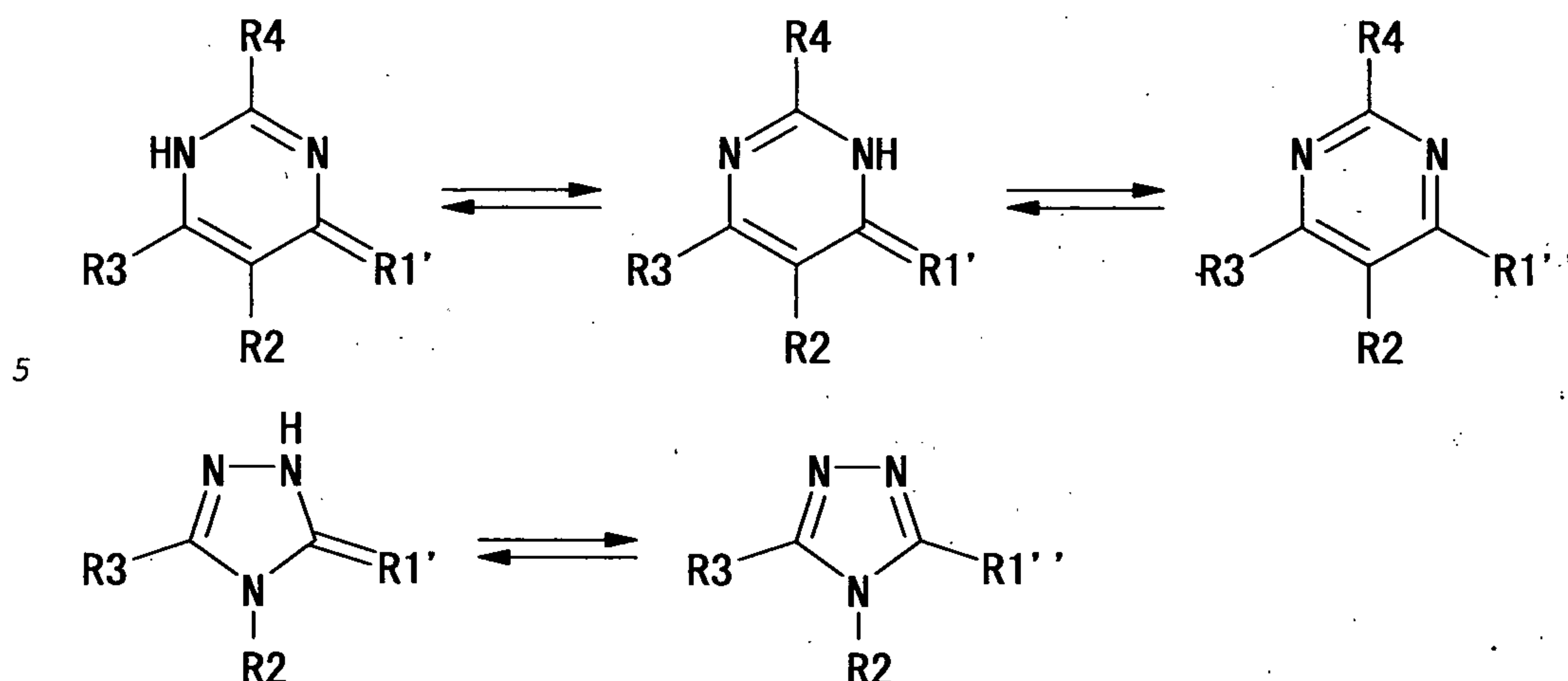
- a C3-C6 cycloalkyl group;
 a C1-C6 alkoxy group;
 a C3-C6 cycloalkyloxy group; or
 25 a di(C1-C6)alkylamino group is preferable, and
 a C1-C6 alkyl group is further more preferable.

In the compounds of the present invention, when R1 is an oxo group, and R5 is bonded to a nitrogen atom on the heterocycle and is hydrogen, a tautomer shown below may be present.





When R1 is =N-R, =N-CO-R', =N-CO-OR' or =N-SO₂-R', and R5 is bonded to the nitrogen atom on the heterocycle and is hydrogen, a tautomer shown below can be present.



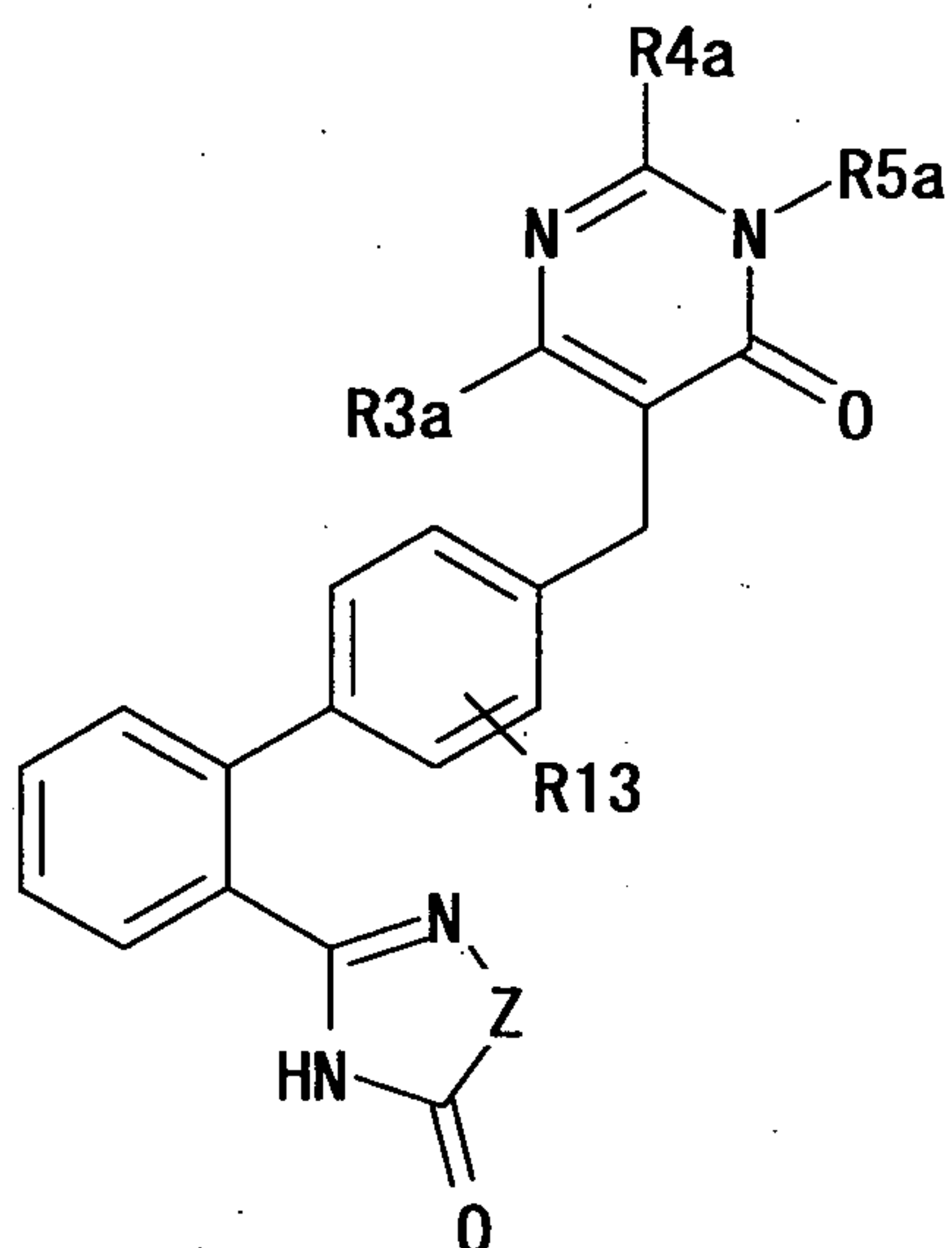
wherein R1' is =N-R, =N-CO-R', =N-CO-OR' or =N-SO₂-R', R1'' is -NH-R, -NH-CO-R', -NH-CO-OR' or -NH-SO₂-R', and R and R' are as defined above.

10 These tautomers are also encompassed in the scope of the present invention.

Preferable embodiments of a compound represented by the formula (I) include the following compounds.

[Compound A]

15 A compound represented by the formula:



wherein R3a, R4a and R5a are as defined for R3, R4 and R5, respectively, and other symbols are as defined above, or a salt thereof.

5 [Compound A-I]

Compound A wherein R3a is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of a C1-C6
alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl
10 group;

(2) a C3-C6 cycloalkyl group;

(3) a C1-C6 alkoxy group; or

(4) a C1-C6 alkylthio group,

R4a is

15 (1) hydrogen;

(2) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of a C1-C6
alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon
group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl
20 group) and a heterocyclic group (preferably, a 5- or 6-
membered, aromatic or a nonaromatic heterocyclic group
containing, as a ring-constituting atom besides carbon atom, 1
to 4 hetero atoms of 1 or 2 kinds selected from the group
consisting of nitrogen atom, sulfur atom and oxygen atom)

25 (e.g., morpholinyl and the like);

- (3) a C3-C6 cycloalkyl group;
- (4) a C1-C6 alkoxy group; or
- (5) a di(C1-C6)alkylamino group,

R5a is

- 5 (1) hydrogen ;
- (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of
 - (i) a hydroxy group,
 - (ii) a carboxy group,
 - 10 (iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and the like),
 - (iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
 - (v) a C3-C10 cycloalkyl-carbonyl group (e.g.,
 - 15 cyclohexylcarbonyl, adamantylcarbonyl and the like),
 - (vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,
 - (vii) a heterocyclyl-carbonyl group (preferably, a
 - 20 heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for
 - 25 example, morpholinocarbonyl and the like),
 - (viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
 - (ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
 - 30 (x) an adamantyl group,
 - (xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3
 - 35 substituents selected from the group consisting of halogen, a

hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a heterocycl-yl-carbonyl group (preferably, a heterocycl-yl-carbonyl group wherein the heterocycl-yl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like) and the like,

(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);

a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like, (xiii) a C1-C6 alkoxyimino group (e.g., isopropoxyimino and the like), and the like;

(3) an indanyl group optionally substituted by an oxo group or a hydroxy group;

(4) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like, preferably phenyl) optionally substituted by 1 to 3 substituents selected from the group consisting of (i) halogen (e.g., F, Cl, Br and the like);

(ii) a hydroxy group;

(iii) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group, a C1-C6 alkoxy group and a C1-C6 alkyl-carbonyl group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);

(iv) a C2-C6 alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;

(v) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like);

(vi) a C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, neopentyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of a C2-C6 alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a C3-C6 cycloalkyl group, a C1-C6 alkoxy-carbonyl group and a

carbamoyl group;

(vii) a C2-C6 alkenyloxy group (e.g., vinyloxy and the like);

(viii) a C2-C6 alkynyloxy group (e.g., 1-methylbut-3-yn-1-yloxy and the like);

5 (ix) a C3-C10 cycloalkyloxy group (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, an oxo group, a hydroxy group, a C1-C6 alkyl group, a C1-C6 alkoxy group
10 optionally substituted by 1 to 3 halogens, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-C1-C6 alkyl group;

(x) a C6-C14 aryloxy group (e.g., phenoxy and the like);

(xi) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered,
15 aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydrofuranyloxy, tetrahydropyranyloxy, piperidinyloxy and the like) optionally
20 substituted by 1 to 3 C1-C6 alkyl groups;

(xii) a heterocyclyl-C1-C6 alkyloxy group (preferably, a heterocyclyl-C1-C6 alkyloxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides
25 carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranylmethoxy and the like);

(xiii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);

30 (xiv) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio and the like);

(xv) a C1-C6 alkylsulfinyl group (e.g., methylsulfinyl, isopropylsulfinyl and the like);

(xvi) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl,
35 isopropylsulfonyl and the like);

- (xvii) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like);
- (xviii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);
- 5 (xix) a di(C1-C6)alkyl-carbamoyl group (e.g., dimethylcarbamoyl and the like);
- (xx) a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero
- 10 atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like)
- and the like;
- (5) a heterocyclic group (preferably, a 5- or 6-membered
- 15 heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with
- 20 benzene ring) (e.g., furyl, thienyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, tetrahydropyranyl, indolyl and the like)
- optionally substituted by 1 to 3 substituents selected from the group consisting of
- 25 (i) halogen (e.g., F, Cl, Br and the like);
- (ii) an oxo group;
- (iii) a hydroxy group;
- (iv) an amino group;
- (v) a C1-C6 alkyl group optionally substituted by 1 to 3
- 30 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
- (vi) a C1-C6 alkoxy group optionally substituted by 1 to 3
- 35 substituents selected from the group consisting of halogen, a

hydroxy group and a C3-C6 cycloalkyl group (e.g., methoxy, ethoxy, isopropoxy, neopentyloxy, trifluoromethoxy and the like);

(vii) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyloxy and the like);

(viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);

(ix) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like);

(6) a C2-C6 alkenyl group; or

(7) a heterocyclyl-oxy group (preferably, wherein the heterocyclyl moiety of the group is a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring (e.g., thienyl, thiazolyl, isoxazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 1,3-benzodioxolyl, 2,3-

dihydrobenzofuranyl)) optionally substituted by 1 to 3 C1-C6 alkyl groups,

R13 is

(1) hydrogen;

(2) halogen (e.g., F, Cl, Br and the like);

(3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);

or

(4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group, and

5 Z is O or S.

Preferably,

R3a is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;

(2) a C3-C6 cycloalkyl group;

(3) a C1-C6 alkoxy group; or

(4) a C1-C6 alkylthio group,

15 R4a is

(1) hydrogen;

(2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl group) and a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like);

(3) a C3-C6 cycloalkyl group;

(4) a C1-C6 alkoxy group; or

(5) a di(C1-C6)alkylamino group,

30 R5a is

(1) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like, preferably phenyl) optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) halogen (e.g., F, Cl, Br and the like);

35 (ii) a hydroxy group;

- (iii) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group, a C1-C6 alkoxy group and a C1-C6 alkyl-carbonyl group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
- (iv) a C2-C6 alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;
- (v) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like);
- 10 (vi) a C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, neopentyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of a C2-C6 alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a C3-C6 cycloalkyl group, a C1-C6 alkoxy-carbonyl group and a carbamoyl group;
- (vii) a C2-C6 alkenyloxy group (e.g., vinyloxy and the like);
- (viii) a C2-C6 alkynyloxy group (e.g., 1-methylbut-3-yn-1-yloxy and the like);
- 20 (ix) a C3-C10 cycloalkyloxy group (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, an oxo group, a hydroxy group, a C1-C6 alkyl group, a C1-C6 alkoxy group optionally substituted by 1 to 3 halogens, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-C1-C6 alkyl group;
- (x) a C6-C14 aryloxy group (e.g., phenoxy and the like);
- (xi) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydrofuranyloxy, tetrahydropyranyloxy, piperidinyloxy and the like) optionally
- 30 substituted by 1 to 3 C1-C6 alkyl groups;
- 35

- (xii) a heterocyclyl-C1-C6 alkyloxy group (preferably, a heterocyclyl-C1-C6 alkyloxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranylmethoxy and the like);
- (xiii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
- 10 (xiv) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio and the like);
- (xv) a C1-C6 alkylsulfinyl group (e.g., methylsulfinyl, isopropylsulfinyl and the like);
- (xvi) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl and the like);
- 15 (xvii) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like);
- (xviii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);
- 20 (xix) a di(C1-C6)alkyl-carbamoyl group (e.g., dimethylcarbamoyl and the like);
- (xx) a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like)
- 25 and the like;
- (2) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with
- 30 benzene ring) (e.g., furyl, thienyl, pyridyl,
- 35

dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, tetrahydropyranyl, indolyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of

- 5 (i) halogen (e.g., F, Cl, Br and the like);
- (ii) an oxo group;
- (iii) a hydroxy group;
- (iv) an amino group;
- (v) a C1-C6 alkyl group optionally substituted by 1 to 3
- 10 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
- (vi) a C1-C6 alkoxy group optionally substituted by 1 to 3
- 15 substituents selected from the group consisting of halogen, a hydroxy group and a C3-C6 cycloalkyl group (e.g., methoxy, ethoxy, isopropoxy, neopentyloxy, trifluoromethoxy and the like);
- (vii) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy
- 20 group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyloxy
- 25 and the like);
- (viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
- (ix) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like)
- 30 and the like; or
- (3) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of
- (i) a hydroxy group,
- (ii) a carboxy group,
- 35 (iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and

- the like),
- (iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
- (v) a C3-C10 cycloalkyl-carbonyl group (e.g.,
- 5 cyclohexylcarbonyl, adamantylcarbonyl and the like),
- (vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,
- (vii) a heterocyclyl-carbonyl group (preferably, a
- 10 heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for
- 15 example, morpholinocarbonyl and the like),
- (viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
- (ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
- 20 (x) an adamantyl group,
- (xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3
- 25 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen
- 30 and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a
- 35 heterocyclyl-carbonyl group (preferably, a heterocyclyl-

carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like) and the like,

(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like,

(xiii) a C1-C6 alkoxyimino group (e.g., isopropoxyimino and the like),

and the like,

R13 is

- 5 (1) hydrogen;
(2) halogen (e.g., F, Cl, Br and the like);
(3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);
or

(4) a C1-C6 alkyl group optionally having 1 to 3 substituents
10 selected from the group consisting of halogen and a C1-C6
alkoxy group, and

Z is O or S.

[Compound A-II]

Compound A wherein R3a is

- 15 (1) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of a C1-C6
alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl
group;
(2) a C3-C6 cycloalkyl group;
20 (3) a C1-C6 alkoxy group; or
(4) a C1-C6 alkylthio group,

R4a is

- (1) hydrogen;
(2) a C1-C6 alkyl group optionally substituted by 1 to 3
25 substituents selected from the group consisting of a C1-C6
alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon
group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl
group) and a heterocyclic group (preferably, a 5- or 6-
membered, aromatic or a nonaromatic heterocyclic group
30 containing, as a ring-constituting atom besides carbon atom, 1
to 4 hetero atoms of 1 or 2 kinds selected from the group
consisting of nitrogen atom, sulfur atom and oxygen atom)
(e.g., morpholinyl and the like);
(3) a C3-C6 cycloalkyl group;
35 (4) a C1-C6 alkoxy group; or

- (5) a di(C1-C6)alkylamino group,
R5a is
a C6-C14 aryl group (e.g., phenyl, naphthyl and the like,
preferably phenyl) optionally substituted by 1 to 3
5 substituents selected from the group consisting of
(i) halogen (e.g., F, Cl, Br and the like);
(ii) a hydroxy group;
(iii) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of halogen, a
10 hydroxy group, a C1-C6 alkoxy group and a C1-C6 alkyl-carbonyl
group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl,
trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
(iv) a C2-C6 alkenyl group (e.g., vinyl and the like)
optionally substituted by 1 to 3 substituents selected from
15 the group consisting of halogen and a hydroxy group;
(v) a C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy,
isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, neopentyloxy
and the like) optionally substituted by 1 to 3 substituents
selected from the group consisting of a C2-C6 alkynyl group, a
20 C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a
C3-C6 cycloalkyl group, a C1-C6 alkoxy-carbonyl group and a
carbamoyl group;
(vi) a C2-C6 alkenyloxy group (e.g., vinyloxy and the like);
(vii) a C2-C6 alkynyloxy group (e.g., 1-methylbut-3-yn-1-yloxy
25 and the like);
(viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino
and the like);
(ix) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio
and the like);
30 (x) a C1-C6 alkylsulfinyl group (e.g., methylsulfinyl,
isopropylsulfinyl and the like);
(xi) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl,
isopropylsulfonyl and the like);
(xii) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the
35 like);

(xiii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);

(xiv) a di(C1-C6)alkyl-carbamoyl group (e.g., dimethylcarbamoyl and the like);

5 and the like,

R13 is

(1) hydrogen;

(2) halogen (e.g., F, Cl, Br and the like);

(3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);

10 or

(4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group, and

Z is O or S.

15 [Compound A-IIA]

3-(4-isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (Example 88);

6-butyl-2-methoxy-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-phenylpyrimidin-4(3H)-one (Example 108);

6-butyl-3-(3,4-dimethylphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 202);

25 6-butyl-3-[3-(1-hydroxy-1-methylethyl)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 217);

6-butyl-3-(4-ethoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 222);

30 3-[4-(1-ethylpropoxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (Example 256);

35 3-(4-tert-butoxyphenyl)-2-ethyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-

4(3H)-one (Example 364);

2-ethyl-3-[4-(2-hydroxy-1,1-dimethylethoxy)phenyl]-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propylpyrimidin-4(3H)-one (Example 377); or

- 5 2-ethyl-3-[4-(2-hydroxy-1,1-dimethylpropoxy)phenyl]-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}-6-propylpyrimidin-4(3H)-one (Example 444);
or a salt thereof.

[Compound A-III]

10 Compound A wherein R3a is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;

15 (2) a C3-C6 cycloalkyl group;

(3) a C1-C6 alkoxy group; or

(4) a C1-C6 alkylthio group,

R4a is

(1) hydrogen;

- 20 (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl group) and a heterocyclic group (preferably, a 5- or 6-
25 membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like);

30 (3) a C3-C6 cycloalkyl group;

(4) a C1-C6 alkoxy group; or

(5) a di(C1-C6)alkylamino group,

R5a is

a C6-C14 aryl group (e.g., phenyl, naphthyl and the like,

35 preferably phenyl) optionally substituted by 1 to 3

substituents selected from the group consisting of

- (i) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like);
- (ii) a C3-C10 cycloalkyloxy group (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, an oxo group, a hydroxy group, a C1-C6 alkyl group, a C1-C6 alkoxy group optionally substituted by 1 to 3 halogens, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-C1-C6 alkyl group;
- 10 (iii) a C6-C14 aryloxy group (e.g., phenoxy and the like);
- (iv) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of
- 15 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydrofuranyloxy, tetrahydropyranyloxy, piperidinyloxy and the like) optionally substituted by 1 to 3 C1-C6 alkyl groups;
- (v) a heterocyclyl-C1-C6 alkyloxy group (preferably, a
- 20 heterocyclyl-C1-C6 alkyloxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen
- 25 atom) (e.g., tetrahydropyranylmethoxy and the like);
- (vi) a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of
- 30 nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like)

and the like,

R13 is

- (1) hydrogen;
- 35 (2) halogen (e.g., F, Cl, Br and the like);

(3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);
or

(4) a C1-C6 alkyl group optionally having 1 to 3 substituents
selected from the group consisting of halogen and a C1-C6

5. alkoxy group, and

Z is O or S.

[Compound A-IIIA]

- 3-[4-(cyclobutyloxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-
dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
10 propylpyrimidin-4(3H)-one (Example 255);
3-[4-(cyclopropyloxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-
dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
propylpyrimidin-4(3H)-one (Example 265);
3-[4-(cyclopentyloxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-
15 dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
propylpyrimidin-4(3H)-one (Example 319);
2-ethyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-
yl)biphenyl-4-yl]methyl}-6-propyl-3-[4-(tetrahydro-2H-pyran-4-
yloxy)phenyl]pyrimidin-4(3H)-one (Example 378);
20 2-ethyl-3-(4-{[(2R)-2-hydroxycyclopentyl]oxy}phenyl)-5-{[2'-(
(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-
6-propylpyrimidin-4(3H)-one (Example 381);
2-ethyl-3-{4-[(trans-4-hydroxycyclohexyl)oxy]phenyl}-5-{[2'-(
(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-
25 6-propylpyrimidin-4(3H)-one (Example 414);
2-ethyl-3-{4-[(cis-4-hydroxycyclohexyl)oxy]phenyl}-5-{[2'-(5-
oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
propylpyrimidin-4(3H)-one (Example 415);
2-ethyl-3-{4-[(4-oxocyclohexyl)oxy]phenyl}-5-{[2'-(5-oxo-4,5-
30 dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
propylpyrimidin-4(3H)-one (Example 416);
3-(4-{[(2R,4s,6S)-2,6-dimethyltetrahydro-2H-pyran-4-
yl]oxy}phenyl)-2-ethyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-
oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-
35 one (Example 417); or

2-ethyl-3-{4-[(3-hydroxycyclohexyl)oxy]phenyl}-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (Example 422);
or a salt thereof.

5. [Compound A-IV]

Compound A wherein R3a is

- (1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;
- (2) a C3-C6 cycloalkyl group;
- (3) a C1-C6 alkoxy group; or
- (4) a C1-C6 alkylthio group,

R4a is

- (1) hydrogen;
- (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl group) and a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like);
- (3) a C3-C6 cycloalkyl group;
- (4) a C1-C6 alkoxy group; or
- (5) a di(C1-C6)alkylamino group,

R5a is

- a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with

- benzene ring) (e.g., furyl, thienyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, tetrahydropyranyl, indolyl and the like) optionally substituted by 1 to 3 substituents selected from
- 5 the group consisting of
- (i) halogen (e.g., F, Cl, Br and the like);
 - (ii) an oxo group;
 - (iii) a hydroxy group;
 - (iv) an amino group;
 - 10 (v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
 - 15 (vi) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C3-C6 cycloalkyl group (e.g., methoxy, ethoxy, isopropoxy, neopentyloxy, trifluoromethoxy and the like);
 - 20 (vii) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen
 - 25 atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyloxy and the like);
 - (viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
 - (ix) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and
 - 30 the like) and the like,
- R13 is
- (1) hydrogen;
 - (2) halogen (e.g., F, Cl, Br and the like);
 - (3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);
- 35 or

(4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group, and
Z is O or S.

5. [Compound A-IVA]

- 6-butyl-2-cyclopropyl-3-(2,3-dihydro-1-benzofuran-5-yl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 112);
6-butyl-3-(2,3-dihydro-1-benzofuran-5-yl)-2-isopropyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 118);
6-butyl-3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 128);
3-(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (Example 131);
3-(4-hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (Example 144);
6-butyl-3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 234);
2-methyl-3-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (Example 235);
3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (Example 239); or
3-(7-fluoro-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (Example 275);
or a salt thereof.

[Compound A-V]

Compound A wherein R3a is

- (1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;
- (2) a C3-C6 cycloalkyl group;
- (3) a C1-C6 alkoxy group; or
- (4) a C1-C6 alkylthio group,

10 R4a is

- (1) hydrogen;
- (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl group) and a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like);
- (3) a C3-C6 cycloalkyl group;
- (4) a C1-C6 alkoxy group; or
- (5) a di(C1-C6)alkylamino group,

25 R5a is

- a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of
- (i) a hydroxy group,
 - (ii) a carboxy group,
 - 30 (iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and the like),
 - (iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
 - (v) a C3-C10 cycloalkyl-carbonyl group (e.g.,
 - 35 cyclohexylcarbonyl, adamantylcarbonyl and the like),

- (vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,
- (vii) a heterocyclyl-carbonyl group (preferably, a
5 heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for
10 example, morpholinocarbonyl and the like),
- (viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
- (ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
- 15 (x) an adamantyl group,
- (xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3
20 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen
25 and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a
30 heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of
35 nitrogen atom, sulfur atom and oxygen atom) (e.g.,

morpholinocarbonyl and the like) and the like,
(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero
5 atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-
10 oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1
15 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
20 a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon
25 atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g.,
30 methoxy, ethoxy, trifluoromethoxy and the like) and the like,
(xiii) a C1-C6 alkoxyimino group (e.g., isopropoxyimino and the like),
and the like,
R13 is
35 (1) hydrogen;

(2) halogen (e.g., F, Cl, Br and the like);

(3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);
or

(4) a C1-C6 alkyl group optionally having 1 to 3 substituents
5 selected from the group consisting of halogen and a C1-C6
alkoxy group, and

Z is O or S.

[Compound A-VA]

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-
10 yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-
one (Example 32);

6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-
4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
yl]methyl}pyrimidin-4(3H)-one (Example 37);

15 3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-
oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one
(Example 47);

6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-
dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
20 4(3H)-one (Example 48);

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-
yl)biphenyl-4-yl]methyl}-3-(pyridin-2-ylmethyl)pyrimidin-
4(3H)-one (Example 50);

6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-
25 dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
4(3H)-one (Example 58);

3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{[2'-(5-
oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
yl]methyl}pyrimidin-4(3H)-one (Example 64);

30 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-
yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-
ylmethyl)pyrimidin-4(3H)-one (Example 81);

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-
yl)biphenyl-4-yl]methyl}-3-[(5-phenyl-1,2,4-oxadiazol-3-
35 yl)methyl]pyrimidin-4(3H)-one (Example 152); or

6-butyl-3-(2,6-difluorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 165);

or a salt thereof.

5 [Compound A1]

Compound A wherein R3a is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a C3-C6 cycloalkyl group and halogen;

10 (2) a C3-C6 cycloalkyl group;

(3) a C1-C6 alkoxy group; or

(4) a C1-C6 alkylthio group,

R4a is

(1) hydrogen;

15 (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl group) and a heterocyclic group (preferably, a 5- or 6-
20 membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like);

25 (3) a C3-C6 cycloalkyl group;

(4) a C1-C6 alkoxy group; or

(5) a di(C1-C6)alkylamino group,

R5a is

(1) hydrogen;

30 (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) a hydroxy group,

(ii) a carboxy group,

(iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and
35 the like),

- (iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
- (v) a C3-C10 cycloalkyl-carbonyl group (e.g., cyclohexylcarbonyl, adamantylcarbonyl and the like),
- 5 (vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,
- (vii) a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is
- 10 a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for example, morpholinocarbonyl and the like),
- 15 (viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
- (ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
- (x) an adamantyl group,
- 20 (xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and
- 25 a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and
- 30 the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the
- 35 heterocyclyl moiety is a 5- or 6-membered, aromatic or non-

aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like)

5 and the like,

(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of

10 nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl,

15 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetan-3-yl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of

20 halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C6-C14 aryl

25 group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of

30 nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like,

35 (xiii) a C1-C6 alkoxyimino group (e.g., isopropoxyimino and

the like),

and the like;

(3) an indanyl group optionally substituted by an oxo group or a hydroxy group;

5 (4) a C₆-C₁₄ aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) halogen (e.g., F, Cl, Br and the like);

(ii) a hydroxy group;

10 (iii) a C₁-C₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group, a C₁-C₆ alkoxy group and a C₁-C₆ alkyl-carbonyl group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);

15 (iv) a C₂-C₆ alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;

(v) a C₃-C₆ cycloalkyl group (e.g., cyclopropyl and the like);

(vi) a C₁-C₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, 20 isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, neopentyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of a C₂-C₆ alkynyl group, a C₁-C₆ alkoxy group, halogen, a cyano group, a hydroxy group, a C₃-C₆ cycloalkyl group, a C₁-C₆ alkoxy-carbonyl group and a 25 carbamoyl group;

(vii) a C₂-C₆ alkenyloxy group (e.g., vinyloxy and the like);

(viii) a C₂-C₆ alkynyloxy group (e.g., 1-methylbut-3-yn-1-yloxy and the like);

(ix) a C₃-C₁₀ cycloalkyloxy group (e.g., cyclopropyloxy, 30 cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of an oxo group, a hydroxy group, a C₁-C₆ alkyl group, a hydroxy-C₁-C₆ alkyl group and a C₁-C₆ alkoxy-C₁-C₆ alkyl group;

35 (x) a C₆-C₁₄ aryloxy group (e.g., phenoxy and the like);

- (xi) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydrofuranyloxy, tetrahydropyranyloxy, piperidinyloxy and the like) optionally substituted by 1 to 3 C1-C6 alkyl groups;
- (vxii) a heterocyclyl-C1-C6 alkyloxy group (preferably, a heterocyclyl-C1-C6 alkyloxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranylmethoxy and the like);
- (xiii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
- (xiv) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio and the like);
- (xv) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl and the like);
- (xvi) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like);
- (xvii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);
- (xviii) a di(C1-C6)alkyl-carbamoyl group (e.g., dimethylcarbamoyl and the like);
- (xix) a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like)
- and the like; or
- (5) a heterocyclic group (preferably, a 5- or 6-membered

heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein
5 said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., furyl, thienyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, tetrahydropyranyl, indolyl and the like) optionally substituted by 1 to 3 substituents selected from
10 the group consisting of
(i) halogen (e.g., F, Cl, Br and the like);
(ii) an oxo group;
(iii) a hydroxy group;
(iv) an amino group;
15 (v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
(vi) a C1-C6 alkoxy group optionally substituted by 1 to 3
20 substituents selected from the group consisting of halogen, a hydroxy group and a C3-C6 cycloalkyl group (e.g., methoxy, ethoxy, isopropoxy, neopentyloxy, trifluoromethoxy and the like);
(vii) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy
25 group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyloxy
30 and the like);
(viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
(ix) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like)
35 and the like,

R13 is hydrogen, halogen or C1-C6 alkoxy group, and
Z is O or S.

[Compound A2]

Compound A wherein R3a is

- 5 (1) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of a C1-C6
alkoxy group, a C3-C6 cycloalkyl group and halogen;
(2) a C3-C6 cycloalkyl group; or
(3) a C1-C6 alkoxy group,

10 R4a is

- (1) hydrogen;
(2) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of a C1-C6
alkoxy group, a hydroxy group, halogen and a cyclic
15 hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a
C6-C14 aryl group);
(3) a C3-C6 cycloalkyl group;
(4) a C1-C6 alkoxy group; or
(5) a di(C1-C6)alkylamino group,

20 R5a is

- (1) hydrogen;
(2) a C1-C6 alkyl group optionally substituted by 1 to 3
substituents selected from the group consisting of
(i) a hydroxy group,
25 (ii) a carboxy group,
(iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and
the like),
(iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the
like),
30 (v) a C3-C10 cycloalkyl-carbonyl group (e.g.,
cyclohexylcarbonyl, adamantylcarbonyl and the like),
(vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like)
optionally substituted by 1 to 3 substituents selected from
the group consisting of halogen and a C1-C6 alkoxy group,
35 (vii) a heterocyclyl-carbonyl group (preferably, a

heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for example, morpholinocarbonyl and the like),
(viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
(ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
(x) an adamantyl group,
(xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like) and the like,
(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero

atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like, and the like;

(3) an indanyl group optionally substituted by an oxo group or a hydroxy group;

(4) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) halogen (e.g., F, Cl, Br and the like);

(ii) a hydroxy group;

(iii) a C1-C6 alkyl group optionally substituted by 1 to 3

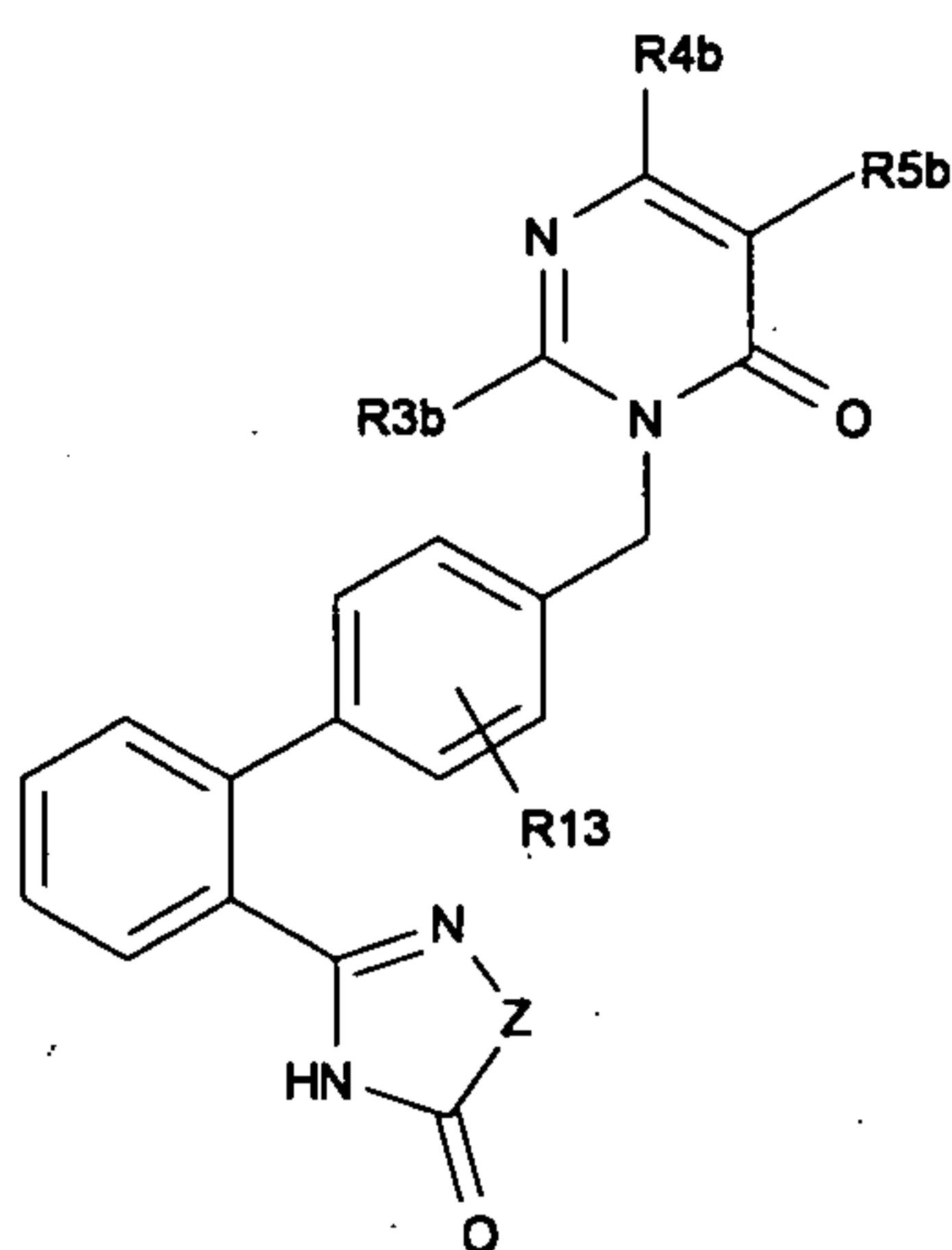
substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);

- 5 (iv) a C2-C6 alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;
- (v) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like);
- (vi) a C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, neopentyloxy and the like) 10 optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group, a C3-C6 cycloalkyl group and a C1-C6 alkoxy-carbonyl group;
- 15 (vii) a C3-C6 cycloalkyloxy group (e.g., cyclopropyloxy, cyclobutyloxy and the like);
- (viii) a C6-C14 aryloxy group (e.g., phenoxy and the like);
- (ix) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
- 20 (x) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio and the like);
- (xi) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl and the like);
- (xii) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the 25 like);
- (xiii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);
- (xiv) a di(C1-C6)alkyl-carbamoyl group (e.g., dimethylcarbamoyl and the like)
- 30 and the like; or
- (5) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur 35 atom and oxygen atom, or a fused heterocyclic group wherein

- said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., furyl, thienyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl and the like) optionally substituted by 1 to 3
- 5 substituents selected from the group consisting of
- (i) halogen (e.g., F, Cl, Br and the like);
 - (ii) an oxo group;
 - (iii) a hydroxy group;
 - (iv) an amino group;
 - 10 (v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
 - (vi) a C1-C6 alkoxy group optionally substituted by 1 to 3
 - 15 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like);
 - (vii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
 - 20 (viii) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like)
- and the like,
- R13 is hydrogen or halogen, and
- Z is O or S.

25 [Compound B]

A compound represented by the formula:



wherein R3b, R4b and R5b are as defined for R3, R4 and R5, respectively, and other symbols are as defined above, or a salt thereof.

[Compound B-I]

5 Compound B wherein R3b is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;

10 (2) a C3-C6 cycloalkyl group;

(3) a C1-C6 alkoxy group; or

(4) a C1-C6 alkylthio group,

R4b is

(1) hydrogen;

15 (2) a C1-C6 alkyl group optionally substituted by 1 to 3

substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl group) and a heterocyclic group (preferably, a 5- or 6-

20 membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like);

25 (3) a C3-C6 cycloalkyl group;

(4) a C1-C6 alkoxy group; or

(5) a di(C1-C6)alkylamino group,

R5b is

(1) hydrogen;

30 (2) a C1-C6 alkyl group optionally substituted by 1 to 3

substituents selected from the group consisting of

(i) a hydroxy group,

(ii) a carboxy group,

(iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and

35 the like),

- (iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
- (v) a C3-C10 cycloalkyl-carbonyl group (e.g., cyclohexylcarbonyl, adamantylcarbonyl and the like),
- 5 (vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,
- (vii) a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is
- 10 a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for example, morpholinocarbonyl and the like),
- 15 (viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
- (ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
- (x) an adamantyl group,
- 20 (xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a
- 25 hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy
- 30 and the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a heterocyclyl-carbonyl group (preferably, a heterocyclyl-
- 35 carbonyl group wherein the heterocyclyl moiety is a 5- or 6-

membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like) and the like,

(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetan-3-yl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like,

(xiii) a C1-C6 alkoxyimino group (e.g., isopropoxyimino and

the like),

and the like;

(3) an indanyl group optionally substituted by an oxo group or a hydroxy group;

5 (4) a C₆-C₁₄ aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) halogen (e.g., F, Cl, Br and the like);

(ii) a hydroxy group;

10 (iii) a C₁-C₆ alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group, a C₁-C₆ alkoxy group and a C₁-C₆ alkyl-carbonyl group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);

15 (iv) a C₂-C₆ alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;

(v) a C₃-C₆ cycloalkyl group (e.g., cyclopropyl and the like);

(vi) a C₁-C₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, 20 isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, neopentyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of a C₂-C₆ alkynyl group, a C₁-C₆ alkoxy group, halogen, a cyano group, a hydroxy group, a C₃-C₆ cycloalkyl group, a C₁-C₆ alkoxy-carbonyl group and a 25 carbamoyl group;

(vii) a C₂-C₆ alkenyloxy group (e.g., vinyloxy and the like);

(viii) a C₂-C₆ alkynyloxy group (e.g., 1-methylbut-3-yn-1-yloxy and the like);

(ix) a C₃-C₁₀ cycloalkyloxy group (e.g., cyclopropyloxy, 30 cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, an oxo group, a hydroxy group, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group optionally substituted by 1 to 3 halogens, a hydroxy-C₁-C₆ 35 alkyl group and a C₁-C₆ alkoxy-C₁-C₆ alkyl group;

- (x) a C6-C14 aryloxy group (e.g., phenoxy and the like);
- (xi) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydrofuranyloxy, tetrahydropyranyloxy, piperidinyloxy and the like) optionally substituted by 1 to 3 C1-C6 alkyl groups;
- 10 (xii) a heterocyclyl-C1-C6 alkyloxy group (preferably, a heterocyclyl-C1-C6 alkyloxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranylmethoxy and the like);
- 15 (xiii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
- (xiv) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio and the like);
- 20 (xv) a C1-C6 alkylsulfinyl group (e.g., methylsulfinyl, isopropylsulfinyl and the like);
- (xvi) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl and the like);
- 25 (xvii) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like);
- (xviii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);
- (xix) a di(C1-C6)alkyl-carbamoyl group (e.g., dimethylcarbamoyl and the like);
- 30 (xx) a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl
- 35

and the like)

and the like;

- (5) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., furyl, thienyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, tetrahydropyranyl, indolyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of
- (i) halogen (e.g., F, Cl, Br and the like);
 - 15 (ii) an oxo group;
 - (iii) a hydroxy group;
 - (iv) an amino group;
 - (v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
 - (vi) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C3-C6 cycloalkyl group (e.g., methoxy, ethoxy, isopropoxy, neopentyloxy, trifluoromethoxy and the like);
 - 25 (vii) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyloxy and the like);
 - 30 (viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
 - 35 and the like);

(ix) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like)

and the like;

(6) a C6-C14 aryl (e.g., phenyl)-carbonyl group;

5 (7) a heterocyclyl-carbonyl group (the heterocyclyl moiety of the group is, preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom,
10 or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring (e.g., thienyl, thiazolyl, isoxazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-
15 benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl));

(8) a C6-C14 aryl (e.g., phenyl)-oxy group optionally having 1 to 3 substituents selected from halogen; a C1-C6 alkyl group;
20 a C1-C6 alkoxy group optionally substituted by a hydroxy group; or

(9) a heterocyclyl-oxy group (preferably, the heterocyclyl moiety of the group is a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1
25 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring (e.g., thienyl, thiazolyl, isoxazolyl, pyrazolyl, 1,2,4-oxadiazolyl,
30 pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl)) optionally substituted by 1 to 3 C1-C6
35 alkyl groups,

R13 is

- (1) hydrogen;
- (2) halogen (e.g., F, Cl, Br and the like);
- (3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);

5 or

- (4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group, and

Z is O or S.

10 Preferably,

R3b is

- (1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl

15 group;

- (2) a C3-C6 cycloalkyl group;
- (3) a C1-C6 alkoxy group; or
- (4) a C1-C6 alkylthio group,

R4b is

20 (1) hydrogen;

- (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl
- 25 group) and a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom)

30 (e.g., morpholinyl and the like);

- (3) a C3-C6 cycloalkyl group;
- (4) a C1-C6 alkoxy group; or
- (5) a di(C1-C6)alkylamino group,

R5b is

35 (1) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like)

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

- (i) halogen (e.g., F, Cl, Br and the like);
- (ii) a hydroxy group;
- 5 (iii) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group, a C1-C6 alkoxy group and a C1-C6 alkyl-carbonyl group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
- 10 (iv) a C2-C6 alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;
- (v) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like);
- (vi) a C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy,
- 15 isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, neopentyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of a C2-C6 alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a C3-C6 cycloalkyl group, a C1-C6 alkoxy-carbonyl group and a
- 20 carbamoyl group;
- (vii) a C2-C6 alkenyloxy group (e.g., vinyloxy and the like);
- (viii) a C2-C6 alkynyloxy group (e.g., 1-methylbut-3-yn-1-yloxy and the like);
- (ix) a C3-C10 cycloalkyloxy group (e.g., cyclopropyloxy,
- 25 cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, an oxo group, a hydroxy group, a C1-C6 alkyl group, a C1-C6 alkoxy group optionally substituted by 1 to 3 halogens, a hydroxy-C1-C6
- 30 alkyl group and a C1-C6 alkoxy-C1-C6 alkyl group;
- (x) a C6-C14 aryloxy group (e.g., phenoxy and the like);
- (xi) a heterocyclyl-oxy group optionally substituted by 1 to 3 C1-C6 alkyl groups (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered,
- 35 aromatic or non-aromatic heterocycle containing, as a ring-

- constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydrofuranyloxy, tetrahydropyranyloxy, piperidinyloxy and the like);
- 5 (xii) a heterocyclyl-C1-C6 alkyloxy group (preferably, a heterocyclyl-C1-C6 alkyloxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from
- 10 the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranylmethoxy and the like);
- (xiii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
- (xiv) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio
- 15 and the like);
- (xv) a C1-C6 alkylsulfinyl group (e.g., methylsulfinyl, isopropylsulfinyl and the like);
- (xvi) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl and the like);
- 20 (xvii) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like);
- (xviii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);
- (xix) a di(C1-C6)alkyl-carbamoyl group (e.g.,
- 25 dimethylcarbamoyl and the like);
- (xix) a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of
- 30 nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like)
- and the like;
- (2) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom
- 35 besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds

- selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., furyl, thienyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, tetrahydropyranyl, indolyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of
- (i) halogen (e.g., F, Cl, Br and the like);
 - 10 (ii) an oxo group;
 - (iii) a hydroxy group;
 - (iv) an amino group;
 - (v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, 15 tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
 - (vi) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C3-C6 cycloalkyl group (e.g., methoxy, 20 ethoxy, isopropoxy, neopentyloxy, trifluoromethoxy and the like);
 - (vii) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring- 25 constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyloxy and the like);
 - 30 (viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
 - (ix) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like)
- and the like; or
- 35 (3) a C1-C6 alkyl group optionally substituted by 1 to 3

substituents selected from the group consisting of

- (i) a hydroxy group,
- (ii) a carboxy group,
- (iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and
5 the like),
- (iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
- (v) a C3-C10 cycloalkyl-carbonyl group (e.g., cyclohexylcarbonyl, adamantylcarbonyl and the like),
- 10 (vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,
- (vii) a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is
15 a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for example, morpholinocarbonyl and the like),
- 20 (viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
- (ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
- (x) an adamantyl group,
- 25 (xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a
30 hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy
35 and the like); a C1-C6 alkylsulfonyl group (e.g.,

methanesulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like) and the like,

(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen

atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like,

5 (xiii) a C1-C6 alkoxyimino group (e.g., isopropoxyimino and the like),

and the like,

R13 is

(1) hydrogen;

10 (2) halogen (e.g., F, Cl, Br and the like);

(3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);

or

(4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6

15 alkoxy group, and

Z is O or S.

[Compound B-IA]

5-benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

20 (Example 4);

6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one (Example 7);

5-(4-isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one (Example 28);

5-benzyl-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one (Example 287);

30 2-butyl-5-[hydroxy(phenyl)methyl]-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (Example 452);

5-benzoyl-2-butyl-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

35 (Example 453);

6-ethyl-5-(morpholin-4-ylmethyl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one (Example 455);

6-ethyl-5-(1-hydroxy-2-methylpropyl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one (Example 473b);

6-ethyl-5-(6-isopropoxyppyridin-3-yl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one (Example 483); or

6-ethyl-5-[4-(2-hydroxy-1,1-dimethylethoxy)phenyl]-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one (Example 512);

or a salt thereof.

[Compound B1]

Compound B wherein R3b is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a C3-C6 cycloalkyl group and halogen;

(2) a C3-C6 cycloalkyl group;

(3) a C1-C6 alkoxy group; or

(4) a C1-C6 alkylthio group,

R4b is

(1) hydrogen;

(2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a C6-C14 aryl group) and a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like);

(3) a C3-C6 cycloalkyl group;

(4) a C1-C6 alkoxy group; or

(5) a di(C1-C6)alkylamino group,

R5b is

(1) hydrogen;

(2) a C1-C6 alkyl group optionally substituted by 1 to 3

5 substituents selected from the group consisting of

(i) a hydroxy group,

(ii) a carboxy group,

(iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and the like),

10 (iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),

(v) a C3-C10 cycloalkyl-carbonyl group (e.g., cyclohexylcarbonyl, adamantylcarbonyl and the like),

(vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,

(vii) a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for example, morpholinocarbonyl and the like),

(viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),

(ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),

(x) an adamantyl group,

(xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like)

30 optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl,

35 trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);

a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like) and the like,

(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably,

- a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like, (xiii) a C1-C6 alkoxyimino group (e.g., isopropoxyimino and the like), and the like;
- (3) an indanyl group optionally substituted by an oxo group or a hydroxy group;
- (4) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of
- (i) halogen (e.g., F, Cl, Br and the like);
 - (ii) a hydroxy group;
 - (iii) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group, a C1-C6 alkoxy group and a C1-C6 alkyl-carbonyl group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
 - (iv) a C2-C6 alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;
 - (v) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like);
 - (vi) a C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, neopentyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of a C2-C6 alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a hydroxy group, a C3-C6 cycloalkyl group, a C1-C6 alkoxy-carbonyl group and a carbamoyl group;
 - (vii) a C2-C6 alkenyloxy group (e.g., vinyloxy and the like);

- (viii) a C2-C6 alkynyloxy group (e.g., 1-methylbut-3-yn-1-yloxy and the like);
- (ix) a C3-C10 cycloalkyloxy group (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of an oxo group, a hydroxy group, a C1-C6 alkyl group, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-C1-C6 alkyl group;
- (x) a C6-C14 aryloxy group (e.g., phenoxy and the like);
- 10 (xi) a heterocyclyl-oxy group optionally substituted by 1 to 3 C1-C6 alkyl groups (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of
- 15 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydrofuranyloxy, tetrahydropyranyloxy, piperidinyloxy and the like);
- (xii) a heterocyclyl-C1-C6 alkyloxy group (preferably, a heterocyclyl-C1-C6 alkyloxy group wherein the heterocyclyl
- 20 moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranylmethoxy and the like);
- 25 (xiii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
- (xiv) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio and the like);
- (xv) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl,
- 30 isopropylsulfonyl and the like);
- (xvi) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like);
- (xvii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl and the like);
- 35 (xviii) a di(C1-C6)alkyl-carbamoyl group (e.g.,

dimethylcarbamoyl and the like);

(xix) a heterocyclic group (preferably, a 5- or 6-membered, aromatic or a nonaromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinyl and the like) and the like; or

(5) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., furyl, thienyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, tetrahydropyranyl, indolyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) halogen (e.g., F, Cl, Br and the like);

(ii) an oxo group;

(iii) a hydroxy group;

(iv) an amino group;

(v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
(vi) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C3-C6 cycloalkyl group (e.g., methoxy, ethoxy, isopropoxy, neopentyloxy, trifluoromethoxy and the like);

(vii) a heterocyclyl-oxy group (preferably, a heterocyclyl-oxy group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-

constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyloxy and the like);

5 (viii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);

(ix) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like)

and the like,

10 R13 is hydrogen, halogen or C1-C6 alkoxy group, and Z is O or S.

[Compound B2]

Compound B wherein R3b is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3
15 substituents selected from the group consisting of a C1-C6 alkoxy group, a C3-C6 cycloalkyl group and halogen;

(2) a C3-C6 cycloalkyl group; or

(3) a C1-C6 alkoxy group,

R4b is

20 (1) hydrogen;

(2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen and a cyclic hydrocarbon group (preferably, a C3-C6 cycloalkyl group or a
25 C6-C14 aryl group);

(3) a C3-C6 cycloalkyl group;

(4) a C1-C6 alkoxy group; or

(5) a di(C1-C6)alkylamino group,

R5b is

30 (1) hydrogen;

(2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) a hydroxy group,

(ii) a carboxy group,

35 (iii) a C1-C6 alkoxy-carbonyl group (e.g., ethoxycarbonyl and

- the like),
- (iv) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
- (v) a C3-C10 cycloalkyl-carbonyl group (e.g., cyclohexylcarbonyl, adamantylcarbonyl and the like),
- (vi) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,
- (vii) a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, for example, morpholinocarbonyl and the like),
- (viii) a C1-C6 alkyl-carbamoyl group (e.g., tert-butylcarbamoyl and the like),
- (ix) a C3-C6 cycloalkyl group (e.g., cyclopropyl, cyclohexyl and the like),
- (x) an adamantyl group,
- (xi) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like); a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl and the like); a carboxy group; a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl and the like); a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like); a heterocyclyl-carbonyl group (preferably, a heterocyclyl-carbonyl group wherein the

heterocyclyl moiety is a 5- or 6-membered, aromatic or non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., morpholinocarbonyl and the like) and the like,

(xii) a heterocyclic group (preferably, a 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 4- to 6-membered (preferably 5- or 6-membered) heterocyclic group is condensed with benzene ring) (e.g., thienyl, isoxazolyl, thiazolyl, pyrazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzo[d]isoxazolyl, benzothiazolyl, 1H-benzotriazolyl, quinolyl, oxetanyl, tetrahydrofuryl, morpholinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g., F, Cl, Br and the like); a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like); a C6-C14 aryl group (e.g., phenyl and the like); a C7-C16 aralkyl group (e.g., benzyl and the like); a heterocyclic group (preferably, a 5- or 6-membered aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., thienyl, pyridyl and the like); a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) and the like,

and the like;

(3) an indanyl group optionally substituted by an oxo group or a hydroxy group;

(4) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) halogen (e.g., F, Cl, Br and the like);

(ii) a hydroxy group;

(iii) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);

(iv) a C2-C6 alkenyl group (e.g., vinyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;

(v) a C3-C6 cycloalkyl group (e.g., cyclopropyl and the like);

(vi) a C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, neopentyloxy and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group, a C3-C6 cycloalkyl group and a C1-C6 alkoxy-carbonyl group;

(vii) a C3-C6 cycloalkyloxy group (e.g., cyclopropyloxy, cyclobutyloxy and the like);

(viii) a C6-C14 aryloxy group (e.g., phenoxy and the like);

(ix) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);

(x) a C1-C6 alkylthio group (e.g., methylthio, isopropylthio and the like);

(xi) a C1-C6 alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl and the like);

(xii) a C1-C6 alkyl-carbonyl group (e.g., acetyl and the like);

(xiii) a C1-C6 alkyl-carbamoyl group (e.g., methylcarbamoyl

and the like);

(xiv) a di(C1-C6)alkyl-carbamoyl group (e.g., dimethylcarbamoyl and the like), and the like; or

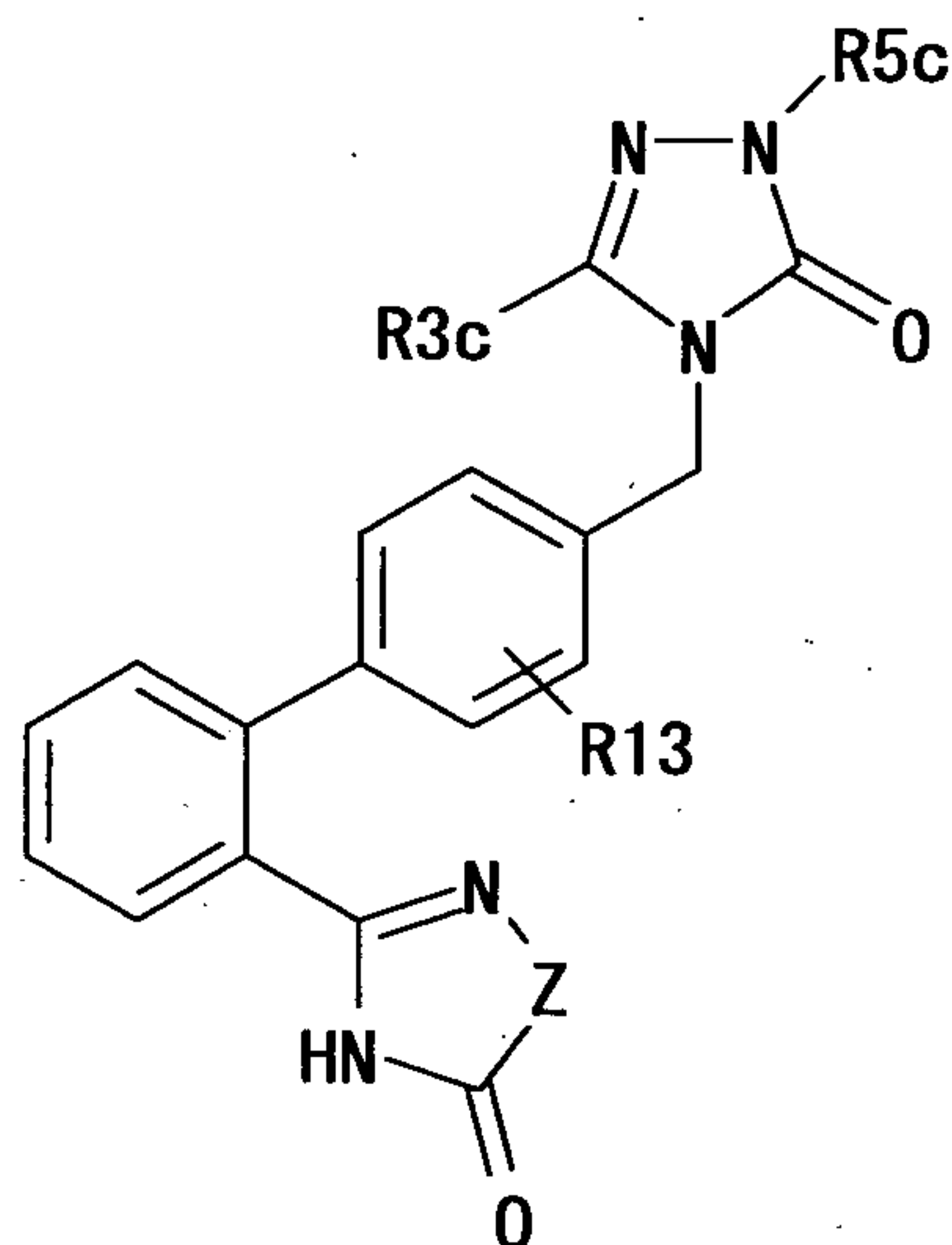
- 5 (5) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein
- 10 said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., furyl, thienyl, pyridyl, dihydrobenzopyranyl, chromenyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of
- 15 (i) halogen (e.g., F, Cl, Br and the like);
(ii) an oxo group;
(iii) a hydroxy group;
(iv) an amino group;
(v) a C1-C6 alkyl group optionally substituted by 1 to 3
- 20 substituents selected from the group consisting of halogen and a hydroxy group (e.g., methyl, ethyl, tert-butyl, trifluoromethyl, hydroxymethyl, 1-hydroxyethyl and the like);
(vi) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and
- 25 a hydroxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like);
(vii) a C1-C6 alkyl-carbonylamino group (e.g., acetylamino and the like);
(viii) a C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl
- 30 and the like)
and the like,

R13 is hydrogen or halogen, and

Z is O or S.

[Compound C]

- 35 A compound represented by the formula:



wherein R3c and R5c are as defined for R3 and R5, respectively, and other symbols are as defined above, or a salt thereof.

[Compound C-I]

5 Compound C wherein R3c is a C1-C6 alkyl group, R5c is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),
 10 (ii) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,
 (iii) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like),

15 (iv) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyl and the like),
 20 and the like;

(2) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like, preferably phenyl); or

(3) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom
 25 besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur

atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., 2,3-dihydrobenzofuranyl and the like) optionally substituted by 1 to 3 C1-C6 alkyl groups,

5. R13 is

(1) hydrogen;

(2) halogen (e.g., F, Cl, Br and the like);

(3) a C1-C6 alkoxy group (e.g., methoxy, ethoxy and the like);

or

10 (4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group, and

Z is O or S.

[Compound C1]

15 Compound C wherein R3c is a C1-C6 alkyl group,

R5c is

(1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) a C1-C6 alkyl-carbonyl group (e.g., pivaloyl and the like),

20 (ii) a C6-C14 aryl-carbonyl group (e.g., benzoyl and the like)

optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group,

(iii) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like),

25 (iv) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom) (e.g., tetrahydropyranyl and the like)

30 and the like;

(2) a C6-C14 aryl group (e.g., phenyl, naphthyl and the like, preferably phenyl); or

(3) a heterocyclic group (preferably, a 5- or 6-membered heterocyclic group containing, as a ring-constituting atom

35 besides carbon atom, 1 to 4 hetero atoms of 1 or 2 kinds

selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom, or a fused heterocyclic group wherein said 5- or 6-membered heterocyclic group is condensed with benzene ring) (e.g., 2,3-dihydrobenzofuranyl and the like)

5 optionally substituted by 1 to 3 C1-C6 alkyl groups,

R13 is hydrogen or halogen, and

Z is O or S.

[Compound C-IA]

3-(4'-{[3-butyl-1-(2,2-dimethylpropyl)-5-oxo-1,5-dihydro-4H-
10 1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-
5(4H)-one (Example 14);

3-(4'-{[3-butyl-1-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-
yl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-
yl)-1,2,4-oxadiazol-5(4H)-one (Example 136);

15 3-(4'-{[3-butyl-5-oxo-1-(2-phenylethyl)-1,5-dihydro-4H-1,2,4-
triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one
(Example 180);

3-{4'-[(3-butyl-1-sec-butyl-5-oxo-1,5-dihydro-4H-1,2,4-
triazol-4-yl)methyl]biphenyl-2-yl}-1,2,4-oxadiazol-5(4H)-one
20 (Example 181);

3-{4'-[(3-butyl-5-oxo-1-phenyl-1,5-dihydro-4H-1,2,4-triazol-4-
yl)methyl]biphenyl-2-yl}-1,2,4-oxadiazol-5(4H)-one (Example
182);

3-(4'-{[3-butyl-5-oxo-1-(tetrahydro-2H-pyran-2-yl)methyl]-1,5-
25 dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-
oxadiazol-5(4H)-one (Example 183);

3-[4'-({3-butyl-1-[2-(4-fluorophenyl)-2-oxoethyl]-5-oxo-1,5-
dihydro-4H-1,2,4-triazol-4-yl)methyl}biphenyl-2-yl]-1,2,4-
oxadiazol-5(4H)-one (Example 200);

30 3-[4'-({3-butyl-1-[2-(4-methoxyphenyl)-2-oxoethyl]-5-oxo-1,5-
dihydro-4H-1,2,4-triazol-4-yl)methyl}biphenyl-2-yl]-1,2,4-
oxadiazol-5(4H)-one (Example 301); or

3-(4'-{[3-butyl-1-(3,3-dimethyl-2-oxobutyl)-5-oxo-1,5-dihydro-
4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-
35 5(4H)-one (Example 302);

or a salt thereof.

As the salt of a compound represented by the formula (I), a pharmacologically acceptable salt and the like can be mentioned. Examples thereof include acid addition salt with an acid such as trifluoroacetic acid, acetic acid, lactic acid, succinic acid, maleic acid, tartaric acid, citric acid, gluconic acid, ascorbic acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, cinnamic acid, fumaric acid, phosphonic acid, hydrochloric acid, nitric acid, hydrobromic acid, hydroiodic acid, sulfamic acid, sulfuric acid and the like; salt with a metal salt such as sodium, potassium, magnesium, calcium and the like; salt with an organic base such as trimethylamine, triethylamine, pyridine, picoline, N-methylpyrrolidine, N-methylpiperidine, N-methylmorpholine and the like, and the like.

A prodrug of the compound (I) means a compound which is converted to the compound (I) with a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to the compound (I) with oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to the compound (I) by hydrolysis etc. due to gastric acid, etc. 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 an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation and tert-butylation, etc.); a compound obtained by subjecting a hydroxy group in compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting a hydroxy group in compound (I) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation,

dimethylaminomethylcarbonylation, etc.); a compound obtained by subjecting a carboxyl group in compound (I) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxy group in compound (I) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification and methylamidation, etc.) and the like. Any of these compounds can be produced from compound (I) by a method known *per se*.

A prodrug of the compound (I) may also be one which is converted into the compound (I) under a physiological condition, such as those described in IYAKUJIN no KAIHATSU (Development of Pharmaceuticals), Vol.7, Design of Molecules, p.163-198, 1990, Published by HIROKAWA SHOTEN.

When the compound (I) has isomers such as optical isomer, stereoisomer, positional isomer, rotational isomer and the like, and any isomers and mixture of isomers are encompassed in the compound (I). For example, when the compound (I) has an optical isomer, an optical isomer separated from a racemate is also encompassed in the compound (I). These isomers can be obtained as independent products by a synthesis means or a separation means (e.g., concentration, solvent extraction, column chromatography, recrystallization and the like), and the like known *per se*.

The compound (I) may be a crystal or an amorphous form. When the compound (I) is a crystal, both a single crystal and crystal mixtures are encompassed in the compound (I). Crystals can be produced by crystallization according to crystallization methods known *per se*.

The compound (I) may be a solvate (e.g., hydrate etc.) or a non-solvate, both of which are encompassed in the compound (I).

The compound (I) may be labeled with an isotope (e.g., ^3H , ^{14}C , ^{35}S , ^{125}I and the like) and the like.

Deuterium-converted compound wherein ^1H has been converted to $^2\text{H(D)}$ are also encompassed in the compound (I).

5 Since the compound of the present invention has a strong angiotensin II antagonistic activity (or inhibitory activity) (particularly, AT1 receptor antagonistic activity), the compound of the present invention is useful as an agent for the prophylaxis or treatment of a disease (or a disease whose
10 onset is promoted) developed by the contraction or growth of blood vessels or organ disorder, which expresses via an angiotensin II receptor, or due to the presence of angiotensin II, or a factor induced by the presence of angiotensin II, in mammals (e.g., human, monkey, cat, pig, horse, bovine, mouse,
15 rat, guinea pig, dog, rabbit etc.).

As such diseases, for example, hypertension, blood pressure circadian rhythm abnormality, heart diseases (e.g., cardiac hypertrophy, heart failure (e.g., acute heart failure, chronic heart failure including congestive heart failure),
20 impaired vasodilation, cardiac myopathy, angina pectoris, myocarditis, atrial fibrillation, arrhythmia, tachycardia, myocardial infarction etc.), cerebrovascular disorders (e.g., asymptomatic cerebrovascular disorder, transient cerebral ischemia, cerebral apoplexy, cerebrovascular dementia,
25 hypertensive encephalopathy, cerebral infarction etc.), cerebral edema, cerebral circulatory disorder, recurrence and sequela of cerebrovascular disorders (e.g., neurotic symptom, psychic symptom, subjective symptom, disorder in daily living activities etc.), ischemic peripheral circulation disorder,
30 myocardial ischemia, venous insufficiency, progression of cardiac insufficiency after myocardial infarction, renal diseases (e.g., nephritis, glomerulonephritis including chronic glomerulonephritis, glomerulosclerosis, renal failure, thrombotic vasculopathy, diabetic nephropathy, complication of
35 dialysis, organ dysfunction including nephropathy by radiation

damage etc.), arteriosclerosis including atherosclerosis (e.g., aneurysm, coronary arteriosclerosis, cerebral arteriosclerosis, peripheral arteriosclerosis etc.), vascular hypertrophy, vascular hypertrophy or obliteration and organ disorders after
5 intervention (e.g., percutaneous transluminal coronary angioplasty, stenting, coronary angioscopy, intravascular ultrasound, intracoronary thrombolysis etc.), vascular re-obliteration and restenosis after bypass, polycythemia, hypertension, organ disorder and vascular hypertrophy after
10 transplantation, rejection after transplantation, ocular diseases (e.g., glaucoma, ocular hypertension etc.), thrombosis, multiple organ disorder, endothelial dysfunction, hypertensive tinnitus, other cardiovascular diseases (e.g., deep vein thrombosis, obstructive peripheral circulatory
15 disorder, arteriosclerosis obliterans, thromboangiitis obliterans, ischemic cerebral circulatory disorder, Raynaud's disease, Buerger's disease etc.), metabolic and/or nutritional disorders (e.g., obesity, hyperlipidemia, hypercholesterolemia, hyperuricacidemia, hyperkalemia, hypernatremia etc.), nerve
20 degeneration diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, AIDS encephalopathy etc.), central nervous system disorders (e.g., disorders such as cerebral hemorrhage, cerebral infarction etc., and their sequela and complication, head injury, spinal injury, cerebral
25 edema, sensory malfunction, sensory functional disorder, autonomic nervous system disorder, autonomic nervous system malfunction, multiple sclerosis etc.), dementia, defects of memory, disorder of consciousness, amnesia, anxiety symptom, catatonic symptom, discomfort mental state, psychopathies
30 (e.g., depression, epilepsy, alcoholism etc.), inflammatory diseases (e.g., arthritis such as rheumatoid arthritis, osteoarthritis, rheumatoid myelitis, periostitis etc.; inflammation after operation and injury; remission of swelling; pharyngitis; cystitis; pneumonia; atopic dermatitis;
35 inflammatory intestinal diseases such as Crohn's disease,

ulcerative colitis etc.; meningitis; inflammatory ocular disease; inflammatory pulmonary disease such as pneumonia, pulmonary silicosis, pulmonary sarcoidosis, pulmonary tuberculosis etc.), allergic diseases (e.g., allergic rhinitis, conjunctivitis, gastrointestinal allergy, pollinosis, anaphylaxis etc.), chronic obstructive pulmonary disease, interstitial pneumonia, pneumocystis carinii pneumonia, collagen diseases (e.g., systemic lupus erythematosus, scleroderma, polyarteritis etc.), hepatic diseases (e.g., hepatitis including chronic hepatitis, hepatic cirrhosis etc.), portal hypertension, digestive system disorders (e.g., gastritis, gastric ulcer, gastric cancer, gastric disorder after operation, dyspepsia, esophageal ulcer, pancreatitis, colon polyp, cholelithiasis, hemorrhoidal disease, varices ruptures of esophagus and stomach etc.), blood and/or myelopoietic diseases (e.g., erythrocytosis, vascular purpura, autoimmune hemolytic anemia, disseminated intravascular coagulation syndrome, multiple myelopathy etc.), bone diseases (e.g., fracture, refracture, osteoporosis, osteomalacia, bone Paget's disease, sclerosing myelitis, rheumatoid arthritis, osteoarthritis of the knee and joint tissue dysfunction and the like caused by diseases similar to these etc.), solid tumor, tumors (e.g., malignant melanoma, malignant lymphoma, cancer of digestive organs (e.g., stomach, intestine etc.) etc.), cancer and cachexia following cancer, metastasis cancer, endocrinopathy (e.g., Addison's disease, Cushing's syndrome, pheochromocytoma, primary aldosteronism etc.), Creutzfeldt-Jakob disease, urinary organ and/or male genital diseases (e.g., cystitis, prostatic hypertrophy, prostatic cancer, sex infectious disease etc.), female disorders (e.g., climacteric disorder, gestosis, endometriosis, hysteromyoma, ovarian disease, breast disease, sex infectious disease etc.), disease relating to environment and occupational factors (e.g., radiation hazard, hazard by ultraviolet, infrared or laser beam, altitude sickness etc.), respiratory diseases (e.g.,

cold syndrome, pneumonia, asthma, pulmonary hypertension, pulmonary thrombosis and pulmonary embolism etc.), infectious diseases (e.g., viral infectious diseases with cytomegalovirus, influenza virus, herpes virus etc., rickettsiosis, bacterial infectious disease etc.), toxemias (e.g., sepsis, septic shock, endotoxin shock, Gram-negative sepsis, toxic shock syndrome etc.), otorhinolaryngological diseases (e.g., Meniere's syndrome, tinnitus, dysgeusia, vertigo, disequilibrium, dysphagia etc.), skin diseases (e.g., keloid, hemangioma, psoriasis etc.), intradialytic hypotension, myasthenia gravis, systemic diseases such as chronic fatigue syndrome and the like can be mentioned.

Since the compound of the present invention can maintain a certain hypotensive action through day and night, the dose and frequency can be reduced as compared to the administration of a compound other than the present invention, and moreover, elevation of blood pressure before and after awakening, which is particularly problematic in patients with hypertension, can be suppressed more effectively.

In addition, long-term suppression of action of angiotensin II by the compound of the present invention results in the improvement or suppression of promotion of disorder or abnormality in the biofunction and physiological action, that causes adult disorders and various diseases linked with aging and the like, which in turn leads to the primary and secondary prophylaxis of diseases or clinical conditions caused thereby or suppression of the progression thereof. As the disorder or abnormality in the biofunction and physiological action, for example, disorder or abnormality in automatic controlling capability of cerebral circulation and/or renal circulation, disorder of circulation (e.g., peripheral, cerebral, microcirculation etc.), disorder of blood-brain-barrier, salt sensitivity, abnormal state of coagulation and fibrinolysis system, abnormal state of blood and blood cell components (e.g., accentuation of platelet

aggregation action, malfunction of erythrocyte deformability, accentuation of leukocyte adhesiveness, rise of blood viscosity etc.), production and function accentuation of growth factor and cytokines (e.g., PDGF, VEGF, FGF, interleukin, TNF- α , MCP-1 etc.), accentuation of production and infiltration of inflammatory cells, accentuation of production of free radical, liposteatosis accentuation, endothelial function disorder, endothelium, cell and organ dysfunction, edema, cell morphogenesis change of smooth muscle etc. (morphogenesis to proliferation type etc.), production and function accentuation of vasoactive substance and thrombosis inducers (e.g., endothelin, thromboxane A₂ etc.), abnormal constriction of blood vessel etc., metabolic disorder (serum lipid abnormalities, dysglycemia etc.), abnormal growth of cell etc., angiogenesis (including abnormal vasculogenesis during abnormal capillary reticular formation in adventitial coat of arteriosclerotic lesion) and the like can be mentioned. The compound of the present invention can be used as an agent for the primary and secondary prophylaxis or treatment of organ disorders associated with various diseases (e.g., cerebrovascular disorder and organ disorder associated therewith, organ disorder associated with cardiovascular disease, organ disorder associated with diabetes, organ disorder after intervention etc.). In particular, since the compound has an activity of inhibiting proteinuria, the compound of the present invention can be used as an agent for protecting kidney.

Therefore, the compound of the present invention can be advantageously used when the patients with insulin resistance, impaired glucose tolerance, diabetes or hyperinsulinemia have concurrently developed the above-mentioned diseases or clinical condition.

The compound of the present invention can be used as insulin sensitizer, agent for enhancing insulin sensitivity, retinoid related receptor function regulator, peroxisome

proliferator-activated receptor ligand, retinoid X receptor ligand and the like. As used herein, the function regulator means both agonist and antagonist.

The compound of the present invention has hypoglycemic
5 action, hypolipidemic action, insulin resistance improving action, insulin sensitizing action and peroxisome proliferator-activated receptor (hereinafter sometimes to be abbreviated as PPAR) γ (GenBank Accession No. L40904) agonist action. As used herein, PPAR γ may form a heterodimer receptor
10 with retinoid X receptor (hereinafter sometimes to be abbreviated as RXR) α (GenBank Accession No. X52773), RXR β (GenBank Accession No. M84820) or RXR γ (GenBank Accession No. U38480). The compound of the present invention has a selective agonist action on PPAR γ .

15 Since the compound of the present invention normalizes the intracellular insulin signal transduction mechanism, which mainly causes insulin resistance, thereby reducing insulin resistance and enhancing insulin action, and has a glucose tolerance improvement action. Therefore, the compound of the
20 present invention or a salt thereof or a prodrug thereof (containing the compound of the present invention) can be used for mammals (e.g., human, monkey, cat, pig, horse, bovine, mouse, rat, guinea pig, dog, rabbit etc.) as an improving agent or an agent for the prophylaxis and/or treatment of the
25 diseases in which insulin resistance is involved.

The compound of the present invention can be used, for example, as an agent for the prophylaxis or treatment of diabetes (e.g., type 1 diabetes, type 2 diabetes, gestational diabetes, obesity type diabetes); an agent for the prophylaxis
30 or treatment of hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypoHDL-emia, postprandial hyperlipemia); an insulin sensitizer; an agent for enhancing insulin sensitivity; an agent for the prophylaxis or treatment of impaired glucose tolerance (IGT); and an agent for
35 preventing progression from impaired glucose tolerance to

diabetes.

In addition, the compound of the present invention can be used, for example, as an agent for the prophylaxis or treatment of hyperinsulinemia, hypertension associated with
5 insulin resistance, hypertension associated with impaired glucose tolerance, hypertension associated with diabetes (e.g., type II diabetes and the like), hypertension associated with hyperinsulinemia, insulin resistance associated with hypertension, impaired glucose tolerance associated with
10 hypertension, diabetes associated with hypertension, and hyperinsulinemia associated with hypertension.

Moreover, the compound of the present invention can also be used for the treatment of patients with diabetes, who shows a normal high blood pressure value.

15 The compound of the present invention can be also used as an agent for the prophylaxis or treatment of, for example, diabetic complications [e.g., neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia, diabetic hyperosmolar coma, infectious diseases (e.g., respiratory
20 infection, urinary tract infection, gastrointestinal tract infection, skin and soft tissue infection, lower limb infection), diabetic gangrene, xerostomia, lowered sense of hearing, cerebrovascular disease, peripheral circulatory disturbance], obesity, osteoporosis, cachexia (e.g., cancer
25 cachexia, tuberculous cachexia, diabetic cachexia, hemopathic cachexia, endocrinopathic cachexia, infectious cachexia, cachexia induced by acquired immunodeficiency syndrome), fatty liver, hypertension, polycystic ovary syndrome, renal diseases (e.g., diabetic nephropathy, glomerular nephritis,
30 glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end-stage renal disease), muscular dystrophy, myocardial infarction, angina pectoris, cerebrovascular disease (e.g., cerebral infarction, cerebral apoplexy), insulin resistant syndrome, syndrome X, metabolic syndrome
35 (clinical conditions showing at least three selected from

hypertriglyceridemia, hypo-HDL-cholesterolemia, hypertension, abdominal obesity and impaired glucose tolerance), hyperinsulinemia, hyperinsulinemia-induced sensory disorder, tumor (e.g., leukemia, breast cancer, prostate cancer, skin cancer), irritable bowel syndrome, acute or chronic diarrhea, inflammatory diseases (e.g., arteriosclerosis (e.g., atherosclerosis etc.), rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, remission of swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis (including non-alcoholic steatohepatitis), pneumonia, pancreatitis, inflammatory colitis, ulcerative colitis), visceral obesity syndrome and the like.

The compound of the present invention can be used for the improvement of symptoms associated with peptic ulcer, acute or chronic gastritis, biliary dyskinesia, cholecystitis or the like, such as abdominal pain, nausea, vomiting, epigastric discomfort and the like.

The compound of the present invention is also used as an agent for the prophylaxis or treatment of inflammatory diseases in which TNF- α is involved. Here, the inflammatory diseases in which TNF- α is involved means inflammatory diseases developed by the presence of TNF- α , and treated by a TNF- α suppressing effect. Examples of such inflammatory diseases include diabetic complications (e.g., retinopathy, nephropathy, neuropathy, macroangiopathy etc.), rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis, pneumonia, gastric mucosal injury (including aspirin-induced gastric mucosal injury) and the like.

The compound of the present invention has an apoptosis inhibitory activity, and can be used as an agent for the prophylaxis or treatment of diseases mediated by promotion of apoptosis. Examples of the diseases mediated by promotion of

apoptosis include viral diseases (e.g., AIDS, fulminant hepatitis etc.), neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration etc.),
5 myelodysplasia (e.g., aplastic anemia etc.), ischemic diseases (e.g., myocardial infarction, cerebral apoplexy etc.), hepatic diseases (e.g., alcoholic hepatitis, hepatitis B, hepatitis C etc.), joint diseases (e.g., osteoarthritis etc.), atherosclerosis and the like.

10 The compound of the present invention can be used for reducing visceral fats, inhibiting accumulation of visceral fats, ameliorating glycometabolism, ameliorating lipid metabolism, ameliorating insulin resistance, inhibiting oxidized LDL production, ameliorating lipoprotein metabolism,
15 ameliorating coronary artery metabolism, preventing or treating cardiovascular complications, preventing or treating heart failure complications, lowering blood remnant, preventing or treating anovulation, preventing or treating hirsutism, preventing or treating hyperandrogenism, and the
20 like.

The compound of the present invention is also used for the secondary prevention of various diseases mentioned above (e.g., cardiovascular event such as myocardial infarction etc.) and suppression of progression thereof.

25 For diagnostic criteria of diabetes, Japan Diabetes Society reported new diagnostic criteria in 1999.

According to this report, diabetes is a condition showing any of a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl, a 75 g oral
30 glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl, and a non-fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 200 mg/dl. A condition not falling under the above-mentioned diabetes and different from "a
35 condition showing a fasting blood glucose level (glucose

concentration of intravenous plasma) of less than 110 mg/dl or a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of less than 140 mg/dl" (normal type) is called a "borderline type".

5 In addition, ADA (American Diabetes Association) reported new diagnostic criteria of diabetes in 1997 and WHO in 1998.

According to these reports, diabetes is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl and a 75 g
10 oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl.

According to the above-mentioned reports, impaired glucose tolerance is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of
15 less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 140 mg/dl and less than 200 mg/dl. According to the report of ADA, a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not
20 less than 110 mg/dl and less than 126 mg/dl is called IFG (Impaired Fasting Glucose). According to the report of WHO, among the IFG (Impaired Fasting Glucose), a condition showing a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of less than 140 mg/dl is
25 called IFG (Impaired Fasting Glycemia).

The compound of the present invention can also be used as an agent for improving or the prophylaxis or treatment of diabetes, borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) and IFG (Impaired Fasting Glycemia),
30 as determined according to the above-mentioned new diagnostic criteria, or further, as an agent for treating hypertension of hypertensive patients having not less than the above-mentioned diagnostic criteria (e.g., fasting blood sugar level of 126 mg/dl). Moreover, the compound of the present invention can
35 prevent progression of borderline type, impaired glucose

tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired Fasting Glycemia) into diabetes.

The compound of the present invention is effective as a drug for the suppression or improvement of cardiac
5 hypofunction, progression of cardiac remodeling and aggravation of conditions in, or a drug for the suppression of decreased survival rate of, cardiac patients (e.g., cardiac hypertrophy, acute cardiac failure, chronic cardiac failure including congestive cardiac failure, impaired vasodilation,
10 cardiomyopathy, angina pectoris, myocarditis, atrial fibrillation, arrhythmia, tachycardia, myocardial infarction and the like) with diabetes. In addition, it is effective for the prevention of the onset of a cardiac disease (e.g., cardiac hypertrophy, acute cardiac failure, chronic cardiac
15 failure including congestive cardiac failure, impaired vasodilation, cardiomyopathy, angina pectoris, myocarditis, atrial fibrillation, arrhythmia, tachycardia, myocardial infarction and the like) and a cerebrovascular disorder (e.g., asymptomatic cerebrovascular disorder, transient cerebral
20 ischemic attack, cerebral apoplexy, cerebrovascular dementia, hypertensive encephalopathia, cerebral infarction and the like) in diabetic patients.

Since the compound of the present invention has an activity of inhibiting body weight gain, the compound of the
25 present invention can be used as a body weight gain inhibitor to mammals. Target mammals may be any mammals of which body weight gain is to be avoided. The mammals may have a risk of body weight gain genetically or may be suffering from lifestyle-related diseases such as diabetes, hypertension and/or
30 hyperlipidemia etc. The body weight gain may be caused by excessive feeding or diet without nutrient balance, or may be derived from combination drug, for example, agents for enhancing insulin sensitivity having PPAR γ -agonistic activity such as troglitazone, rosiglitazone, englitazone, ciglitazone,
35 pioglitazone etc. and the like. In addition, body weight gain

may be preliminary to obesity, or may be body weight gain of obesity patients. Here, obesity is defined that BMI (body mass index; body weight (kg)/[height (m)]²) is at least twenty-five for Japanese (criterion by Japan Society for the Study of Obesity), or at least thirty for westerner (criterion by WHO).

The compound of the present invention is useful as an agent for the prophylaxis or treatment of metabolic syndrome. Because patients with metabolic syndrome have an extreme high incidence of cardiovascular diseases as compared to patients with single lifestyle-related diseases, the prophylaxis or treatment of metabolic syndrome is quite important to prevent cardiovascular diseases.

Criteria for diagnosis of metabolic syndrome are announced by WHO in 1999, and by NCEP in 2001. According to the criterion of WHO, patients with at least two of abdominal obesity, dyslipidemia (high serum triglycerides or low HDL cholesterol) and hypertension in addition to hyperinsulinemia or impaired glucose tolerance are diagnosed as metabolic syndrome (World Health Organization: Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part I: Diagnosis and Classification of Diabetes Mellitus, World Health Organization, Geneva, 1999). According to the criterion of Adult Treatment Panel III of National Cholesterol Education Program, that is an indicator for managing ischemic heart diseases in the United States, patients with at least three of abdominal obesity, hypertriglyceridemia, hypo-HDL cholesterolemia, hypertension and impaired glucose tolerance are diagnosed as metabolic syndrome (National Cholesterol Education Program: Executive Summary of the Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adults Treatment Panel III). The Journal of the American Medical Association, Vol. 285, 2486-2497, 2001).

The compound of the present invention can be used for treating patients of hypertension with metabolic syndrome.

Since the compound of the present invention has an anti-inflammatory action, the compound of the present invention can be used as an anti-inflammatory agent for preventing or treating inflammatory diseases. Examples of inflammatory diseases include inflammatory diseases due to various diseases such as arthritis (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid myelitis, gouty arthritis, synovitis), asthma, allergic diseases, arteriosclerosis including atherosclerosis (aneurysm, coronary sclerosis, cerebral arterial sclerosis, peripheral arterial sclerosis etc.), digestive tract disease such as inflammatory intestine disease (e.g. Crohn's disease, ulcerative colitis), diabetic complication (diabetic neuropathy, diabetic vascular disorder), atopic dermatitis, chronic obstructive pulmonary disease, systemic lupus erythematosus, visceral inflammatory disease (nephritic, hepatitis), autoimmune hemolytic anemia, psoriasis, nervous degenerative disease (e.g. Alzheimer's disease, Parkinson's diseases, amyotrophic lateral sclerosis, AIDS encephalopathy), central nervous disorder (e.g. cerebrovascular disorder such as cerebral hemorrhage and cerebral infarct, head trauma, spinal damage, cerebral edema, multiple sclerosis), meningitis, angina pectoris, cardiac infarct, congestive cardiac failure, vascular hypertrophy or occlusion and organ disorder after intervention (percutaneous transluminal coronary angioplasty, stenting, coronary angioscopy, intravascular ultrasound, intracoronary thrombolysis etc), vascular reocclusion or restenosis after bypass operation, endothelial functional disorder, other circulatory disease (intermittent claudication, obstructive peripheral circulatory disorder, arteriosclerosis obliterans, thromboangiitis obliterans, ischemic cerebral circulatory disorder, Raynaud's disease, Buerger's disease), inflammatory ocular disease, inflammatory pulmonary disease (e.g. chronic pneumonia, silicosis, pulmonary sarcoidosis, pulmonary tuberculosis), endometritis, toxemia (e.g. sepsis, septic shock, endotoxin shock, gram negative sepsis, toxin shock syndrome), cachexia

(e.g. cachexia due to infection, carcinomatous cachexia, cachexia due to acquired immunodeficiency syndrome), cancer, Addison's disease, Creutzfeldt-Jakob disease, virus infection (e.g. infection of virus such as cytomegalovirus, influenza virus, herpes virus etc.), disseminated intravascular coagulation.

In addition, since the compound of the present invention has an analgesic action, the compound of the present invention can be also used as an analgesic agent for preventing or treating pain. Examples of pain diseases include acute pain due to inflammation, pain associated with chronic inflammation, pain associated with acute inflammation, pain after operation (pain of incisional, deep pain, organ pain, chronic pain after operation etc.), muscular pain (muscular pain associated with chronic pain disease, shoulder stiffness etc.), arthralgia, toothache, gnathicarthralgia, headache (migraine, catatonic headache, headache associated with fever, headache associated hypertension), organ pain (cardiac pain, angina pain, abdominal pain, renal pain, ureterane pain, bladder pain), pain in obstetrics area (mittelschmerz, dysmenorrheal, labor pain), neuralgia (disc hernia, nerve root pain, neuralgia after herpes zoster, trigeminal neuralgia), carcinomatous pain, reflex sympathetic atrophy, complex local pain syndrome, and the like. The compound of the present invention is effective in alleviate directly and rapidly various pains such as nervous pain, carcinomatous pain and inflammatory pain, and exhibits the particularly excellent analgesic effect to patients and pathologies in which a pain sense threshold is lowered.

The compound of the present invention is particularly useful as an analgesic agent for pain associated with chronic inflammation or pain associated with hypertension, or as an agent for preventing or treating inflammatory disease or pain due to (1) arteriosclerosis including atherosclerosis, (2) vascular hypertrophy, occlusion or organ disorder after intervention, (3) reocclusion, restenosis or endothelial

functional disorder after bypass operation, (4) intermittent claudication, (5) obstructive peripheral circulatory disorder, or (6) arteriosclerosis obliterans.

In one embodiment, since the compound of the present invention has an angiotensin II receptor antagonistic action (particularly an AT1 receptor antagonistic action) and a PPAR agonistic action (particularly a selective agonist action on PPAR γ), the compound is useful as an agent for the prophylaxis or treatment of circulatory diseases such as hypertension, cardiac disease (cardiac hypertrophy, cardiac failure, myocardial infarction and the like), arteriosclerosis, kidney disease (diabetic nephropathy, chronic glomerulonephritis and the like), cerebral apoplexy and the like; metabolic diseases such as hyperlipidemia, obesity, diabetes and the like; and/or central nervous system diseases such as depression, dementia, Alzheimer's disease and the like.

In further embodiment, the compound of the present invention is useful as an agent for the prophylaxis or treatment of hypertension, cardiac disease (cardiac hypertrophy, cardiac failure, myocardial infarction and the like), arteriosclerosis, kidney disease (diabetic nephropathy, chronic glomerulonephritis and the like), cerebral apoplexy, hyperlipidemia, obesity, diabetes, dementia, Alzheimer's disease and the like.

The content of the compound of the present invention in a pharmaceutical composition is generally about 0.01 - about 99.9 wt%, preferably about 0.1 - about 50 wt%, relative to the entire preparation.

The dose of the compound of the present invention is determined in consideration of age, body weight, general health condition, sex, diet, administration time, administration method, clearance rate, combination of drugs, the level of disease for which the patient is under treatment then, and other factors.

While the dose varies depending on the target disease, condition, subject of administration, administration method and

the like, for oral administration as a therapeutic agent for essential hypertension in adult, the daily dose of 0.1 - 600 mg is preferably administered in a single dose or in 2 or 3 portions.

5. In addition, since the compound of the present invention is superior in safety, it can be administered for a long period.

The compound of the present invention can be used in combination with pharmaceutical agents such as a therapeutic agent for diabetes, a therapeutic agent for diabetic complications, an anti-hyperlipidemia agent, an anti-arteriosclerotic agent, an anti-hypertensive agent, an anti-obesity agent, a diuretic, an antigout agent, an antithrombotic agent, an anti-inflammatory agent, a chemotherapeutic agent, an immunotherapeutic agent, a therapeutic agent for osteoporosis, an anti-dementia agent, an erectile dysfunction amelioration agent, a therapeutic agent for urinary incontinence/urinary frequency, a therapeutic agent for dysurea and the like (hereinafter to be abbreviated as a concomitant drug). These concomitant drugs may be low-molecular-weight compounds, high-molecular-weight proteins, polypeptides, antibodies, vaccines and the like. In this case, the administration mode of the compound of the present invention and the concomitant drug is not particularly restricted, and it is sufficient that the compound of the present invention and the concomitant drug are combined in administration. Examples of such administration mode include the following:

- (1) administration of a single preparation obtained by simultaneously processing the compound of the present invention and the concomitant drug, (2) simultaneous administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by the same administration route, (3) administration of two kinds of preparations of the compound of the present invention and the concomitant drug,

which have been separately produced, by the same administration route in a staggered manner, (4) simultaneous administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have
5 been separately produced, by different administration routes, (5) administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by different administration routes in a staggered manner (e.g.,
10 administration in the order of the compound of the present invention and the concomitant drug, or in the reverse order) and the like. The dose of the concomitant drug can be appropriately determined based on the dose clinically employed. The mixing ratio of the compound of the present invention and
15 the concomitant drug can be appropriately selected according to the administration subject, administration route, target disease, condition, combination, and other factors. In cases where the administration subject is human, for example, the concomitant drug may be used in an amount of 0.01 to 100 parts
20 by weight per part by weight of the compound of the present invention.

Examples of other therapeutic agents for diabetes include insulin preparations (e.g., animal insulin preparations extracted from pancreas of bovine and swine; human insulin
25 preparations genetically synthesized using *Escherichia coli*, yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1), oral insulin preparation), insulin sensitizers (e.g., pioglitazone or a salt thereof (preferably hydrochloride), rosiglitazone or a salt thereof
30 (preferably maleate), Netoglitazone (MCC-555), Rivoglitazone (CS-011), FK-614, compounds described in WO01/38325, Tesaglitazar (AZ-242), Ragaglitazar (NN-622), Muraglitazar (BMS-298585), Edaglitazone (BM-13-1258), Metaglidasen (MBX-102), Naveglitazar (LY-519818), MX-6054, LY-510929, AMG131 (T-
35 131) or a salt thereof, THR-0921), α -glucosidase inhibitors

(e.g., voglibose, acarbose, miglitol, emiglitate), biguanides (e.g., phenformin, metformin, buformin or a salt thereof (e.g., hydrochloride, fumarate, succinate)), insulin secretagogues [sulfonylureas (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole), repaglinide, nateglinide, mitiglinide or a calcium salt hydrate thereof], dipeptidyl peptidase IV inhibitors (e.g., Vidagliptin (LAF237), P32/98, Sitagliptin (MK-431), P93/01, PT-100, Saxagliptin (BMS-477118), T-6666, TS-021), β 3 agonists (e.g., AJ-9677), GPR40 agonists, GLP-1 receptor agonists [e.g., GLP-1, GLP-1MR agent, NN-2211, AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH₂, CJC-1131], amylin agonists (e.g., pramlintide), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists), SGLUT (sodium-glucose cotransporter) inhibitors (e.g., T-1095), 11 β -hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498), adiponectin or agonists thereof, IKK inhibitors (e.g., AS-2868), leptin resistance improving drugs, somatostatin receptor agonists (compounds described in WO01/25228, WO03/42204, WO98/44921, WO98/45285, WO99/22735 etc.), glucokinase activators (e.g., Ro-28-1675) and the like.

Examples of the therapeutic agents for diabetic complications include aldose reductase inhibitors (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidarestat, CT-112, ranirestat (AS-3201)), neurotrophic factors and enhancers thereof (e.g., NGF, NT-3, BDNF, neurotrophin production/secretion promoting agents described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole)), PKC inhibitors (e.g., ruboxistaurin mesylate), AGE inhibitors (e.g., ALT946, pimagedine, N-phenacylthiazolium bromide (ALT766), EXO-226, Pyridorin, pyridoxamine), active oxygen scavengers (e.g., thiocetic acid), cerebral vasodilators (e.g.,

tiapride, mexiletine), somatostatin receptor agonists (e.g., BIM23190), apoptosis signal regulating kinase-1 (ASK-1) inhibitors and the like.

Examples of the anti-hyperlipidemia agents include statin
5 compounds which are cholesterol synthesis inhibitors (e.g., cerivastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, itavastatin or salts thereof (e.g., sodium salt etc.) etc.), squalene synthetase inhibitors (e.g. TAK-475 etc.)
or fibrate compounds having a triglyceride lowering effect (e.g.,
10 bezafibrate, clofibrate, simfibrate, clinofibrate etc.), anion exchange resin (e.g., colestyramine), probucol, nicotinic acid drug (e.g., nicomol, niceritrol), phytosterol (e.g., soysterol, γ -oryzanol), EPA, DHA and the like.

Examples of the anti-arteriosclerotic agents include an
15 acyl-Coenzyme A cholesterol acyltransferase (ACAT) inhibitor (e.g. melinamide, Avasimibe, Eflucimibe etc.) and a lipid rich plaque regressing agent (e.g. compounds described in WO 02/06264, WO 03/059900 etc.) and the like.

Examples of the anti-hypertensive agents include
20 angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril etc.), angiotensin II antagonists (e.g., candesartan cilexetil, candesartan, losartan, losartan potassium, eprosartan, valsartan, termisartan, irbesartan, tasosartan, olmesartan, olmesartan medoxomil etc.), calcium antagonists
25 (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine etc.), β -blocker (e.g., metoprolol, atenolol, propranolol, carvedilol, pindolol etc.), clonidine and the like.

Examples of the anti-obesity agents include anti-obesity agents acting on the central nervous system (e.g.,
30 dexfenfluramine, fenfluramine, phentermine, sibutramine, amfepramone, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex etc.), MCH receptor antagonists (e.g., SB-568849; SNAP-7941; compounds described in WO01/82925 and WO01/87834), neuropeptide Y antagonists (e.g., CP-422935), cannabinoid
35 receptor antagonists (e.g., SR-141716, SR-147778), ghrelin

antagonists, 11β -hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498), pancreatic lipase inhibitors (e.g., orlistat etc.), $\beta 3$ agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 etc.), peptide anorexiant (e.g., leptin, CNTF (Ciliary Neurotropic Factor) etc.), cholecystokinin agonists (e.g., lintitript, FPL-15849 etc.), feeding deterrent (e.g., P-57) and the like.

Examples of the diuretics include xanthine derivatives (e.g., sodium salicylate and theobromine, calcium salicylate and theobromine etc.), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide etc.), antialdosterone preparations (e.g., spironolactone, triamterene etc.), carbonate dehydratase inhibitors (e.g., acetazolamide and the like), chlorobenzenesulfonamide preparations (e.g., chlortalidone, mefruside, indapamide etc.), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, furosemide and the like.

Examples of the antigout agents include allopurinol, probenecid, colchicine, benzbromarone, febuxostat, citrate and the like.

Examples of the antithrombotic agents include anticoagulating agent [e.g., heparin sodium, heparin potassium, warfarin potassium (warfarin), anti-thrombin drug (e.g., argatroban), activated blood coagulation factor X inhibitor (e.g., compounds described in WO 2004/048363 etc.) and the like], thrombolytic agent [e.g., tPA, urokinase], antiplatelet agent [e.g., aspirin, sulfinpyrazone (Anturan), dipyridamole (Persantin), ticlopidine (Panaldine), cilostazol (Pletal), GPIIb/IIIa antagonist (e.g., ReoPro), clopidogrel etc.], and the like.

Examples of the anti-inflammatory agents include non-steroidal anti-inflammatory agents, such as acetaminophen, fenasetin, ethenzamide, sulpyrine, antipyrine, migrenin, aspirin,

mefenamic acid, flufenamic acid, diclofenac sodium, loxoprofen sodium, phenylbutazone, indomethacin, ibuprofen, ketoprofen, naproxen, oxaprozin, flurbiprofen, fenbufen, pranoprofen, floctafenine, epirizol, tiaramide hydrochloride, zaltoprofen, 5 gabexate mesylate, camostat mesylate, ulinastatin, colchicine, probenecid, sulfinpyrazone, benzbromarone, allopurinol, sodium gold thiomalate, sodium hyaluronate, sodium salicylate, morphine hydrochloride, salicylic acid, atropine, scopolamine, morphine, pethidine, levorphanol, ketoprofen, naproxen, oxymorphone and 10 their salts etc., and the like.

Examples of the chemotherapeutic agents include alkylating agents (e.g., cyclophosphamide, ifosfamide etc.), metabolic antagonists (e.g., methotrexate, 5-fluorouracil etc.), antitumor antibiotics (e.g., mitomycin, adriamycin 15 etc.), plant-derived antitumor agent (e.g., vincristine, vindesine, Taxol etc.), cisplatin, carboplatin, etoposide and the like. Of these, Furtulon or NeoFurtulon, which are 5-fluorouracil derivatives, and the like are preferable.

Examples of the immunotherapeutic agents include 20 microorganism or bacterial components (e.g., muramyl dipeptide derivative, Picibanil etc.), polysaccharides having immunity potentiating activity (e.g., lentinan, schizophyllan, krestin etc.), cytokines obtained by genetic engineering techniques (e.g., interferon, interleukin (IL) etc.), colony stimulating 25 factors (e.g., granulocyte colony stimulating factor, erythropoietin etc.) and the like, with preference given to IL-1, IL-2, IL-12 and the like.

Examples of the therapeutic agents for osteoporosis include alfacalcidol, calcitriol, elcatonin, calcitonin salmon, 30 estriol, ipriflavone, pamidronate disodium, alendronate sodium hydrate, incadronate disodium and the like.

Examples of the anti-dementia agents include tacrine, donepezil, rivastigmine, galanthamine and the like.

Examples of the erectile dysfunction amelioration agents 35 include apomorphine, sildenafil citrate and the like.

Examples of the therapeutic agents for urinary incontinence/urinary frequency include flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride and the like.

- 5 Examples of the therapeutic agents for dysuria include acetylcholine esterase inhibitors (e.g., distigmine) and the like.

Furthermore, drugs having a cachexia-improving action established in animal models and clinical situations, such as
10 cyclooxygenase inhibitors (e.g., indomethacin etc.) [Cancer Research, Vol. 49, pages 5935-5939, 1989], progesterone derivatives (e.g., megestrol acetate) [Journal of Clinical Oncology, Vol. 12, pages 213-225, 1994], glucosteroids (e.g., dexamethasone etc.), metoclopramide agents,
15 tetrahydrocannabinol agents (publications are all as mentioned above), fat metabolism improving agents (e.g., eicosapentanoic acid etc.) [British Journal of Cancer, Vol. 68, pages 314-318, 1993], growth hormones, IGF-1, or antibodies to a cachexia-inducing factor such as TNF- α , LIF, IL-6, oncostatin M and the
20 like, can be used in combination with the compound of the present invention.

Furthermore, examples of the concomitant drug include nerve regeneration promoting drugs (e.g., Y-128, VX853, prosaptide), antidepressants (e.g., desipramine, amitriptyline,
25 imipramine), antiepileptics (e.g., lamotrigine), antiarrhythmic agents (e.g., mexiletine), acetylcholine receptor ligands (e.g., ABT-594), endothelin receptor antagonists (e.g., ABT-627), monoamine uptake inhibitors (e.g., tramadol), narcotic analgesics (e.g., morphine), GABA receptor
30 agonists (e.g., gabapentin), α 2 receptor agonists (e.g., clonidine), local analgesics (e.g., capsaicin), antianxiety drugs (e.g., benzodiazepines), dopamine agonists (e.g., apomorphine), midazolam, ketoconazole and the like.

The combination drug preferably includes a diuretic, an
35 insulin preparation, an insulin sensitizer, an α -glucosidase

inhibitor, a biguanide agent, an insulin secretagogue (preferably sulfonylurea agent) and the like. Particularly, a diuretic such as hydrochlorothiazide and the like and an insulin sensitizer such as pioglitazone hydrochloride and the like are
5 preferable.

The above-mentioned combination drug may be a combination of two or more kinds thereof combined at appropriate ratios.

When the compound of the present invention is used in combination with a drug for combined use, the amount of each
10 drug can be reduced within a safe range in consideration of the opposite effect of these drugs. Particularly, the dose of the insulin sensitizer, insulin secretagogue and biguanide can be reduced from conventional level. As a result, the side effects possibly caused by the combination of these agents can
15 be prevented safely. In addition, the dose of the therapeutic agent for diabetic complications, anti-hyperlipidemia agent or anti-hypertensive agent can be reduced and, as a result, the side effects possibly caused by these drugs can be effectively prevented.

20 Since the compound of the present invention potentiates hypoglycemic activity of other insulin sensitizers, a combined use of the compound of the present invention or a salt thereof or a prodrug thereof (particularly, the compound of the present invention) and other insulin sensitizers (preferably
25 pioglitazone hydrochloride) markedly enhances a prophylactic and/or therapeutic effect against diseases in which insulin resistance is involved, such as type II diabetes and the like.

In the pharmaceutical agent of the present invention, the compound (I) can be administered orally or parenterally as it
30 is or after mixing with a pharmacologically acceptable carrier.

The dosage form of a pharmaceutical agent containing compound (I) of the present invention when used for oral administration include tablet (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrating
35 tablet), pill, granule, powder, capsule (including soft capsule,

microcapsule), syrup, emulsion, suspension, film (e.g., orally disintegrating film) and the like, and the dosage form thereof for parenteral administration is, for example, injection, injecting agent, instillation, suppository and the like. In addition, it is effective to make a sustained release preparation by combining with a suitable base (e.g., polymer of butyric acid, polymer of glycolic acid, copolymer of butyric acid-glycolic acid, a mixture of polymer of butyric acid and polymer of glycolic acid, polyglycerol fatty acid ester etc.).

10 As a method to produce the compound (I) in the above-mentioned dosage form, a known production method generally used in the pertinent field can be applied. When the above-mentioned dosage form is produced, suitable amounts of additives such as an excipients, a binder, a disintegrant, a lubricant, a sweetener, a surfactant, a suspending agent, an emulsifier and the like generally used in the pertinent field are appropriately added as necessary, and produced.

When the compound (I) is prepared into a tablet, for example, it can be produced by adding an excipient, a binder, a disintegrant, a lubricant and the like, and when a pill and a granule are to be prepared, they can be produced by adding an excipient, a binder, a disintegrant and the like. When a powder and a capsule are to be prepared, they can be produced by adding an excipient and the like, and when a syrup is to be prepared, it can be produced by adding a sweetener and the like, and when an emulsion or a suspension is to be prepared, it can be produced by adding a suspending agent, a surfactant, an emulsifier and the like.

Examples of the excipient include lactose, sucrose, glucose, starch, saccharose, microcrystalline cellulose, powdered glycyrrhiza, mannitol, sodium hydrogen carbonate, calcium phosphate, calcium sulfate and the like.

Examples of the binder include 5 - 10 wt% starch liquid paste, 10 - 20 wt% gum arabic solution or gelatin solution, 1 - 5 wt% tragacanth solution, carboxymethyl cellulose solution,

sodium alginate solution, glycerin and the like.

Examples of the disintegrant include starch, calcium carbonate and the like.

Examples of the lubricant include magnesium stearate,
5 stearic acid, calcium stearate, purified talc and the like.

Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

Examples of the surfactant include sodium lauryl sulfate,
10 polysorbate 80, sorbitan monofatty acid ester, polyoxyl 40 stearate and the like.

Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, bentonite and the like.

15 Examples of the emulsifier include gum arabic, tragacanth, gelatin, polysorbate 80 and the like.

Furthermore, when the compound (I) is produced in the above-mentioned dosage form, a suitable amount of a colorant, a preservative, an aromatic, a corrigent, a stabilizer, a
20 thickening agent and the like typically used in the field of preparation can be added on demand.

When the compound (I) is administered parenterally, it is generally administered in the form of a liquid formulation (e.g., injection). While the dose varies depending on the
25 subject of administration, target organ, symptom, administration method and the like, it is, for example, about 0.01 mg to about 100 mg, preferably about 0.01 to about 50 mg, more preferably about 0.01 to about 20 mg, in the form of an injection, relative to 1 kg of body weight, which is preferably
30 given by intravenous injection. As the injection, intravenous injection as well as subcutaneous injection, intracutaneous injection, intramuscular injection, instillation and the like are mentioned, and as a sustained release preparation, iontophoresis transdermal agent and the like are mentioned.
35 Such injections are prepared by methods known per se, or by

dissolving, suspending or emulsifying the compound (I) in a sterilized aqueous solution or oily liquid. As an aqueous solution for injection, physiological saline, isotonic solutions containing glucose or other auxiliary drugs (e.g., D-
5 sorbitol, D-mannitol, sodium chloride and the like) and the like can be mentioned, and they can be used in combination with suitable solubilizing agents, such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol), nonionic surfactants (e.g., polysorbate 80, HCO-50) and the
10 like. As an oily liquid, sesame oil, soybean oil and the like can be mentioned, which may be used in combination with solubilizing agents such as benzyl benzoate, benzyl alcohol and the like. In addition, buffers (e.g., phosphate buffer, sodium acetate buffer), soothing agents (e.g., benzalkonium chloride,
15 procaine hydrochloride and the like), stabilizers (e.g., human serum albumin, polyethylene glycol and the like), preservatives (e.g., benzyl alcohol, phenol and the like) and the like may be mixed therewith. A prepared injection is generally filled in an ampoule.

20 Production Methods

The production methods of the compound of the present invention are explained in the following.

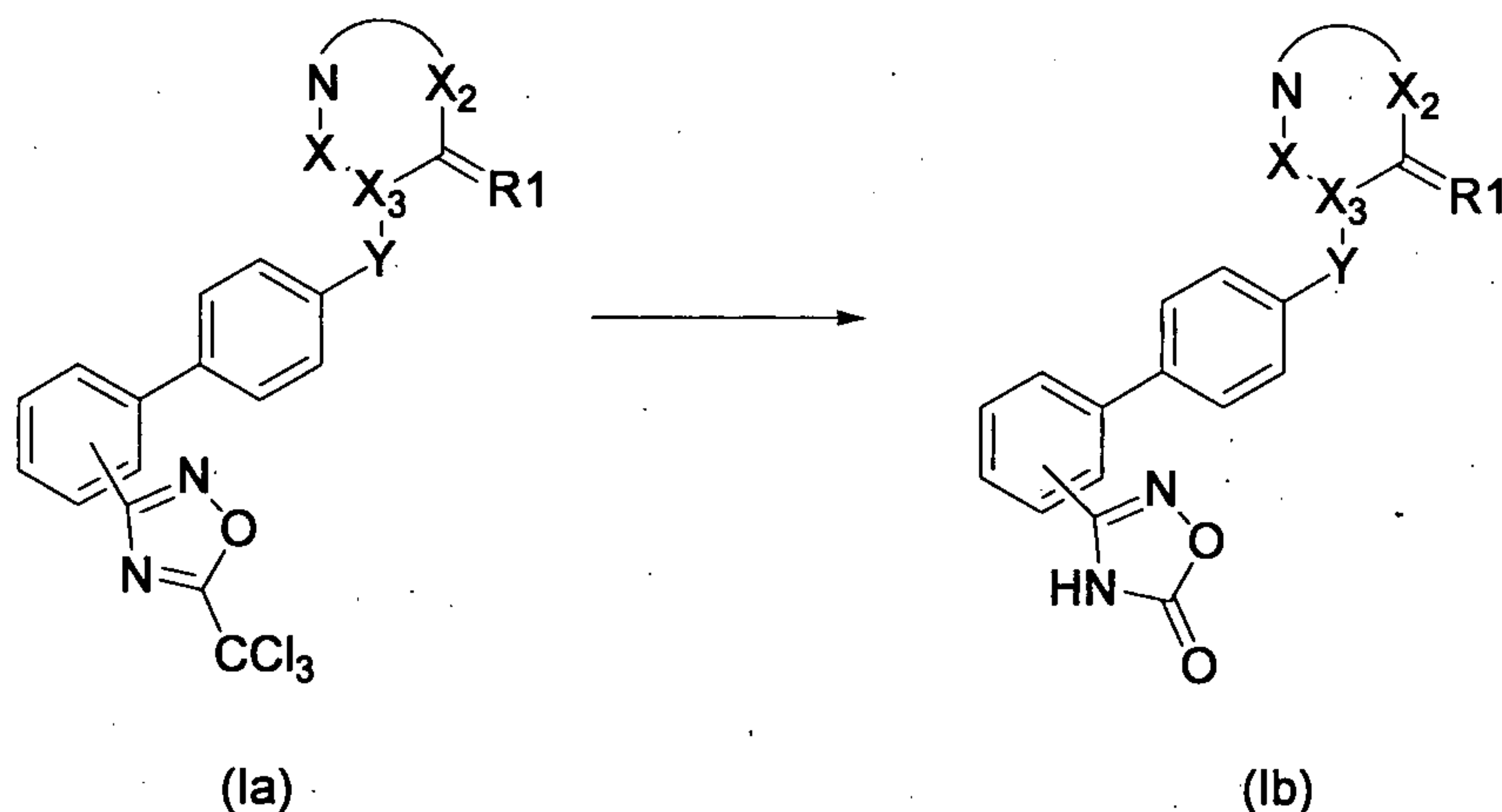
In the following Production Methods, unless otherwise specified, the starting compound is easily commercially
25 available, or can be produced by a method known per se or a method analogous thereto.

Compound (I) of the present invention can be produced, for example, by the method shown below or a method analogous thereto and the like. In the following synthetic methods, the
30 starting compounds may be used in the form of salt and, as such salt, those exemplified as the salt of compound (I) can be used.

While the yield of compound (I) obtained by each of the following methods may vary depending on the reaction
35 conditions used, compound (I) can be obtained easily at a high

purity from the resultant products by a conventional separation and purification means (recrystallization, column chromatography and the like).

5. Reaction (a)



wherein R1, X, X2 and Y are as defined above, X3 is carbon or nitrogen, and biphenyl group may further have substituent(s).

10 In reaction (a), 5-trichloromethyloxadiazole compound (Ia) obtained in the below-mentioned reaction (d) is reacted in the presence of an aqueous alkaline solution to give oxadiazolone compound (Ib). Generally, the reaction is performed in an inert solvent using about 1 to 3 molar
15 equivalents of the aqueous alkaline solution relative to compound (Ia).

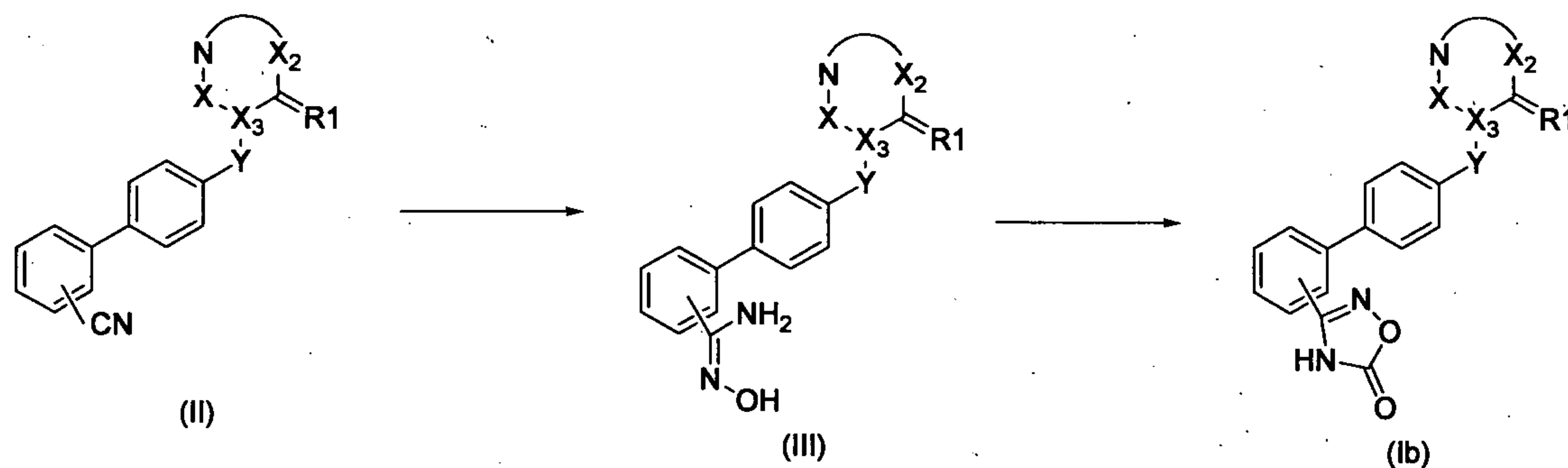
Examples of the inert solvent for reaction include ethers such as 1,4-dioxane, tetrahydrofuran and the like; alcohols such as methanol, ethanol and the like; water and the like.
20 These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

Examples of the alkali to be used for alkaline aqueous solution include sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate and
25 the like.

The reaction temperature is generally about -50°C to about 150°C, preferably about 0°C to about 60°C.

The reaction time is generally about 0.5 to about 20 hr.

Reaction (b)



5

wherein R₁, X, X₂, X₃ and Y are as defined above, and biphenyl group may further have substituent(s).

In reaction (b), cyano compound (II) obtained in the below-mentioned reactions (d) to (g) is converted to amidoxime compound (III), which is then subjected to ring closure to give oxadiazolone compound (Ib).

The reaction to obtain compound (III) is performed in an inert organic solvent using about 1 to 20 mol of hydroxylamine per 1 mol of compound (II).

Examples of such solvent include sulfoxides such as dimethyl sulfoxide and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; alcohols such as methanol, ethanol and the like; ethers such as 1,4-dioxane, tetrahydrofuran etc. and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

When an inorganic acid salt such as hydroxylamine hydrochloride, hydroxylamine sulfate and the like, or an organic acid salt such as hydroxylamine oxalate and the like is used as hydroxylamine, the reaction is performed in the presence of an equivalent amount or a small excess of a suitable base such as potassium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, sodium methoxide, sodium hydride and the like.

When an inorganic acid salt or organic acid salt of hydroxylamine is used, the reaction may be performed with addition of about 5 to 20 wt% of water to an organic solvent.

The reaction temperature is generally about -50°C to about 150°C, preferably about 25°C to about 100°C.

The reaction time is generally about 3 to about 48 hr.

The reaction to obtain oxadiazolone compound (Ib) from amidoxime compound (III) is performed using about 1 to 2 molar equivalents of a carbonylation reagent relative to amidoxime compound (III) in a solvent that does not adversely influence the reaction in the presence of an equivalent amount or a small excess of a base.

Examples of the carbonylation reagent include N,N'-carbonyldiimidazole, triphosgene, methyl chlorocarbonate, ethyl chlorocarbonate and the like.

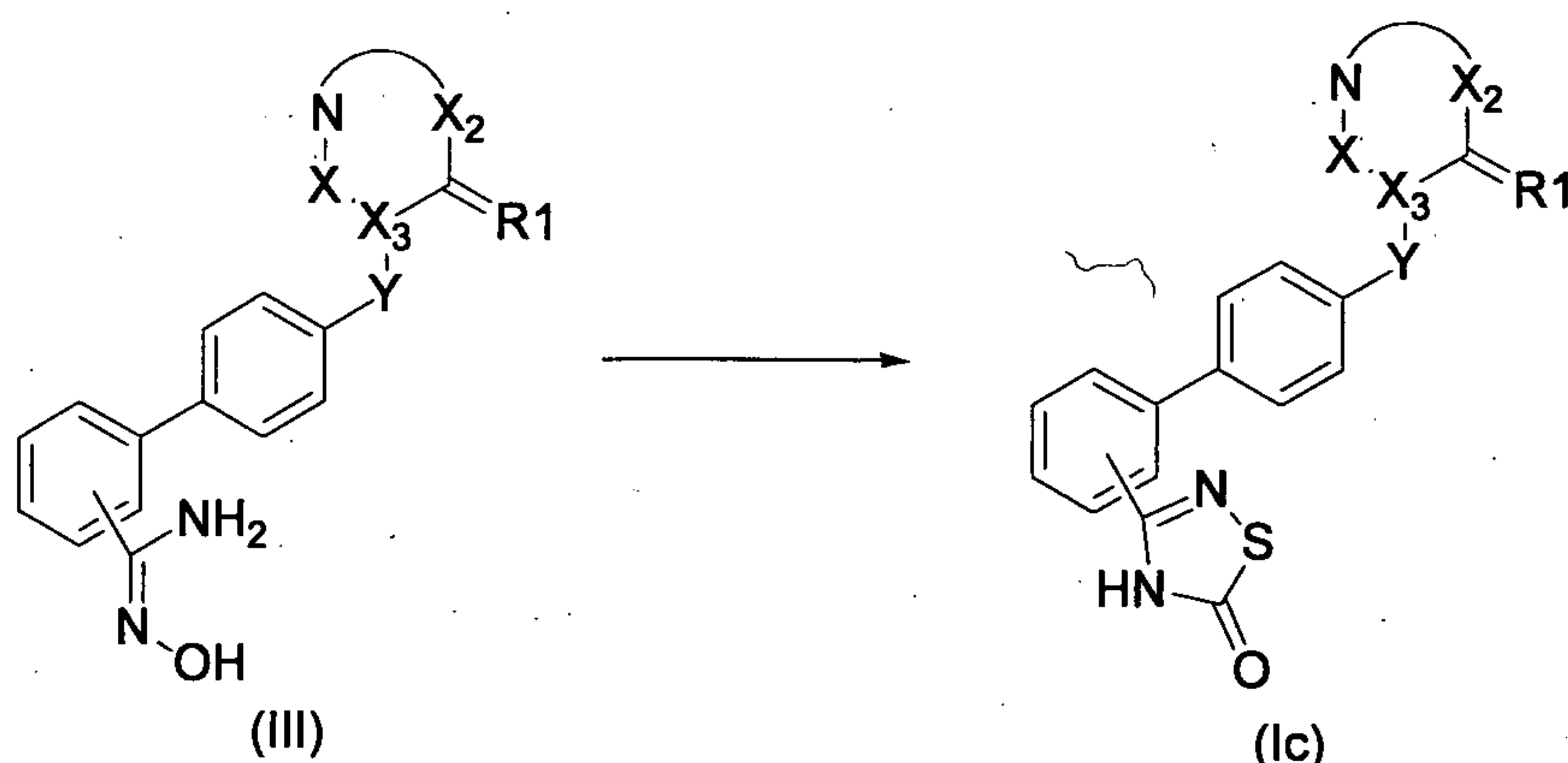
Examples of the base include organic amines such as triethylamine, pyridine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; inorganic salts such as potassium carbonate, sodium carbonate etc. and the like.

Examples of the solvent include halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; ethers such as diethyl ether, 1,4-dioxane, tetrahydrofuran etc. and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

The reaction temperature is generally about -50°C to about 100°C, preferably about 0°C to about 50°C.

The reaction time is generally about 0.1 to about 5 hr.

Reaction (c)



wherein R_1 , X , X_2 , X_3 and Y are as defined above, and biphenyl group may further have substituent(s).

5 In reaction (c), amidoxime compound (III) obtained in reaction (b) is subjected to ring closure to give thiadiazolone compound (Ic).

The reaction to obtain compound (Ic) is performed using about 1 to 2 mol of 1,1'-thiocarbonyldiimidazole per 1 mol of
 10 compound (III) in the presence of Lewis acid in an organic solvent that does not adversely influence the reaction.

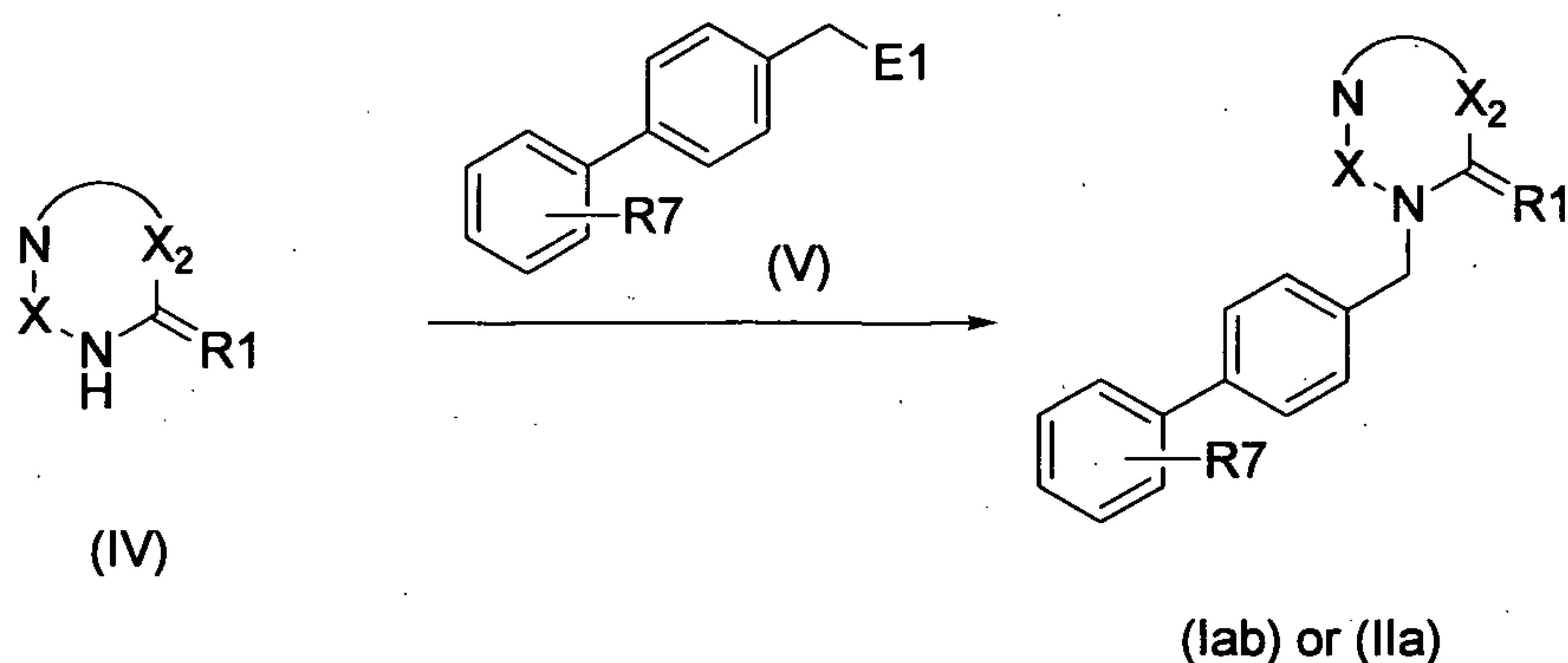
The Lewis acid is not particularly limited as long as the reaction proceeds and, for example, boron trifluoride diethyl ether complex, tin(II) chloride, zinc chloride, copper(I)
 15 chloride, silica gel and the like can be mentioned. The amount of the Lewis acids to be used is preferably about 1 to 3 mol per 1 mol of compound (III).

Examples of the solvent include halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride and
 20 the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; dimethyl sulfoxide and the like; ethers such as diethyl ether, 1,4-dioxane, tetrahydrofuran etc. and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate
 25 ratio.

The reaction temperature is generally about -50°C to about 100°C , preferably about 0°C to about 50°C .

The reaction time is generally about 0.1 to about 5 hr.

Reaction (d)



wherein R1, X and X₂ are as defined above, R7 is a cyano group
 5 or a 5-trichloromethyl-1,2,4-oxadiazol-3-yl group, E1 is a
 leaving group (e.g., halogen atom such as chlorine, bromine,
 iodine and the like; substituted sulfonic acid ester such as
 methanesulfonic acid ester, p-toluenesulfonic acid ester and
 the like; hydroxy group and the like), and biphenyl group may
 10 further have substituent(s).

In reaction (d), compound (IV) is reacted with compound
 (V) to give, from among the starting compounds (Ia) to be used
 in the above-mentioned reaction (a), compound (Iab) wherein X₃
 is nitrogen or, from among the starting compounds (II) to be
 15 used in the above-mentioned reaction (b), compound (IIa)
 wherein X₃ is nitrogen. Generally, the reaction is performed
 using 1 to 3 mol of compound (V) per 1 mol of compound (IV) in
 an organic solvent that does not adversely influence the
 reaction.

20 The starting compound (V) to be used in the above-
 mentioned reaction (d) can be produced by a method known per
 se, for example, the method described in US Patent No.
 5,243,054 (JP-A-5-271228) or a method analogous thereto.

In reaction (d), when E1 is halogen atom or substituted
 25 sulfonic acid ester, the reaction is performed according to a
 conventional method in a solvent that does not adversely
 influence the reaction in the presence of base.

Examples of the base include alkali metal salts such as
 potassium hydroxide, sodium hydroxide, sodium hydrogen

carbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide etc. and the like.

The amount of the bases to be used is preferably about 1 to about 5 molar equivalents relative to compound (IV).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; nitriles such as acetonitrile, propionitrile and the like; ethers such as tetrahydrofuran, 1,4-dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide etc. and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.

In reaction (d), when E1 is a hydroxy group, this reaction is performed by a method known *per se*, for example, the method described in Synthesis, p. 1 (1981) and the like or a method analogous thereto. That is, this reaction is generally performed in the presence of an organic phosphorus compound and an azo reagent, in a solvent that does not adversely influence the reaction.

Examples of the organic phosphorus compound include triphenylphosphine, tri(n-butyl)phosphine and the like.

Examples of the azo reagent include diethyl azodicarboxylate, diisopropyl azodicarboxylate, 1,1'-(azodicarbonyl)dipiperidine and the like.

The amount of the organic phosphorus compound and azo

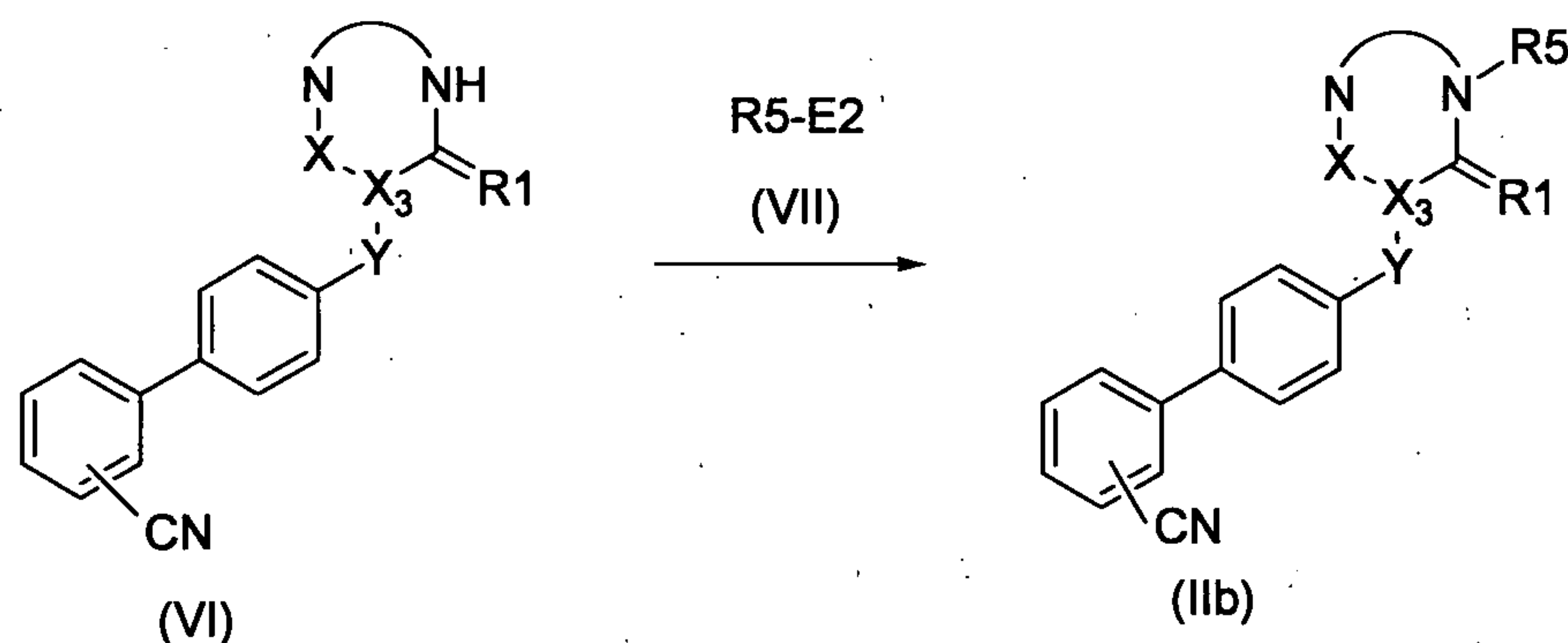
reagent to be used is preferably about 1 to about 5 molar equivalents relative to compound (IV).

Examples of the solvent that does not adversely influence the reaction include ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like, and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.

Reaction (e)



wherein R1, X, X₃ and R5 are as defined above, and E2 is a leaving group (e.g., a halogen atom such as chlorine, bromine, iodine and the like; a substituted sulfonic acid ester such as methanesulfonic acid ester, p-toluenesulfonic acid ester and the like; boronic acid or a boronic acid ester; a hydroxy group and the like). The biphenyl group may further have substituent(s).

In reaction (e), compound (VI) is reacted with compound (VII) to give compound (IIb), which is starting compound (II) (used in the above-mentioned reaction (b)) wherein X₂ is a N-R5 group. The reaction is generally performed using 1 to 4 molar

equivalents of compound (VII) relative to starting compound (VI).

The starting compound (VI) to be used in the above-mentioned reaction (e) can be produced by a method known per se, for example, the method described in Journal of Medicinal Chemistry, vol. 37, p. 2371 (1994) or a method analogous thereto.

When E2 is a halogen atom, a substituted sulfonic acid ester or a hydroxy group, the above-mentioned reaction (e) can be performed by a method similar to the method shown in reaction (d).

Particularly when E2 is a halogen atom or a substituted sulfonic acid ester, and R5 is an aryl group, reaction (e) can be also promoted by a method known per se, for example, the method described in Journal of the American Chemical Society, vol. 124, p. 7421 (2002) and the like or a method analogous thereto, in the presence of a metal catalyst. Examples of the metal catalyst include palladium complexes (e.g., palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium and the like), copper compounds (e.g., copper powder, copper(I) chloride, copper(I) iodide, copper(I) acetate and the like), nickel compounds (e.g., tetrakis(triphenylphosphine)nickel and the like), rhodium compounds (e.g., tris(triphenylphosphine)rhodium chloride and the like), platinum compounds and the like.

The amount of the metal catalyst to be used is about 0.000001 to 5 molar equivalents, preferably 0.0001 to 1 molar equivalent, relative to compound (VII).

The above-mentioned reaction may be performed using a base and a ligand. Examples of the base include metal alkoxides such as potassium phenoxide, sodium tert-butoxide and the like; inorganic salts such as potassium carbonate,

sodium carbonate, cesium carbonate, potassium phosphate etc., and the like. Examples of the ligand include organic phosphorus compounds such as triphenylphosphine, tri-tert-butylphosphine, tricyclohexylphosphine, BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) and the like; organic amine compounds such as N,N'-dimethyl-cyclohexane-1,2-diamine, 2,2'-bipyridyl and the like, and the like.

When a metal catalyst unstable to oxygen is used, this reaction is preferably performed under an inert gas (e.g., argon, nitrogen and the like) atmosphere.

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.

In reaction (e), when E2 is a boronic acid or a boronic acid ester, this reaction is performed by a method known per se, for example, the method described in Tetrahedron Letters, vol. 39, p. 2933 (1998) and the like or a method analogous thereto, in the presence of a base and a metal catalyst, in a solvent that does not adversely influence the reaction.

Examples of the base include inorganic salts such as potassium carbonate, sodium carbonate, cesium carbonate and the like; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene etc. and the like. These bases may be used as a mixture of two or more kinds thereof at an appropriate ratio.

Examples of the metal catalyst include copper or salts thereof (e.g., copper(II) acetate, copper(II) chloride and the like), palladium complexes (e.g., palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium and the like), nickel compounds (e.g., tetrakis(triphenylphosphine)nickel and the like), rhodium

compounds (e.g., tris(triphenylphosphine)rhodium chloride and the like), platinum compounds and the like. Of these, copper or salts thereof is preferable.

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, 1,4-dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide etc. and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

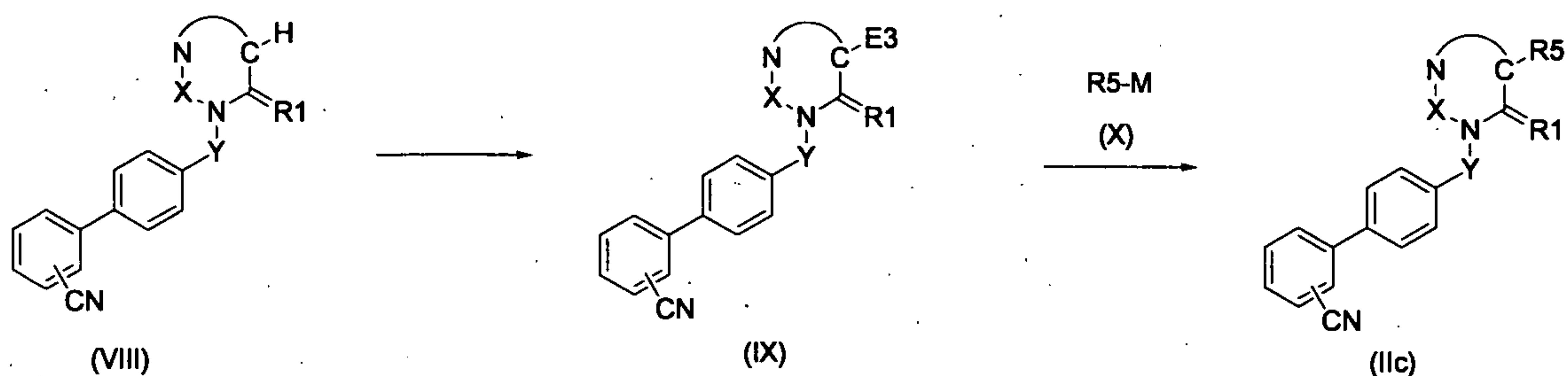
When copper or a salt thereof is used as a metal catalyst, this reaction is preferably performed under an air atmosphere or an oxygen atmosphere. When a metal catalyst unstable to oxygen is used, this reaction is preferably performed under an inert gas (e.g., argon, nitrogen and the like) atmosphere. In addition, this reaction may be performed using molecular sieves.

The amount of the metal catalyst to be used is about 0.000001 to 5 molar equivalents, preferably 0.0001 to 1 molar equivalent, relative to compound (VII).

The reaction temperature is generally about 0°C to about 200°C, preferably 10°C to about 100°C.

The reaction time is generally about 2 to about 96 hr.

Reaction (f)



30

wherein R1, X, Y and R5 are as defined above, E3 is a leaving

group (e.g., a halogen atom such as chlorine, bromine, iodine etc. and the like), and M is a metal (e.g., potassium, sodium, lithium, magnesium, copper, mercury, zinc, thallium, boron, tin and the like, they may form a complex). The biphenyl group
5 may further have substituent(s).

In reaction (f), the leaving group E3 is introduced into compound (VIII) to give compound (IX), which is then reacted with compound (X) to give compound (IIc), which is starting compound (II) (used in the aforementioned reaction (b))
10 wherein X₂ is a C-R5 group.

The starting compound (VIII) to be used in the above-mentioned reaction (f) can be produced by the method shown in reaction (d) or a method analogous thereto.

In the above-mentioned reaction (f), the reaction to
15 obtain compound (IX) from compound (VIII) is performed by a method known *per se*, for example, the method described in Journal of the Chemical Society, vol. 37, p. 3478 and the like or a method analogous thereto, using a halogenating agent (e.g., chlorine, bromine, iodine, halogenated succinimide,
20 dihalogenated barbituric acid and the like). The amount of the halogenating agent to be used is preferably about 1 to about 5 molar equivalents relative to compound (VIII).

In the above-mentioned reaction (f), the reaction to obtain compound (IX) from compound (VIII) is performed in a
25 solvent that does not adversely influence the reaction. Examples of the solvent include alcohols (e.g., methanol, ethanol, ethylene glycol and the like), halogenated hydrocarbons (e.g., dichloromethane, chloroform and the like), organic acids (e.g., acetic acid, formic acid and the like)
30 and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.
35 Compound (X) to be used in the above-mentioned reaction

(f) can be produced according to a method known *per se* or a method analogous thereto. The amount of compound (X) to be used is preferably about 1 to about 5 molar equivalents relative to compound (IX).

5 In the above-mentioned reaction (f), the reaction to obtain compound (IIc) from compound (IX) and compound (X) is performed in a solvent that does not adversely influence the reaction. Preferable examples of such solvent include alcohols (e.g., methanol, ethanol, ethylene glycol and the like),
10 ethers (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like), amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like), aromatic hydrocarbons (e.g., toluene, xylene and the like) and the like. These solvents may be used as a
15 mixture of two or more kinds thereof at an appropriate ratio. Furthermore, water may be mixed with the above-mentioned solvent at an appropriate ratio.

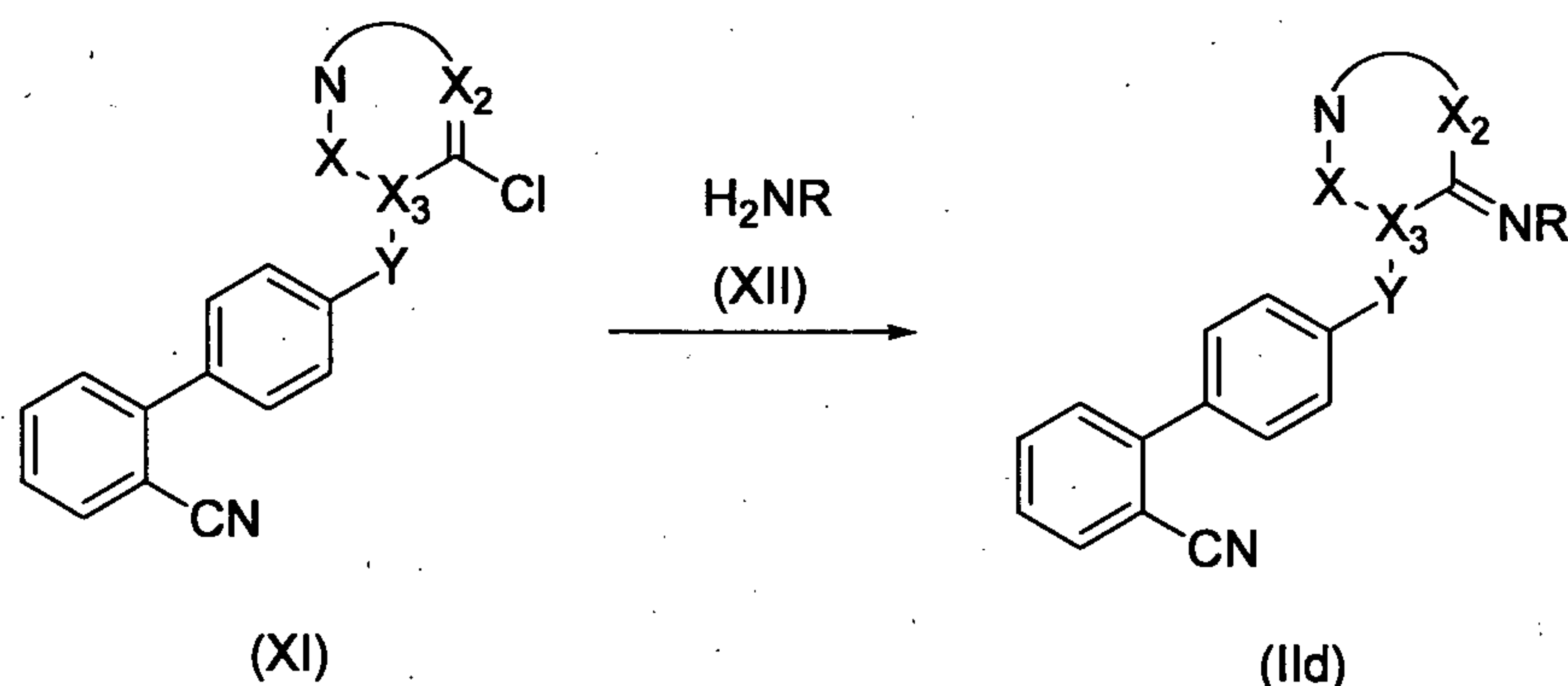
In the above-mentioned reaction (f), the reaction to obtain compound (IIc) from compound (IX) and compound (X) can
20 be generally promoted using a metal catalyst. Examples of the metal catalyst include various metal complex having a ligand, for example, palladium compounds (e.g., palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, [1,1'-
25 bis(diphenylphosphino)ferrocene]dichloropalladium and the like), nickel compounds (e.g., tetrakis(triphenylphosphine)nickel and the like), rhodium compounds (e.g., tris(triphenylphosphine)rhodium chloride and the like), platinum compounds and the like. Of these,
30 palladium compounds are preferable. The amount of the metal catalyst to be used is about 0.000001 to 5 molar equivalents, preferably 0.0001 to 1 molar equivalent, relative to compound (IX). When a metal catalyst unstable to oxygen is used, this reaction is preferably performed under an inert gas (e.g.,
35 argon, nitrogen and the like) atmosphere.

In the above-mentioned reaction (f), the reaction to obtain compound (IIc) from compound (IX) and compound (X) may be performed using an inorganic salt. Examples of the inorganic salt include potassium carbonate, sodium carbonate, cesium carbonate, potassium phosphate, lithium chloride, sodium chloride and the like. The amount of the inorganic salt to be used is preferably about 1 to about 10 molar equivalents relative to compound (IX).

The reaction temperature is generally about -50°C to about 150°C , preferably about -10°C to about 100°C .

The reaction time is generally about 0.5 to about 24 hr.

Reaction (g)



wherein X, X_2 , X_3 , Y and R are as defined above, and biphenyl group may further have substituent(s).

In reaction (g), compound (XI) is reacted with compound (XII) in the presence of a base to give compound (IIId), which is starting compound (II) (used in the above-mentioned reaction (b)) wherein R1 is =N-R group. Generally, the amount of compound (XII) to be used is preferably about 1 to about 5 molar equivalents relative to compound (XI).

Examples of the base include alkali metal salts such as sodium hydrogen carbonate, potassium carbonate, sodium carbonate, cesium carbonate and the like; amines such as pyridine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene etc. and the like. The amount of the base to be used is preferably about 1 to about 5 molar

equivalents relative to compound (XI).

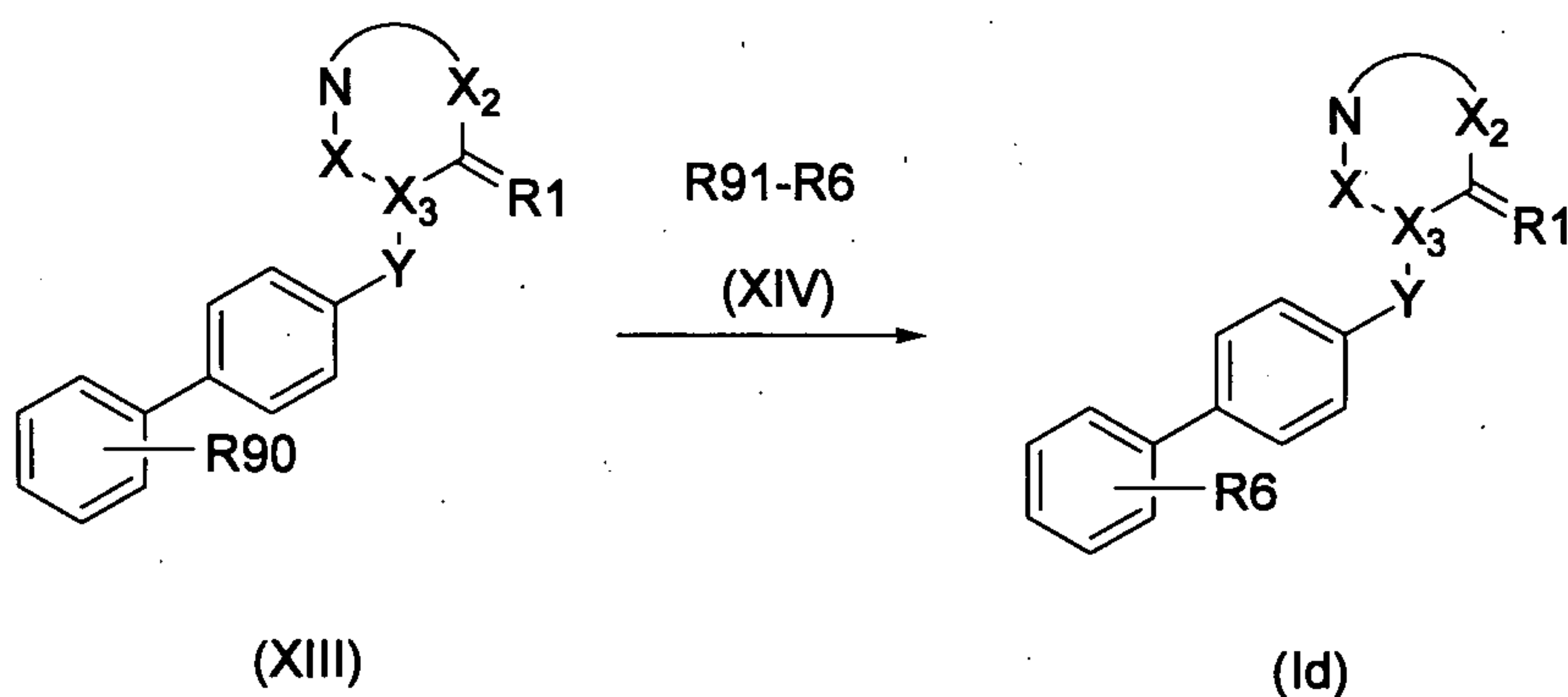
The starting compound (XI) to be used in the above-mentioned reaction (g) can be produced by a method known *per se*, for example, the method described in Journal of Medicinal Chemistry, vol. 37, p. 2371 (1994) or a method analogous thereto. Compound (XII) to be used in the above-mentioned reaction (g) can be produced according to a method known *per se* or a method analogous thereto.

The above-mentioned reaction (g) is performed in a solvent that does not adversely influence the reaction. Preferable examples of such solvent include ethers (e.g., tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like), amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like), aromatic hydrocarbons (e.g., toluene, xylene and the like) and the like.

The reaction temperature is generally about -50°C to about 250°C, preferably about 50°C to about 170°C.

The reaction time is generally about 0.5 to about 48 hr.

20 Reaction (h)



wherein X, X₂, X₃, Y, R₁ and R₆ are as defined above, one of R₉₀ and R₉₁ is a leaving group (e.g., a halogen atom such as chlorine, bromine, iodine and the like; a substituted sulfonic acid ester such as trifluoromethanesulfonic acid ester, methanesulfonic acid ester, p-toluenesulfonic acid ester and the like; a hydroxy group and the like), and the other is a

metal (e.g., potassium, sodium, lithium, magnesium, copper, mercury, zinc, thallium, boron, tin and the like).

In the above-mentioned reaction (h), compound (XIII) is reacted with compound (XIV) to give compound (Id).

5 The reaction to obtain compound (Id) is performed using 1 to 3 mol of compound (XIV) per 1 mol of compound (XIII) in an organic solvent that does not adversely influence the reaction.

Examples of the solvent include alcohols such as methanol, ethanol, ethylene glycol and the like; ethers such as diethyl
10 ether, tetrahydrofuran, 1,4-dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide etc. and the like. These
15 solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio. Furthermore, water may be mixed with the above-mentioned solvent at an appropriate ratio.

The starting compound (XIII) used in the above-mentioned reaction (h) can be produced by a method known *per se*, for
20 example, the method described in Journal of Medicinal Chemistry, vol. 37, p. 2371 (1994) or a method analogous thereto, or the production methods shown in the aforementioned reactions (d) to (g) or methods analogous thereto.

The above-mentioned reaction (h) may be also promoted by
25 a method known *per se*, for example, the method described in Journal of the American Chemical Society, vol. 124, p. 7421 (2002) and the like or a method analogous thereto, in the presence of a metal catalyst.

Examples of the metal catalyst include palladium
30 compounds (e.g., palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium and the like), copper compounds (e.g., copper powder, copper(I)
35 chloride, copper(I) iodide, copper(I) acetate and the like),

nickel compounds (e.g., tetrakis(triphenylphosphine)nickel and the like), rhodium compounds (e.g., tris(triphenylphosphine)rhodium chloride and the like), platinum compounds and the like.

- 5 The amount of the metal catalyst to be used is about 0.000001 to 5 molar equivalents, preferably 0.0001 to 1 molar equivalent, relative to compound (XIII).

The above-mentioned reaction may be performed using a base and a ligand.

- 10 Examples of the base include metal alkoxides such as potassium phenoxide, sodium tert-butoxide and the like; inorganic salts such as potassium carbonate, sodium carbonate, cesium carbonate, potassium phosphate etc. and the like.

- 15 The amount of the base to be used is about 0.1 to 10 molar equivalents, preferably about 1 to 3 molar equivalents, relative to compound (XIII).

- 20 Examples of the ligand include organic phosphorus compounds such as triphenylphosphine, tri-tert-butylphosphine, tricyclohexylphosphine, BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) and the like; organic amine compounds such as N,N'-dimethyl-cyclohexane-1,2-diamine, 2,2'-bipyridyl etc. and the like.

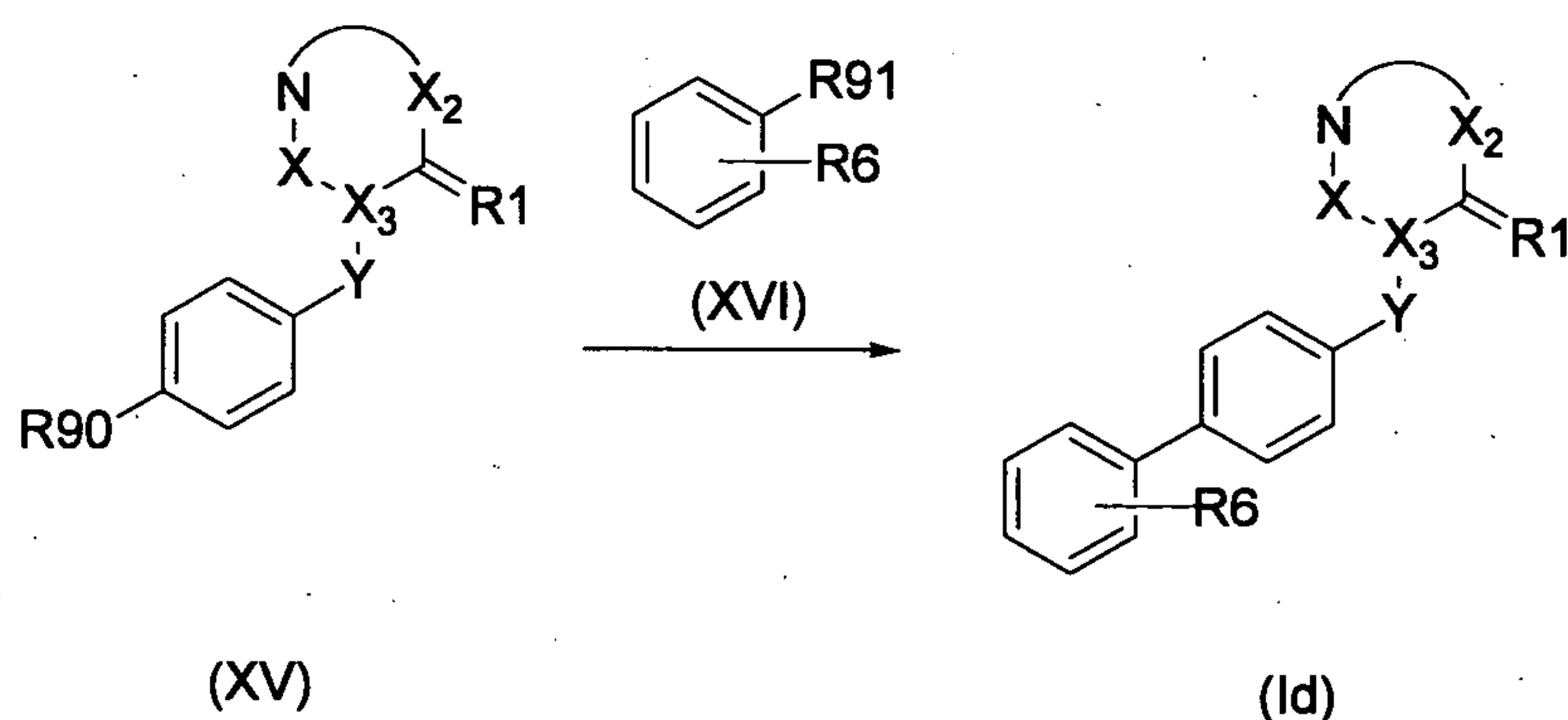
- 25 The amount of the ligand to be used is about 0.000001 to 5 molar equivalents, preferably about 0.0001 to 1 molar equivalent, relative to compound (XIII).

When a metal catalyst unstable to oxygen is used in the above-mentioned reaction, the reaction is preferably performed under an inert gas (e.g., argon, nitrogen and the like) atmosphere.

- 30 The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 120°C.

The reaction time is generally about 0.5 to about 20 hr.

Reaction (i)



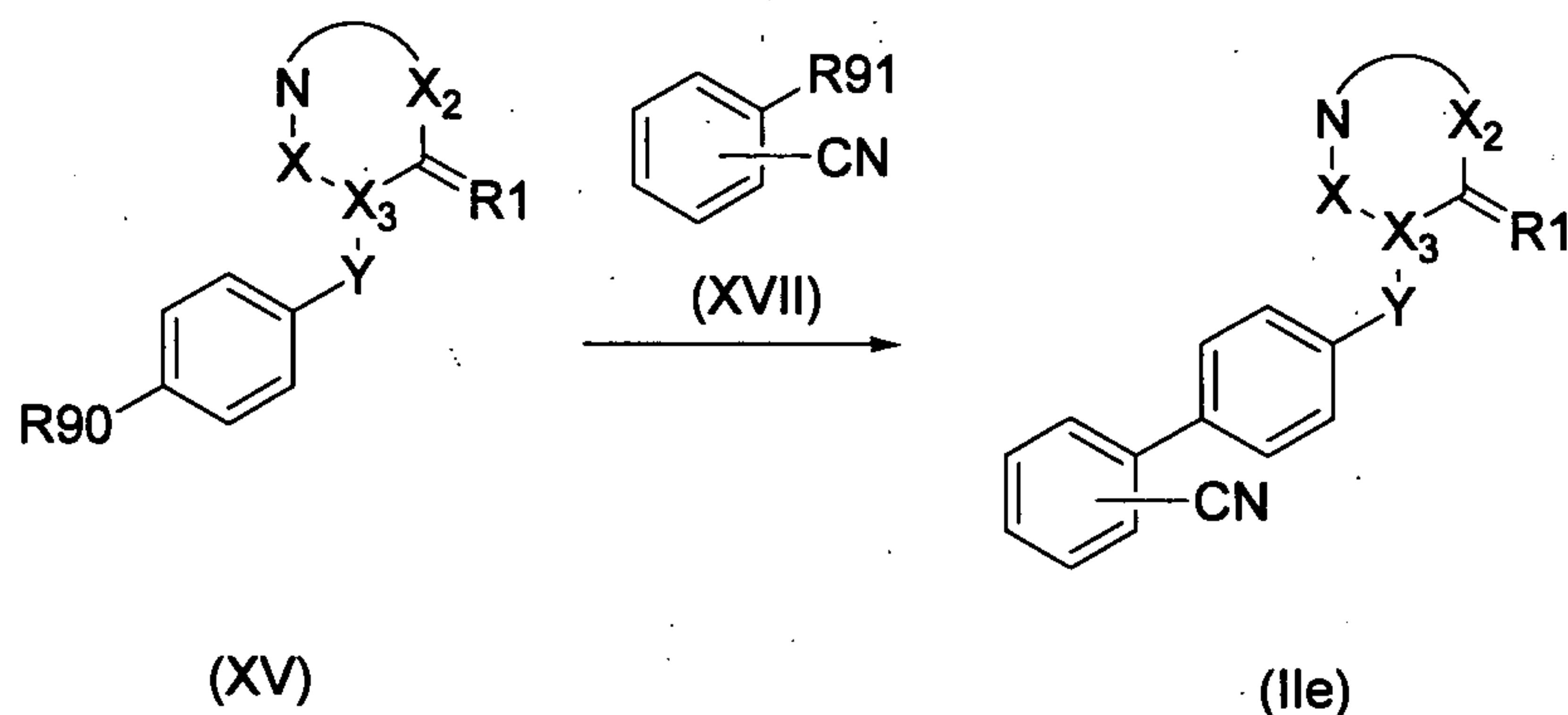
wherein X, X₂, X₃, Y, R₁, R₆, R₉₀ and R₉₁ are as defined above.

In the above-mentioned reaction (i), compound (XV) is reacted with compound (XVI) to give compound (Id).

5 The above-mentioned reaction (i) can be performed by a method similar to the method shown in reaction (h).

The starting compound (XV) used in the above-mentioned reaction (i) can be produced by a method known *per se*, for example, the method described in Journal of Medicinal
 10 Chemistry, vol. 37, p. 2371 (1994) or a method analogous thereto, or the production methods shown in the aforementioned reactions (d) to (g) or methods analogous thereto.

Reaction (j)

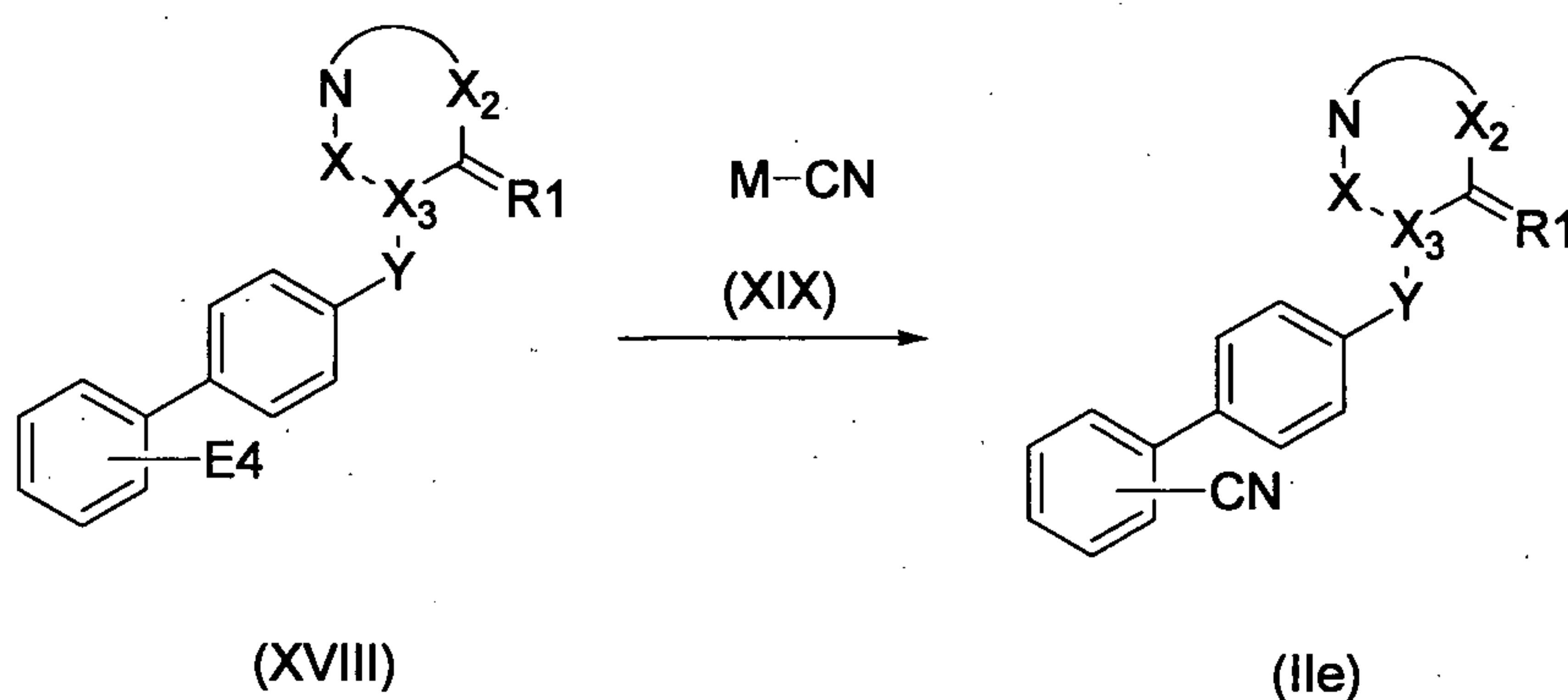


15 wherein X, X₂, X₃, Y, R₁, R₉₀ and R₉₁ are as defined above.

In the above-mentioned reaction (j), compound (XV) is reacted with compound (XVII) to give compound (IIe).

The above-mentioned reaction (j) can be performed by a
 20 method similar to the method shown in reaction (h).

Reaction (k)



wherein X, X₂, X₃, Y and R₁ are as defined above, E₄ is a leaving group (e.g., a halogen atom such as chlorine, bromine, iodine etc. and the like; a substituted sulfonic acid ester such as trifluoromethanesulfonic acid ester etc. and the like), and M is a metal (e.g., potassium, sodium, lithium, magnesium, copper, mercury, zinc, thallium, boron, tin, silicon and the like).

10 In the above-mentioned reaction (k), compound (XVIII) is reacted with compound (XIX) to give compound (IIe). The amount of compound (XIX) to be used is preferably about 1 to about 5 molar equivalents relative to compound (XVIII).

In the above-mentioned reaction (k), the reaction to
15 obtain compound (IIe) from compound (XVIII) is performed in a solvent that does not adversely influence the reaction.

Preferable examples of such solvent include alcohols (e.g., methanol, ethanol, ethylene glycol and the like), ethers (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane,
20 1,2-dimethoxyethane and the like), amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like), aromatic hydrocarbons (e.g., toluene, xylene and the like) and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.
25 Furthermore, water may be mixed with the above-mentioned solvent at an appropriate ratio.

In the above-mentioned reaction (k), the reaction to obtain compound (IIe) from compound (XVIII) can be also

promoted by a method known *per se*, for example, the method described in Tetrahedron Letters, vol. 40, p. 8193 (1999) and the like or a method analogous thereto, in the presence of a metal catalyst.

5 Examples of the metal catalyst include palladium compounds (e.g., palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium and the
10 like), copper compounds (e.g., copper powder, copper(I) chloride, copper(I) iodide, copper(I) acetate and the like), nickel compounds (e.g., tetrakis(triphenylphosphine)nickel and the like), rhodium compounds (e.g., tris(triphenylphosphine)rhodium chloride and the like),
15 platinum compounds and the like.

The amount of the metal catalyst to be used is about 0.000001 to 5 molar equivalents, preferably 0.0001 to 1 molar equivalent, relative to compound (XVIII).

The above-mentioned reaction may be performed using a
20 ligand. Examples of the ligand include organic phosphorus compounds such as triphenylphosphine, tri-tert-butylphosphine, tricyclohexylphosphine, BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) and the like; organic amine compounds such as N,N'-dimethyl-cyclohexane-1,2-diamine, 2,2'-bipyridyl etc. and
25 the like.

The amount of the ligand to be used is about 0.000001 to 5 molar equivalents, preferably about 0.00001 to 1 molar equivalent, relative to compound (XVIII).

When a metal catalyst unstable to oxygen is used, this
30 reaction is preferably performed under an inert gas (e.g., argon, nitrogen and the like) atmosphere.

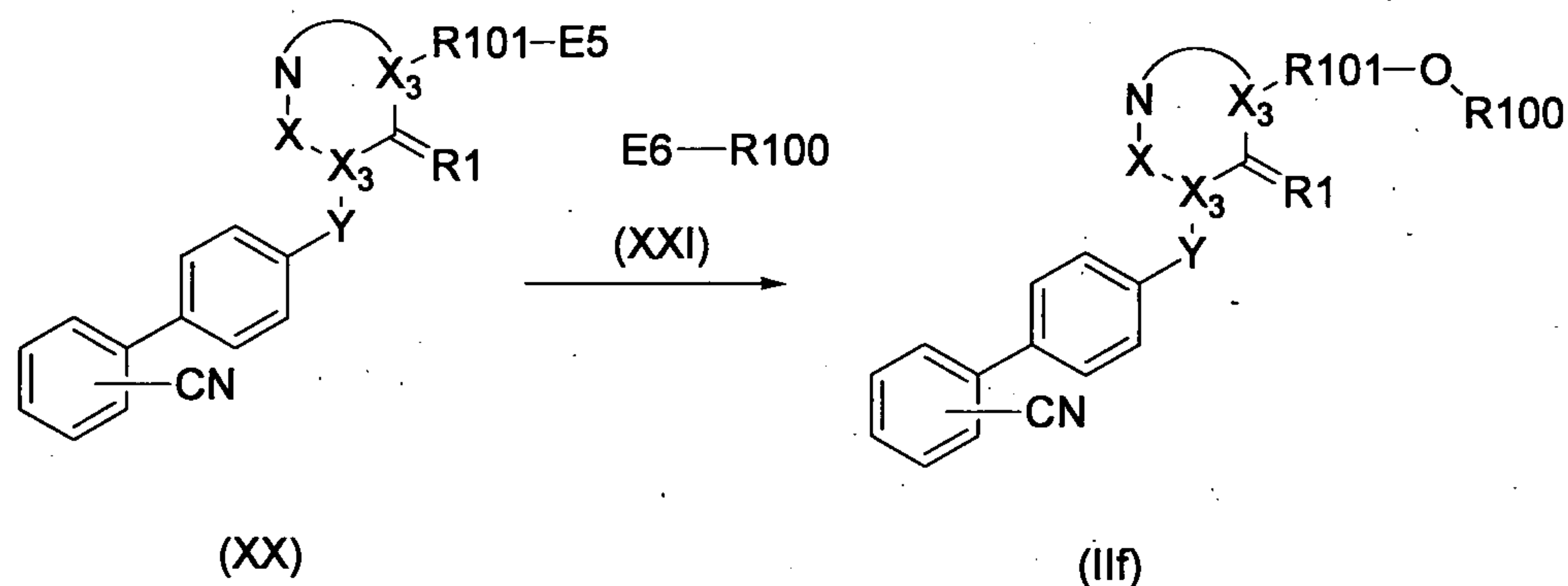
The reaction temperature is generally about -50°C to about 300°C, preferably about -10°C to about 150°C.

The reaction time is generally about 0.5 to about 20 hr.

35 The starting compound (XVIII) used in the above-mentioned

reaction (k) can be produced by a method known *per se*, for example, the method described in Journal of Medicinal Chemistry, vol. 37, p. 2371 (1994) or a method analogous thereto, or the production methods shown in the aforementioned
 5 reactions (d) to (g) or methods analogous thereto.

Reaction (1)



wherein X, X₃, Y and R1 are as defined above, R101 is a C6-C14
 10 aryl group or a aromatic heterocyclic group, and R100 is a C1-
 C6 alkyl group or a C3-C10 cycloalkyl group (these groups may
 be optionally substituted by 1 to 3 substituents selected from
 a halogen, a hydroxy group and the like, respectively). E5 and
 E6 are both leaving groups (e.g., a halogen atom such as
 15 chlorine, bromine, iodine and the like; a substituted sulfonic
 acid ester such as methanesulfonic acid ester, p-
 toluenesulfonic acid ester and the like), and/or a hydroxy
 group.

In the above-mentioned reaction (1), compound (XX) is
 20 reacted with compound (XXI) to give compound (IIIf).

The reaction to obtain compound (IIIf) is performed using
 about 1 to 10 mol of compound (XXI) per 1 mol of compound (XX),
 in an organic solvent that does not adversely influence the
 reaction.

25 The starting compound (XX) used in the above-mentioned
 reaction (1) can be produced by a method known *per se*, for
 example, the method described in Journal of Medicinal
 Chemistry, vol. 37, p. 2371 (1994) or a method analogous

thereto, or the production methods shown in the aforementioned reactions (d) to (g) or methods analogous thereto.

In the above-mentioned reaction (1), when E5 is a leaving group (e.g., a halogen atom such as chlorine, bromine, iodine and the like; a substituted sulfonic acid ester such as trifluoromethanesulfonic acid ester etc. and the like), and E6 is a hydroxy group, the reaction can be also promoted by a method known *per se*, for example, the method described in Journal of the American Chemical Society, vol. 127, p. 8146 (2005) and the like or a method analogous thereto, in the presence of a metal catalyst.

Examples of the metal catalyst include palladium compounds (e.g., palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium and the like), copper compounds (e.g., copper powder, copper(I) chloride, copper(I) iodide, copper(I) acetate and the like), nickel compounds (e.g., tetrakis(triphenylphosphine)nickel and the like), rhodium compounds (e.g., tris(triphenylphosphine)rhodium chloride and the like), platinum compounds and the like.

The amount of the metal catalyst to be used is about 0.000001 to 5 molar equivalents, preferably 0.0001 to 1 molar equivalent, relative to compound (XX).

The above-mentioned reaction may be performed using a base and a ligand.

Examples of the base include metal alkoxides such as potassium phenoxide, sodium tert-butoxide and the like; inorganic salts such as potassium carbonate, sodium carbonate, cesium carbonate, potassium phosphate and the like, and the like.

The amount of the base to be used is about 0.1 to 10 molar equivalents, preferably about 1 to 3 molar equivalents, relative to compound (XX).

Examples of the ligand include organic phosphorus compounds such as triphenylphosphine, tri-tert-butylphosphine, tricyclohexylphosphine, BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) and the like; organic amine compounds such as
5 N,N'-dimethyl-cyclohexane-1,2-diamine, 2,2'-bipyridyl and the like, and the like.

The amount of the ligand to be used is about 0.000001 to 5 molar equivalents, preferably about 0.00001 to 1 molar equivalent, relative to compound (XX).

10 Examples of the solvent that does not adversely influence the reaction include alcohols such as methanol, ethanol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like;
15 aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide etc. and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio. Furthermore, water may be mixed with
20 the above-mentioned solvent at an appropriate ratio.

When a metal catalyst unstable to oxygen is used in the above-mentioned reaction, the reaction is preferably performed under an inert gas (e.g., argon, nitrogen and the like) atmosphere.

25 The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 120°C.

The reaction time is generally about 0.5 to about 20 hr.

In the above-mentioned reaction (1), when E5 and E6 are both hydroxy groups, the reaction is performed by a method
30 known per se, for example, the method described in Organic Reactions, vol. 42, p. 335 (1992) and the like or a method analogous thereto. This reaction is performed in the presence of an organic phosphorus compound and an azo reagent.

Examples of the organic phosphorus compound include
35 triphenylphosphine, tri(n-butyl)phosphine and the like.

Examples of the azo reagent include diethyl azodicarboxylate, diisopropyl azodicarboxylate, 1,1'-(azodicarbonyl)dipiperidine and the like.

The amount of the organic phosphorus compound and azo reagent to be used is preferably about 1 to about 5 molar equivalents relative to compound (XX), respectively.

Examples of the solvent that does not adversely influence the reaction include ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide etc. and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

The reaction temperature is generally about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.5 to about 20 hr.

In the above-mentioned reaction (1), when E5 is a hydroxy group and E6 is a leaving group (e.g., a halogen atom such as chlorine, bromine, iodine and the like; a substituted sulfonic acid ester such as trifluoromethanesulfonic acid ester etc. and the like), this reaction is performed according to a conventional method, in a solvent that does not adversely influence the reaction, in the presence of a base.

Examples of the base include alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide etc. and the like.

The amount of the base to be used is preferably about 1 to about 5 molar equivalents relative to compound (XX).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; nitriles such as acetonitrile, propionitrile and the like; ethers such as tetrahydrofuran, 1,4-dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide etc. and the like. These solvents may be used as a mixture of two or more kinds thereof at an appropriate ratio.

The reaction temperature is generally about -50°C to about 150°C , preferably about -10°C to about 100°C .

The reaction time is generally about 0.5 to about 20 hr.

The starting compound (XX) used in the above-mentioned reaction (1) can be produced by a method known *per se*, for example, the method described in Journal of Medicinal Chemistry, vol. 37, p. 2371 (1994) or a method analogous thereto, or the production methods shown in the aforementioned reactions (d) to (g) and (j) to (k) or methods analogous thereto.

In each of the aforementioned reactions, when the starting compound has a hydroxy group, an amino group, a carboxyl group or a carbonyl group as a substituent, a protecting group generally used in the peptide chemistry and the like may be introduced into these groups. By removing the protecting group as necessary after the reaction, the object compound can be obtained.

Examples of the protecting group of hydroxy group include C1-C6 alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl), phenyl group, trityl group, C7-C10 aralkyl group (e.g., benzyl), formyl group, C1-C6 alkyl-carbonyl group (e.g., acetyl, propionyl), benzoyl group, C7-C10 aralkyl-carbonyl group (e.g., benzylcarbonyl), 2-tetrahydropyranyl group, 2-tetrahydrofuranyl group, silyl group (e.g.,

trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyl dimethylsilyl, tert-butyl diethylsilyl), C2-C6 alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from
5 halogen atom (e.g., fluorine, chlorine, bromine, iodine), C1-C6 alkyl group (e.g., methyl, ethyl, propyl), C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy), nitro group and the like.

Examples of the amino-protecting group include formyl
10 group, C1-C6 alkyl-carbonyl group (e.g., acetyl, propionyl), C1-C6 alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl), benzoyl group, C7-C10 aralkyl-carbonyl group (e.g., benzylcarbonyl), C7-C14 aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-
15 fluorenylmethoxycarbonyl), trityl group, phthaloyl group, N,N-dimethylaminomethylene group, silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyl dimethylsilyl, tert-butyl diethylsilyl), C2-C6 alkenyl group (e.g., 1-allyl) and the like. These groups are
20 optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine), C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy), nitro group and the like.

Examples of the protecting group of carboxyl group
25 include C1-C6 alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl), C7-C10 aralkyl group (e.g., benzyl), phenyl group, trityl group, silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyl dimethylsilyl, tert-butyl diethylsilyl, tert-
30 butyl diphenylsilyl), C2-C6 alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine), C1-C6 alkoxy group (e.g., methoxy, ethoxy, propoxy), nitro group and the like.

35 Examples of the protecting group of carbonyl group

include cyclic acetal (e.g., 1,3-dioxane), acyclic acetal (e.g., di-C1-C6 alkyl acetal) and the like.

These protecting groups can be removed according to a method known *per se*, for example, the method described in
5 Protective Groups in Organic Synthesis, John Wiley and Sons (1980) and the like. For example, a method using acid, base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide,
10 trimethylsilyl bromide and the like) and the like, reduction method and the like can be used.

When compound (I) contains an optical isomer, a stereoisomer, a regioisomer or a rotamer, these are also encompassed in compound (I), and can be obtained as a single
15 product according to synthesis and separation methods known *per se*. For example, when compound (I) has an optical isomer, an optical isomer resolved from this compound is also encompassed in compound (I).

The optical isomer can be produced by a method known *per se*. To be specific, an optically active synthetic intermediate
20 is used, or the final racemate product is subjected to optical resolution according to a conventional method to give an optical isomer.

The method of optical resolution may be a method known *per se*, such as a fractional recrystallization method, a chiral
25 column method, a diastereomer method, etc.

1) Fractional recrystallization method

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

35 2) Chiral column method

A method wherein a racemate or a salt thereof is applied 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 (manufactured by Daicel Chemical Industries, Ltd.) and the like, and developed with water, various buffers (phosphate buffer, etc.) and organic solvents (ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.) solely or in admixture to separate the optical isomer.

3) Diastereomer method

A method wherein a racemic mixture 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 (a fractional recrystallization method, a chromatography method, etc.) and the like, and is 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 in a molecule, the compound and an optically active organic acid (MTPA [α -methoxy- α -(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid, etc.) and the like are subjected to condensation reaction to give diastereomers in the ester form or in the amide form, respectively. When compound (I) has a carboxylic acid group, this compound and an optically active amine or an alcohol reagent are subjected to condensation reaction to give diastereomers in the amide form or in the ester form, respectively. The separated diastereomer is converted to an optical isomer of the original compound by acid hydrolysis or base hydrolysis.

Examples

The present invention is described in detail by way of the following Experimental Examples, Reference Examples,

Examples and Formulation Examples, which are not to be construed as limitative.

In the following Reference Examples and Examples, the room temperature means 1°C - 30°C.

5. As for NMR spectra, the chemical shift was indicated by δ , and a coupling constant was indicated by Hz. The numeric value in parenthesis with regard to a mixed solvent is a volumetric mixing ratio of each solvent. Moreover, "%" in the solution represents the number of grams in 100 ml of a
10 solution. The abbreviations used in the present specification mean the following.

s: singlet

d: doublet

t: triplet

15 q: quartet

dd: double doublet

dt: double triplet

m: multiplet

br: broad

20 J: coupling constant

CDCl₃: deuterated chloroform

DMSO-d₆: dimethyl sulfoxide-d₆

¹H NMR: proton nuclear magnetic resonance

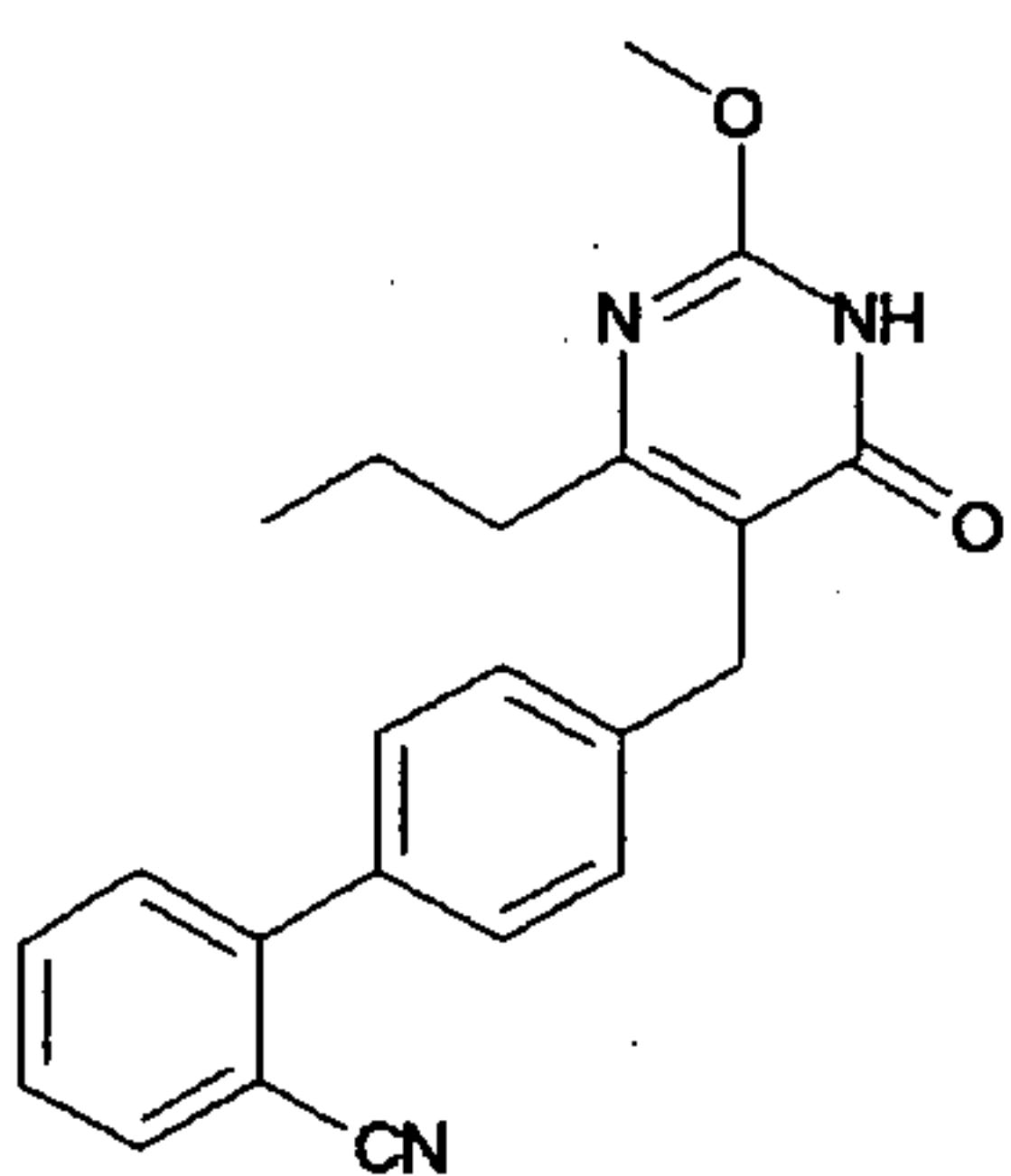
TBS: tert-butyl(dimethyl)silyl

25 TBDMS: tert-butyl(dimethyl)silyl

TIPS: triisopropylsilyl

Example 1

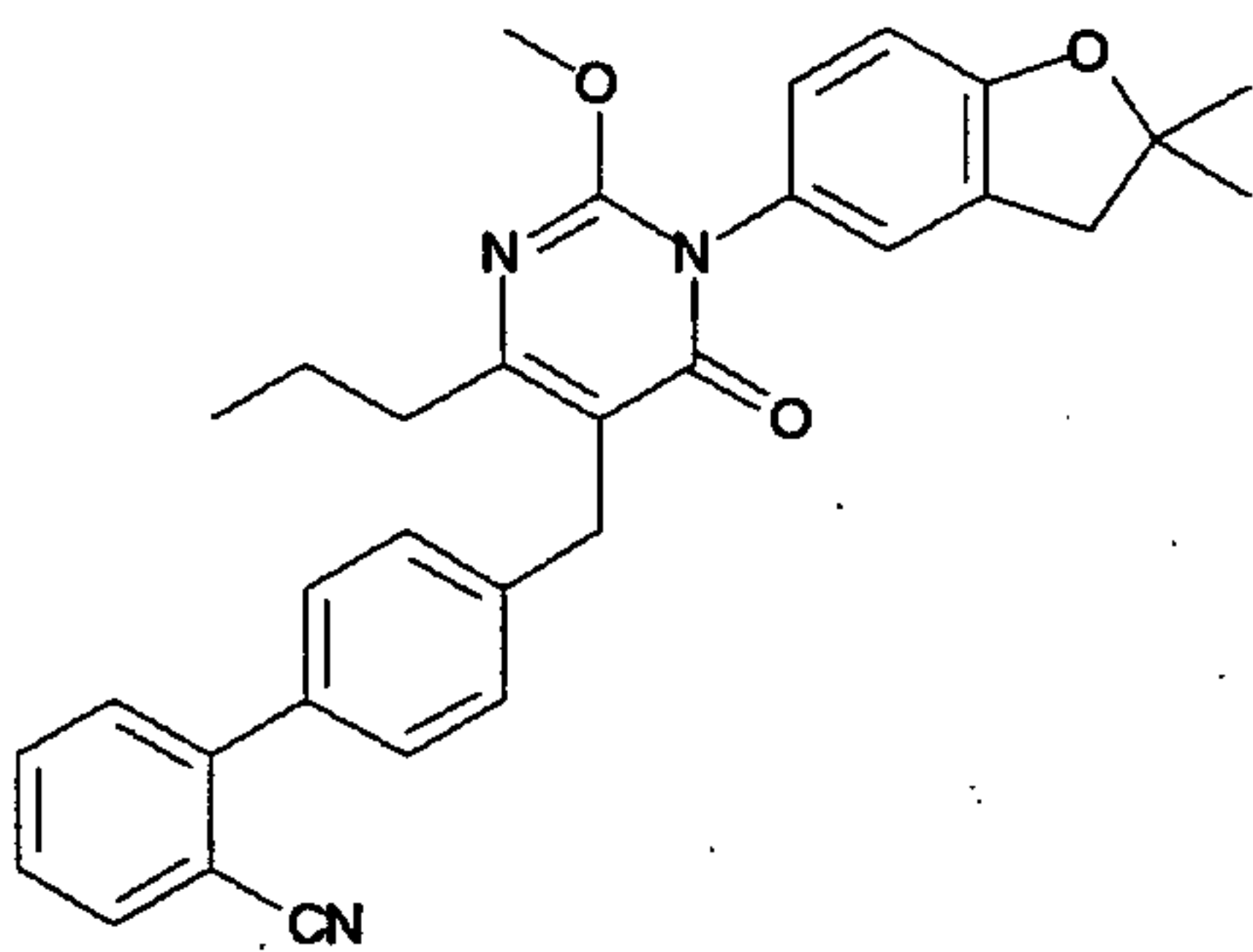
3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methoxy-5-
{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
30 yl]methyl}-6-propylpyrimidin-4(3H)-one



1a) 4'-[(2-methoxy-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile

A solution of methyl imidocarbamate sulfate (10 g), 28% sodium methoxide (26 mL) and ethyl 2-[(2'-cyanobiphenyl-4-yl)methyl]-3-oxohexanoate (15.8 g) in methanol (100 mL) was stirred overnight at room temperature. The solvent was evaporated under reduced pressure, and water and acetic acid were added. The precipitated solid was collected by filtration, washed with water and diethyl ether to give the title compound (2.62 g, 16%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.86 (3H, t, J = 7.2), 1.46-1.64 (2H, m), 2.46 (2H, t, J = 7.2), 3.82 (2H, s), 3.86 (3H, s), 7.32 (2H, d, J = 8.4), 7.47 (2H, d, J = 8.4), 7.52-7.63 (2H, m), 7.72-7.82 (1H, m), 7.92 (1H, d, J = 6.6), 12.21 (1H, br)

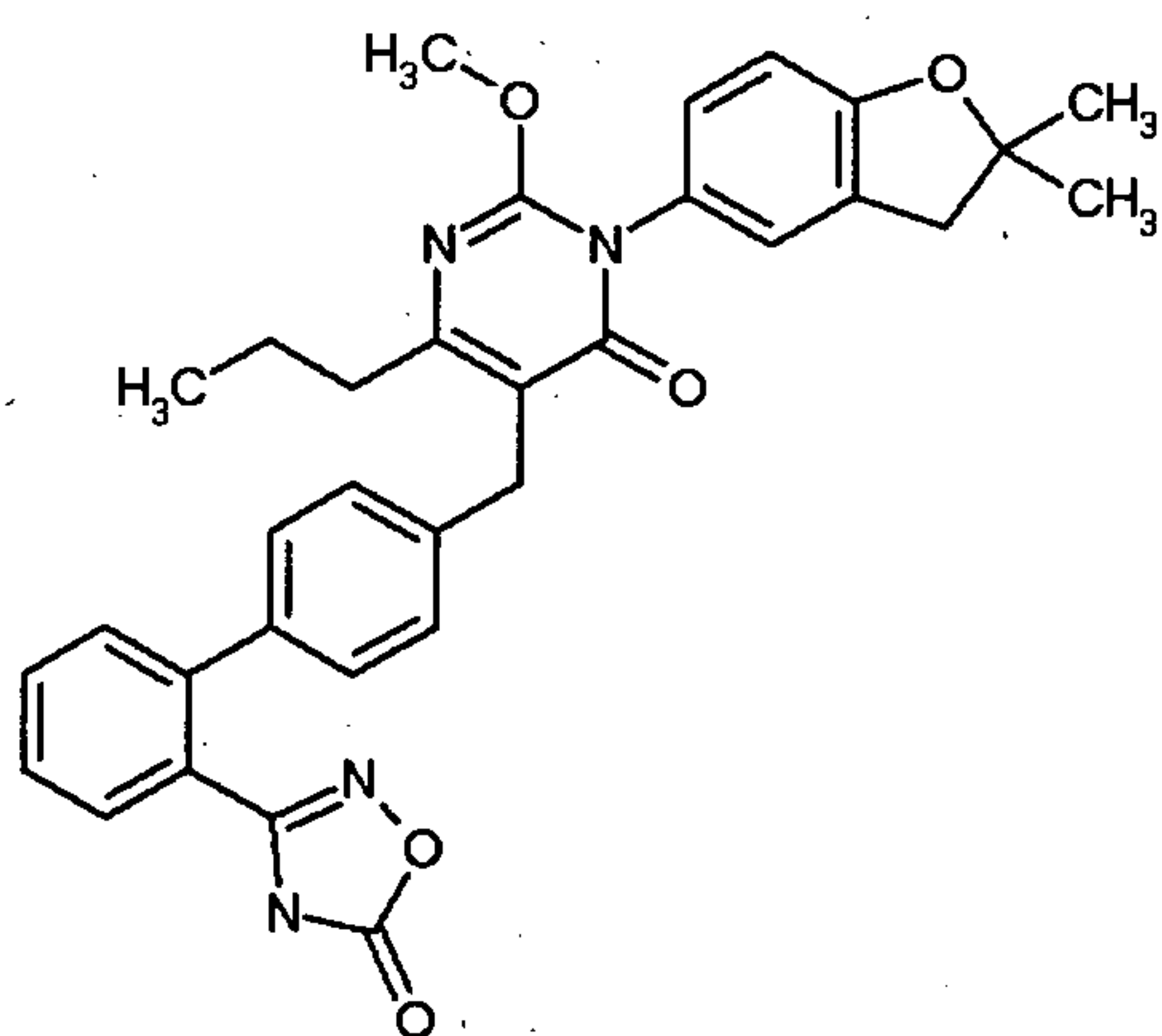


1b) 4'-{[1-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methoxy-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

To a suspension of 4'-[(2-methoxy-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (2.6 g), (2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)boronic acid (2.78 g), triethylamine (5.0 mL), pyridine (2.9 mL) and molecular sieves 4A (5.2 g) in dichloromethane (50 mL) was added copper(II) acetate (2.6 g), and the mixture was stirred for 2

days. The reaction mixture was diluted with ethyl acetate, the insoluble material was filtered off through celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the title compound as
 5 colorless crystals (1.85 g, 51%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.92 (3H, t, J = 7.2), 1.44 (6H, s), 1.55-1.70 (2H, m), 2.54 (2H, t, J = 7.2), 3.04 (2H, s), 3.82 (3H, s), 3.83 (2H, s), 6.75 (1H, d, J = 8.4), 6.99 (1H, d, J = 8.4), 7.09 (1H, s), 7.37 (2H, d, J = 8.4), 7.48 (2H, d, J =
 10 8.4), 7.52-7.62 (2H, m), 7.73-7.81 (1H, m), 7.93 (1H, d, J = 7.8)



1c) 3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methoxy-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one
 15

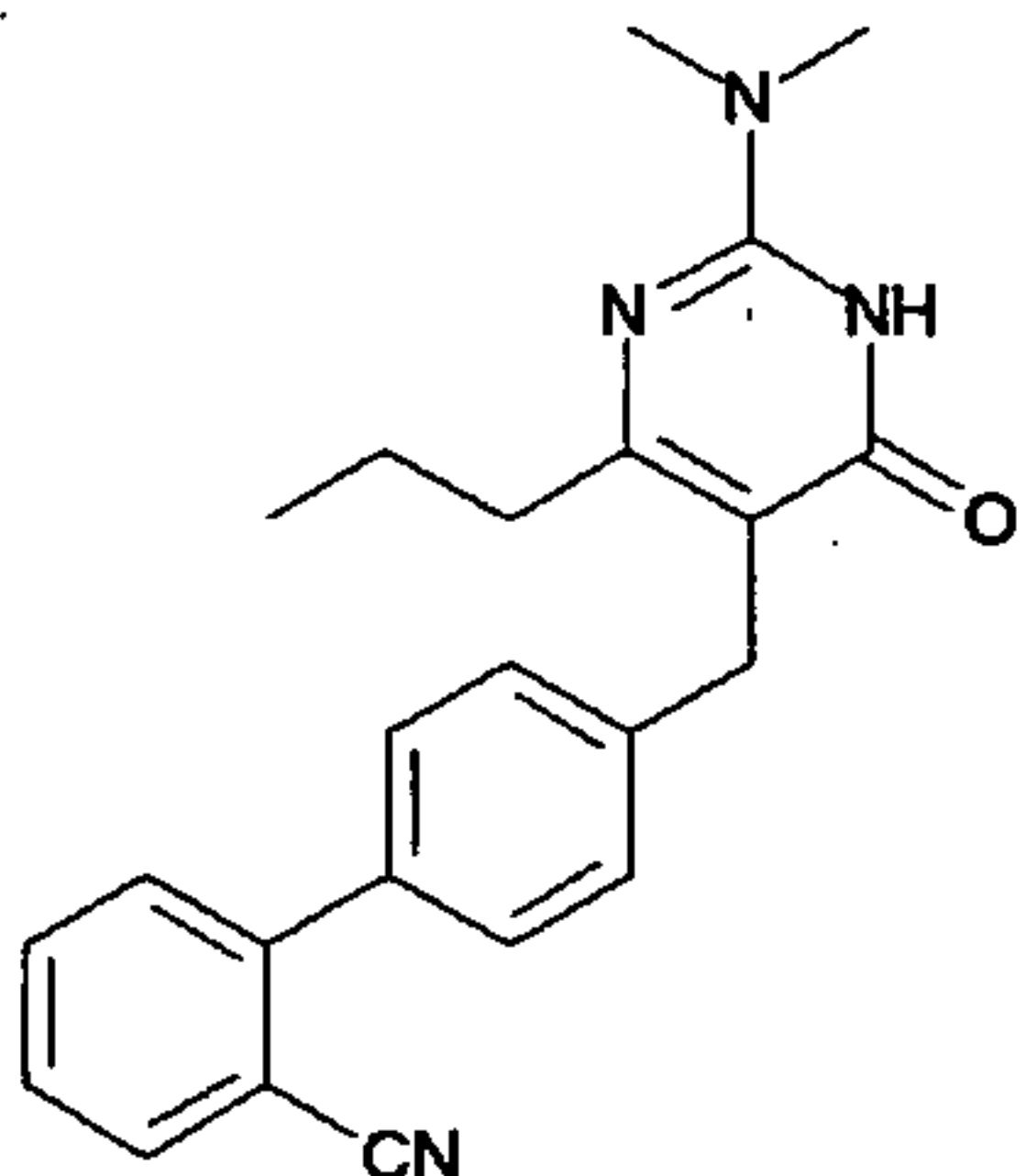
A mixture of hydroxylammonium chloride (4.33 g), sodium hydrogen carbonate (6.16 g) and dimethyl sulfoxide (20 mL) was stirred at 40°C for 30 min, 4'-{[1-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methoxy-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1.85 g)
 20 was added, and the mixture was stirred at 90°C for 5 hr. The mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the precipitated solid was collected by filtration. The obtained solid was dissolved in
 25 ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.48 g) and then 1,8-

diazabicyclo[5.4.0]undec-7-ene (0.45 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.74 g, 66%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.90 (3H, t, J = 7.2), 1.44 (6H, s), 1.50-1.67 (2H, m), 2.50-2.60 (2H, m), 3.04 (2H, s), 3.81 (3H, s), 3.83 (2H, s), 6.75 (1H, d, J = 8.4), 6.97 (1H, d, J = 8.4), 7.08 (1H, s), 7.17-7.32 (4H, m), 7.46-7.58 (2H, m), 7.61-7.73 (2H, m), 12.37 (1H, s).

Example 2

2-(dimethylamino)-3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one

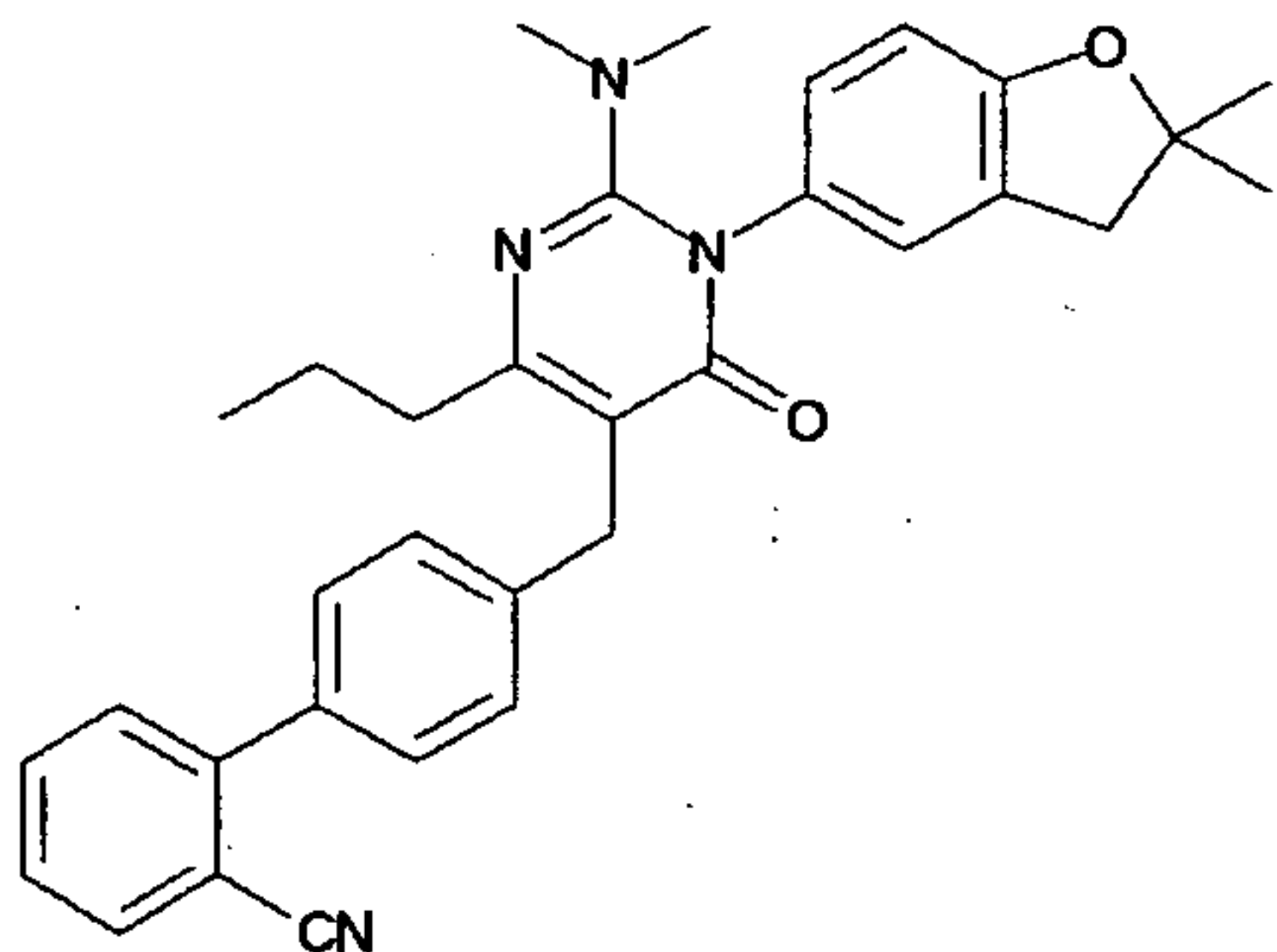


2a) 4'-{[2-(dimethylamino)-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

To a solution of ethyl 2-[(2'-cyanobiphenyl-4-yl)methyl]-3-oxohexanoate (6.41 g) and N,N-dimethylguanidine sulfate (5.0 g) in ethanol (100 mL) was added 20% sodium ethoxide-ethanol solution (11 mL), and the mixture was heated under reflux for 24 hr. The reaction mixture was allowed to cool to room temperature, and the solvent was evaporated under reduced pressure. The residue was washed with water and diethyl ether to give the title compound (2.06 g, 30%) as a pale-yellow solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.5), 1.42-1.63

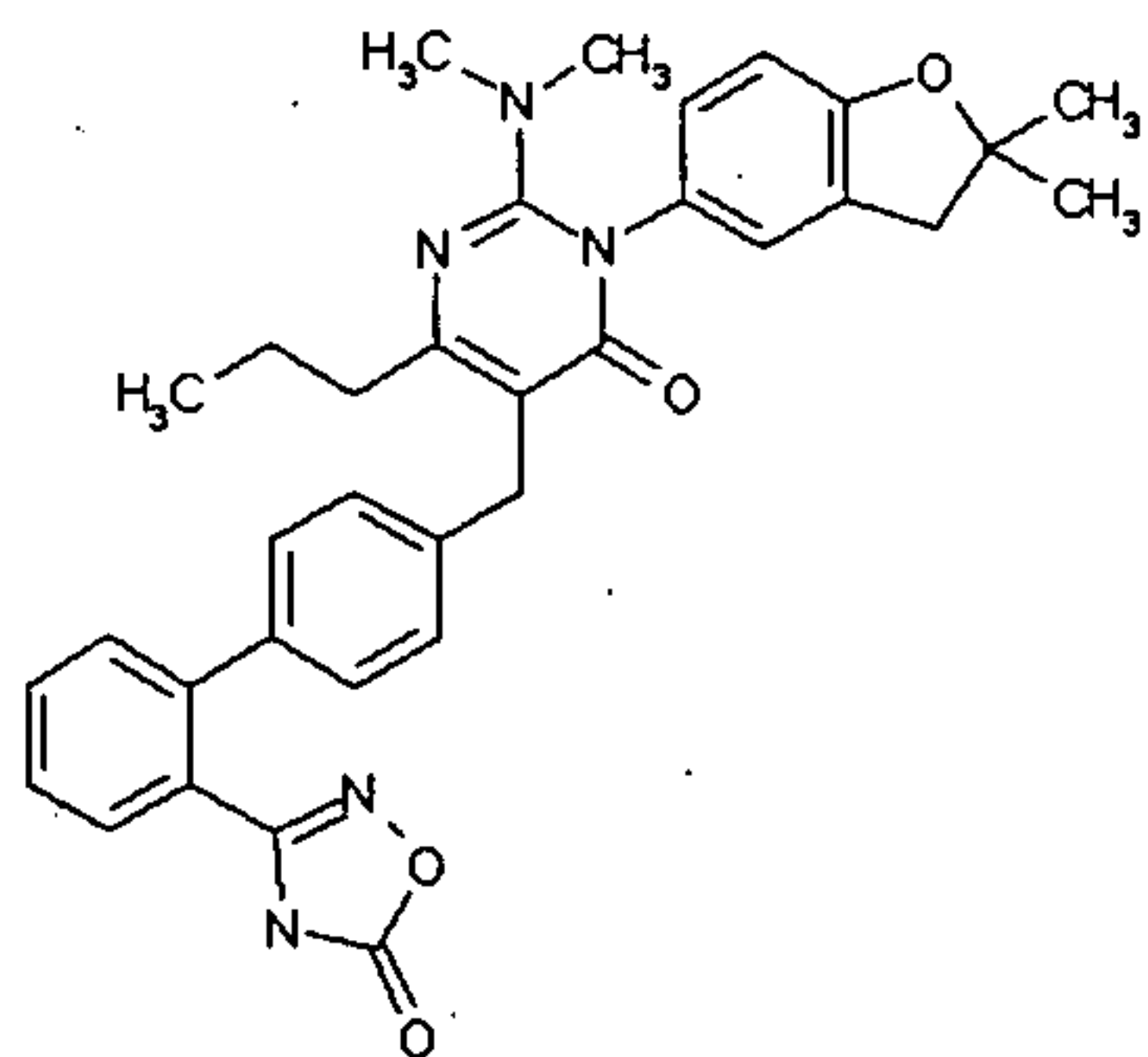
(2H, m), 2.37 (2H, t, $J = 7.5$), 3.02 (6H, s), 3.78 (2H, s), 7.31 (2H, d, $J = 7.8$), 7.46 (2H, d, $J = 7.8$), 7.50-7.63 (2H, m), 7.70-7.82 (1H, m), 7.92 (1H, d, $J = 8.1$), 10.94 (1H, br)



5 2b) 4'-{[2-(dimethylamino)-1-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

To a suspension of 4'-{[2-(dimethylamino)-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (2.1
10 g), (2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)boronic acid (2.1 g), triethylamine (3.8 mL), pyridine (2.2 mL) and molecular sieves 4A (4 g) in dichloromethane (50 mL) was added copper(II) acetate (2 g), and the mixture was stirred for 2 days. The reaction mixture was diluted with ethyl acetate, the
15 insoluble material was filtered off through celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.31 g, 11%).

¹H NMR (300 MHz, CDCl₃) δ 0.95 (3H, t, $J = 7.2$), 1.47 (6H, s),
20 1.52-1.62 (2H, m), 2.17 (2H, s), 2.61 (2H, t, $J = 7.2$), 2.99 (6H, s), 4.04 (2H, s), 6.65 (1H, d, $J = 9.3$), 6.78-6.87 (2H, m), 7.30-7.52 (6H, m), 7.57-7.66 (1H, m), 7.74 (1H, d, $J = 7.5$)



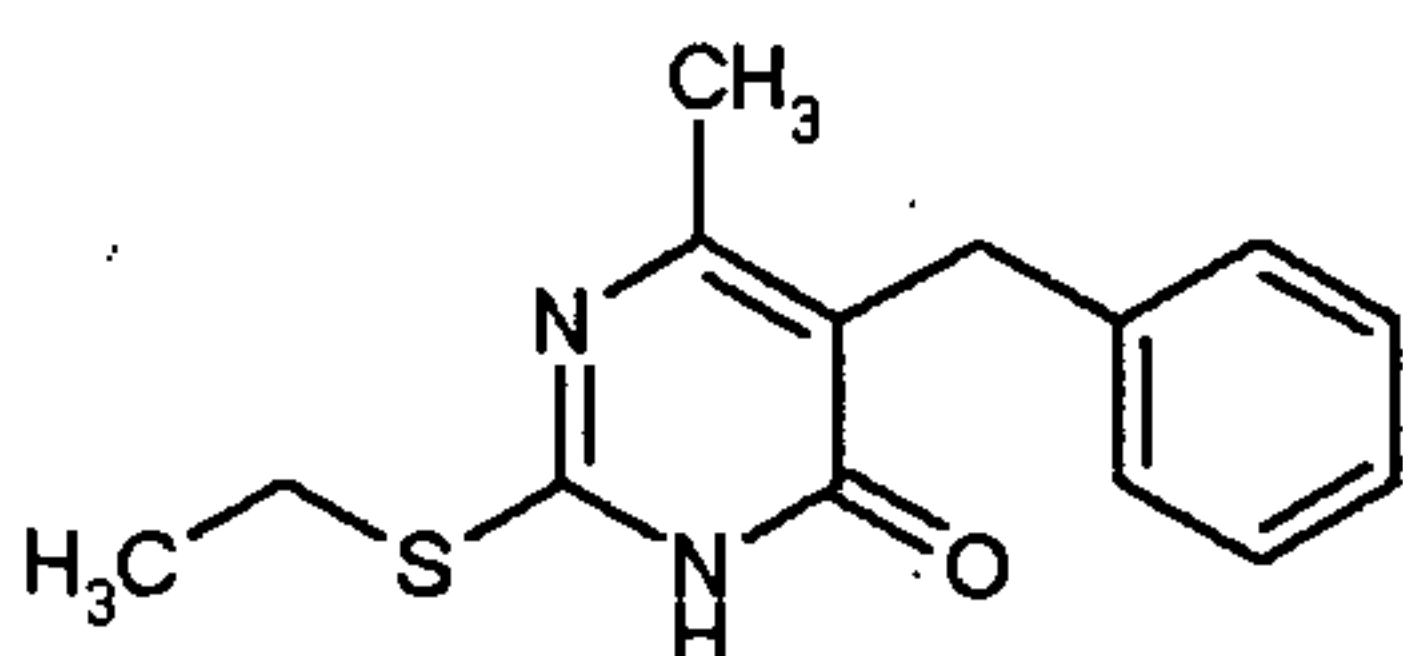
2c) 2-(dimethylamino)-3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.71 g), sodium
 5 hydrogen carbonate (1.01 g) and dimethyl sulfoxide (5 mL) was
 stirred at 40°C for 30 min, 4'-{[2-(dimethylamino)-1-(2,2-
 dimethyl-2,3-dihydro-1-benzofuran-5-yl)-6-oxo-4-propyl-1,6-
 dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.31 g)
 was added, and the mixture was stirred at 90°C for 16 hr. The
 10 mixture was allowed to cool to room temperature, water was
 added to the reaction mixture, and the precipitated solid was
 collected by filtration. The obtained solid was dissolved in
 ethyl acetate. The solution was washed with saturated brine
 and dried over anhydrous sodium sulfate, and the solvent was
 15 evaporated. The residue was dissolved in tetrahydrofuran (20
 mL), N,N'-carbonyldiimidazole (0.13 g) and then 1,8-
 diazabicyclo[5.4.0]undec-7-ene (0.12 mL) were added, and the
 mixture was stirred at room temperature for 30 min. The
 reaction mixture was diluted with ethyl acetate, washed with 1
 20 M hydrochloric acid and then with saturated brine, and dried
 over anhydrous sodium sulfate. The solvent was evaporated
 under reduced pressure. The residue was purified by silica gel
 column chromatography to give the title compound as colorless
 crystals (0.1 g, 33%).

25 ¹H NMR (300 MHz, DMSO-d₆) δ 0.88 (3H, t, J = 7.2), 1.40 (6H, s),
 1.49-1.65 (2H, m), 2.50-2.58 (2H, m), 2.91 (6H, s), 2.99 (2H,
 s), 3.98 (2H, s), 6.66 (1H, d, J = 8.7), 6.81 (1H, d, J = 8.7),
 6.90 (1H, s), 7.25 (4H, s), 7.47-7.59 (2H, m), 7.61-7.72 (2H,
 m), 12.36 (1H, br)

30 Example 3

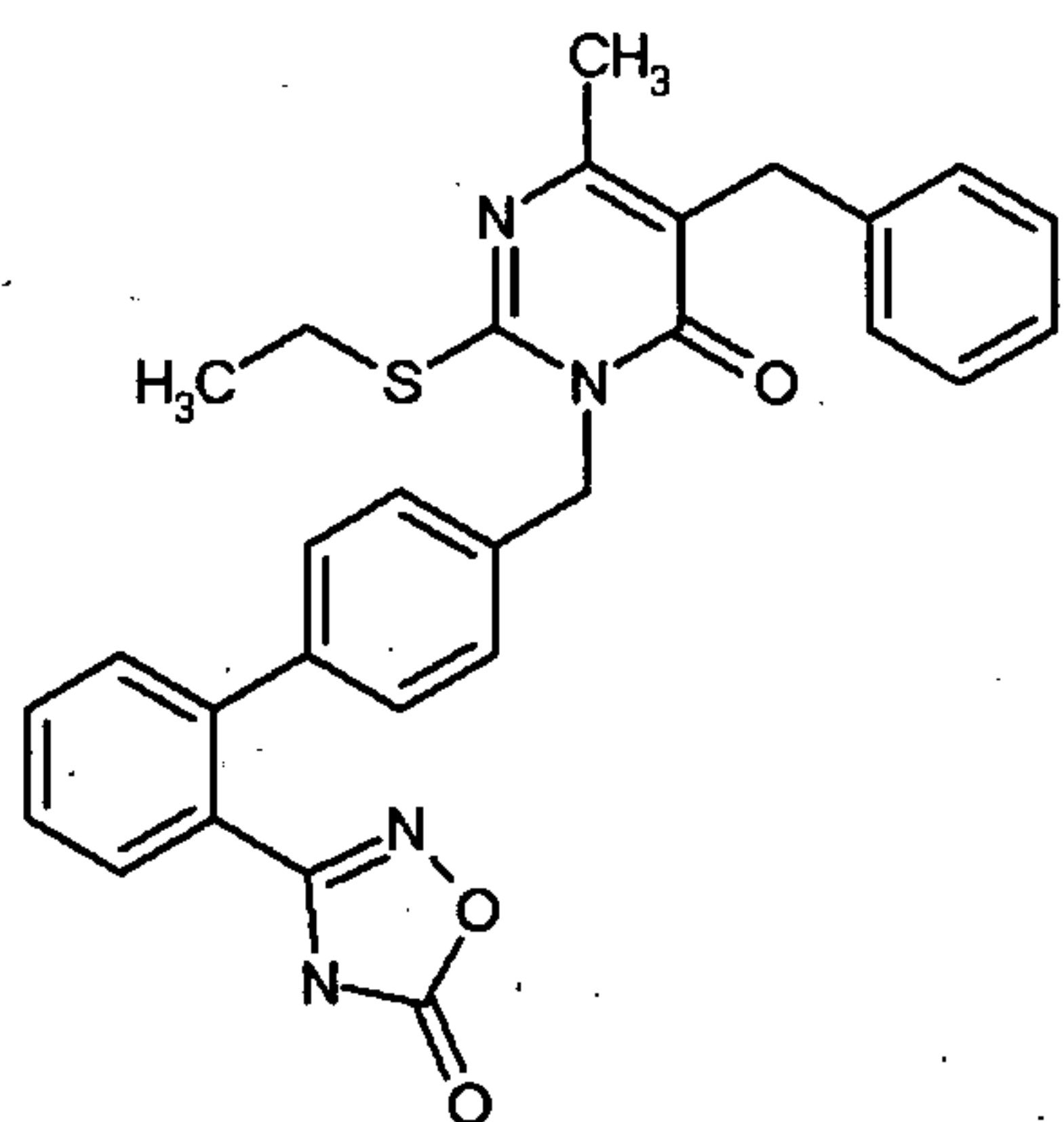
5-benzyl-2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



3a) 5-benzyl-2-(ethylthio)-6-methylpyrimidin-4(3H)-one

To a solution of 5-benzyl-6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (0.2 g) and potassium carbonate (0.24 g) in N,N-dimethylformamide (4 mL) was added ethyl iodide (0.035 mL), and the mixture was stirred for 4 hr. The insoluble material was filtered off. The filtrate was diluted with ethyl acetate, washed with 1 M hydrochloric acid and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the title compound (0.22 g, 97%) as a pale-yellow solid.

¹H NMR (300 MHz, DMSO-d₆) δ 1.28 (3H, t, J = 7.5), 2.18 (3H, s), 3.08 (2H, q, J = 7.5), 3.74 (2H, s), 7.02-7.34 (5H, m)

3b) 5-benzyl-2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

To a solution of 5-benzyl-2-(ethylthio)-6-methylpyrimidin-4(3H)-one (0.22 g) and 3-[4'-(bromomethyl)biphenyl-2-yl]-5-(trichloromethyl)-1,2,4-oxadiazole (0.44 g) in N,N-dimethylformamide (5 mL) was added cesium carbonate (0.36 g), and the mixture was stirred for 12 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran-ethanol (1:1, 4 mL), 1 M sodium hydroxide (2 mL) was added and the mixture was stirred for 30 min. The reaction mixture was weakly acidified with 1 M hydrochloric acid and extracted with ethyl acetate. The organic layer was

washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.025 g, 6%) as a colorless solid.

5 ^1H NMR (300 MHz, CDCl_3) δ 1.35 (3H, t, $J = 7.5$), 2.27 (3H, s), 3.17 (2H, q, $J = 7.5$), 3.76 (2H, s), 5.20 (2H, s), 7.07-7.30 (9H, m), 7.37-7.47 (2H, m), 7.52-7.62 (1H, m), 7.66 (1H, d, $J = 7.5$)

10 5-Benzyl-2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

15 5-benzyl-2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one sodium salt

5-benzyl-2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one potassium salt

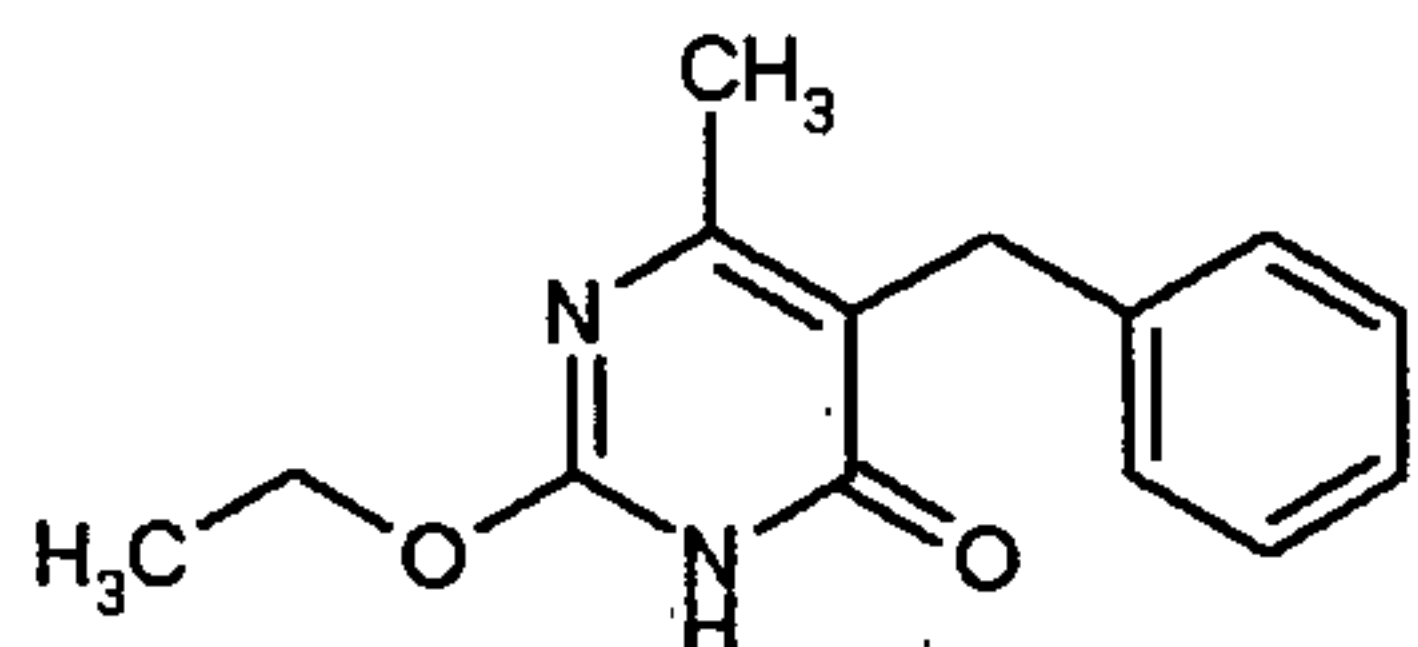
20 5-benzyl-2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one 0.5 calcium salt

5-benzyl-2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrochloride

25 5-benzyl-2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrobromide

Example 4

30 5-benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

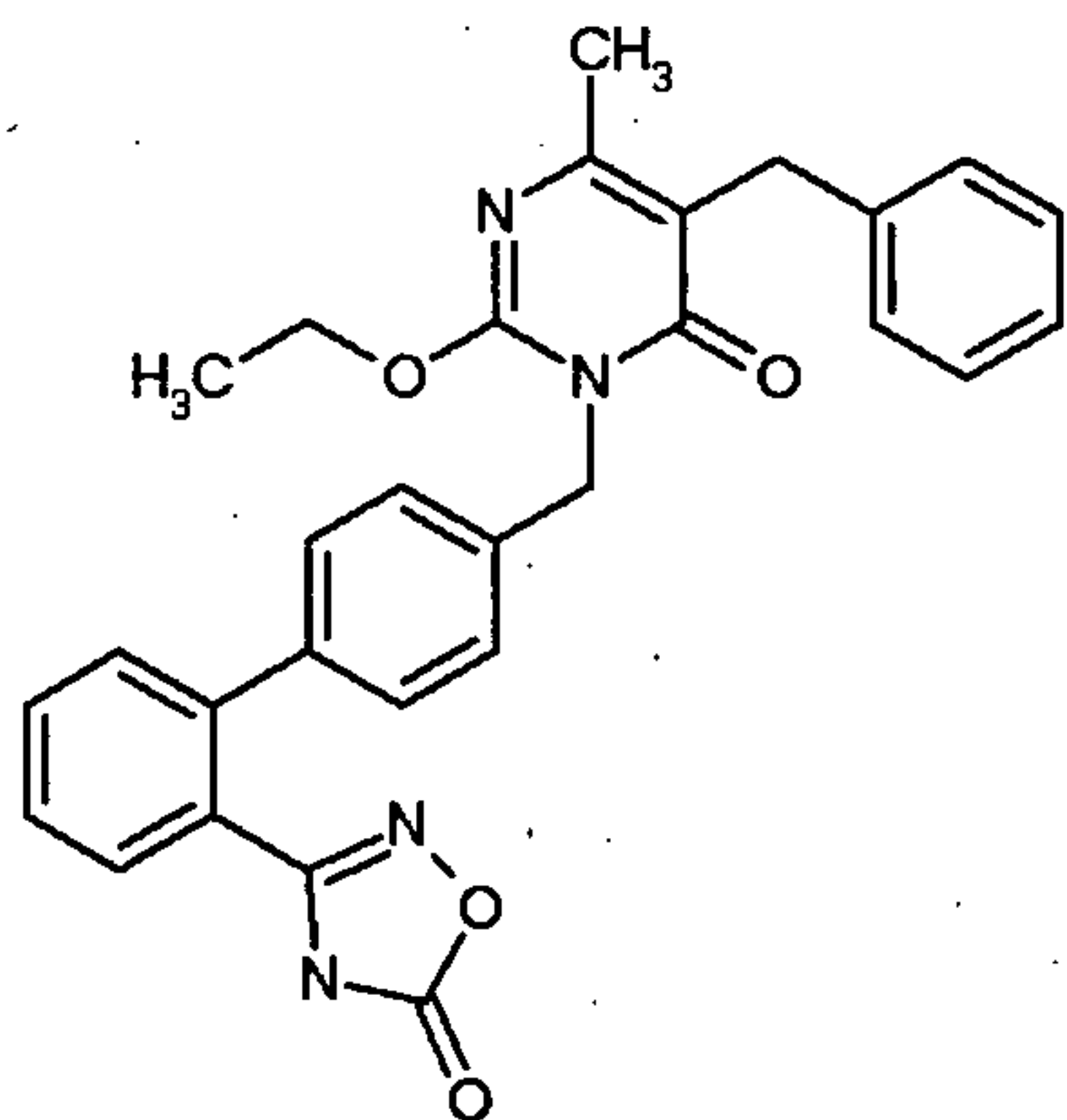


4a) 5-benzyl-2-ethoxy-6-methylpyrimidin-4(3H)-one

To a solution of ethyl imidocarbamate tetrafluoroborate

(2.4 g) and ethyl 2-benzyl-3-oxobutanoate (1 g) in methanol (20 mL) was added sodium methoxide (28% methanol solution, 5.25 mL), and the mixture was stirred for 12 hr. The reaction mixture was concentrated, and the residue was dissolved in water. The solution was weakly acidified with acetic acid, extracted with ethyl acetate, washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from diisopropyl ether to give the title compound (0.27 g, 24%) as a colorless solid.

^1H NMR (300 MHz, DMSO- d_6) δ 1.28 (3H, t, J = 7.2), 2.12 (3H, s), 3.70 (2H, s), 4.31 (2H, q, J = 7.2), 7.03-7.33 (5H, m), 12.17 (1H, br)



4b) 5-benzyl-2-ethoxy-6-methyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

To a solution of 5-benzyl-2-ethoxy-6-methylpyrimidin-4(3H)-one (0.27 g) and 3-[4'-(bromomethyl)biphenyl-2-yl]-5-(trichloromethyl)-1,2,4-oxadiazole (0.58 g) in N,N-dimethylformamide (5 mL) was added cesium carbonate (0.44 g), and the mixture was stirred for 12 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran-ethanol (1:1, 4 mL), 1 M sodium hydroxide (2 mL) was added and the mixture was stirred for 30 min. The reaction mixture was weakly acidified with 1 M hydrochloric acid and extracted with ethyl acetate.

The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.11 g, 20%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 1.38 (3H, t, J = 7.2), 2.20 (3H, s), 3.78 (2H, s), 4.43 (2H, q, J = 7.2), 5.14 (2H, s), 7.10-7.30 (7H, m), 7.34-7.51 (4H, m), 7.55-7.64 (1H, m), 7.75 (1H, d, J = 7.8)

5-Benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

5-benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one sodium salt

5-benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one potassium salt

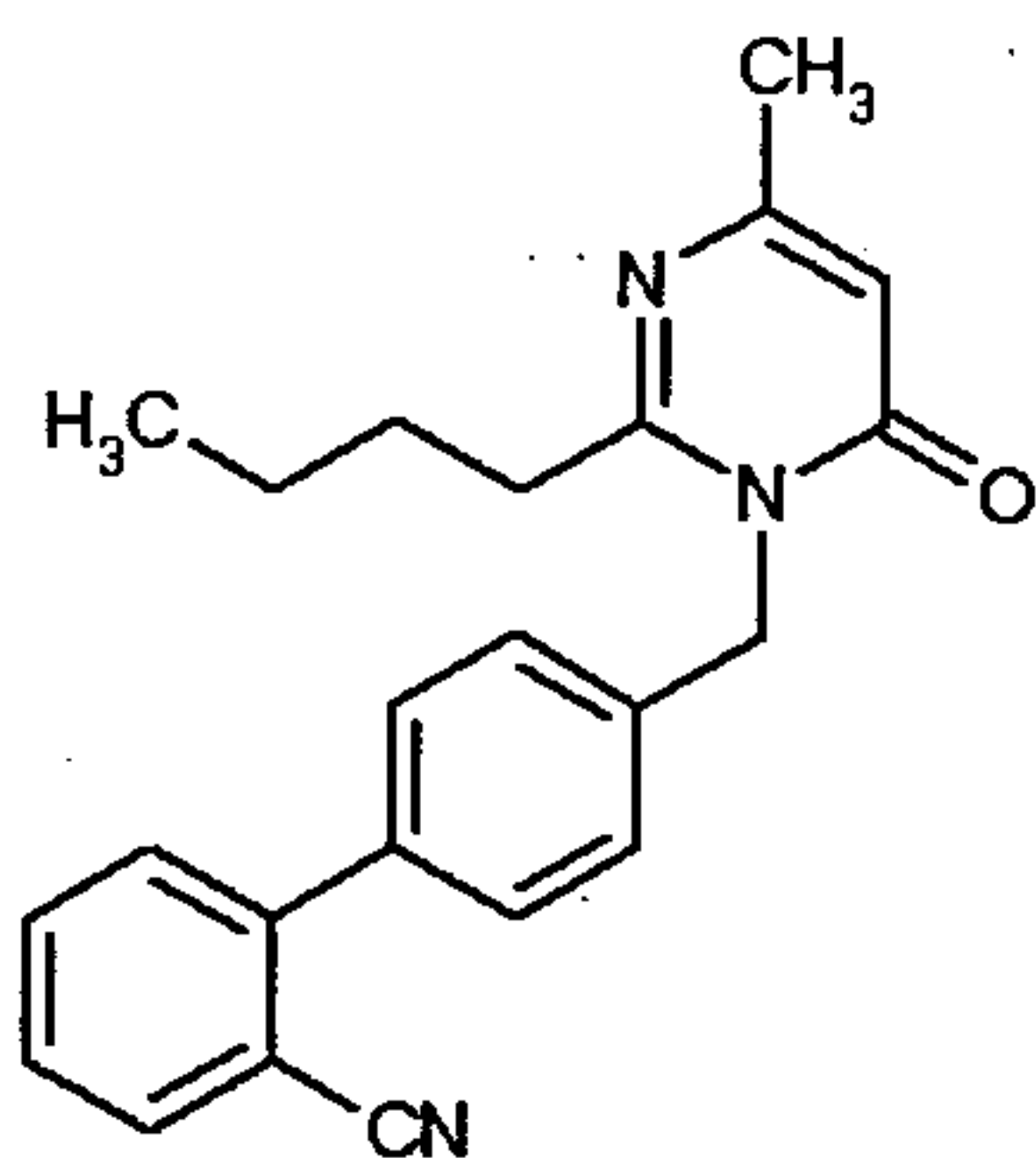
5-benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one 0.5 calcium salt

5-benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrochloride

5-benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrobromide

Example 5

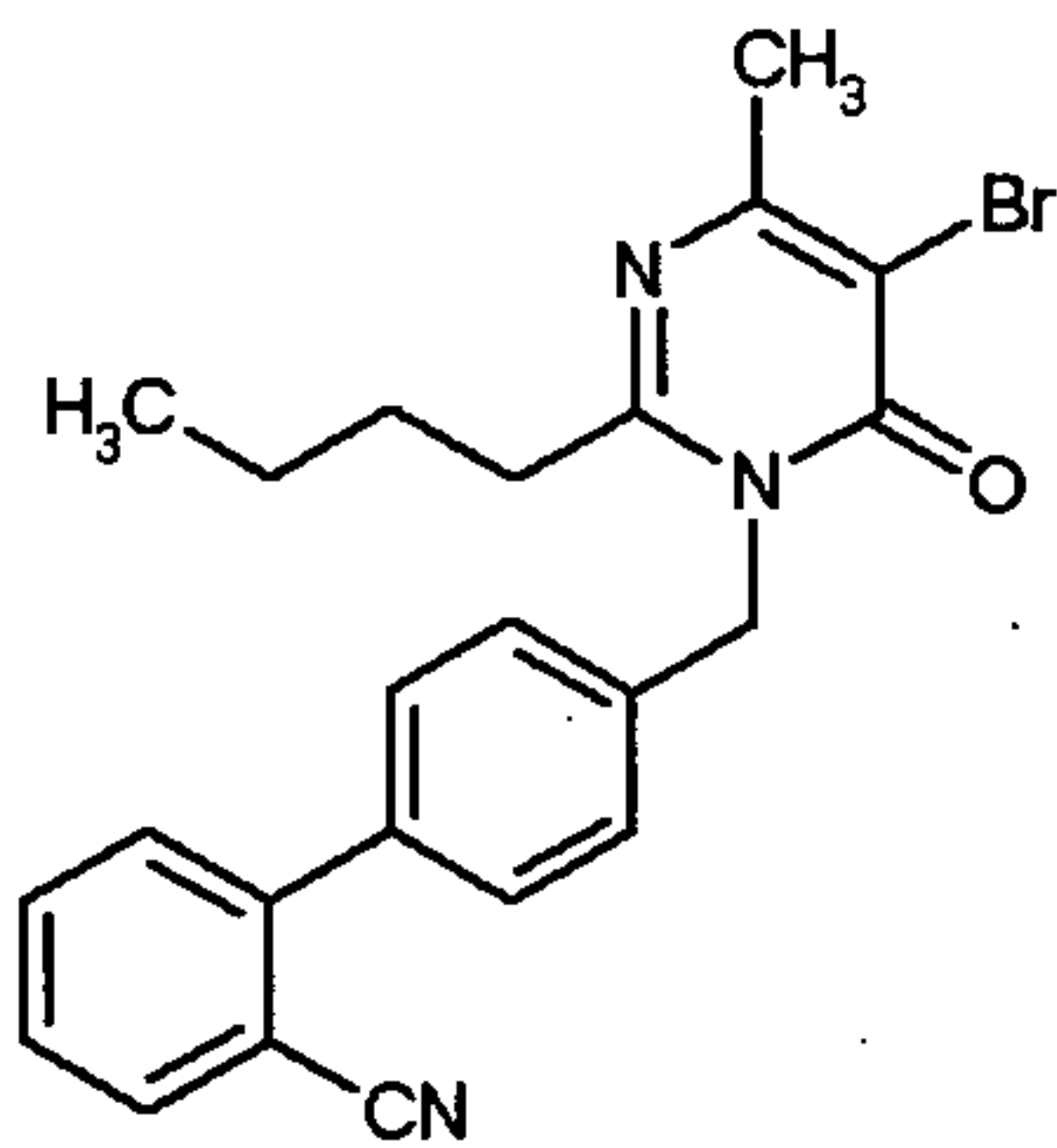
2-butyl-5-(4-fluorophenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



5a) 4'-[(2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 2-butyl-6-methylpyrimidin-4(3H)-one (3.38 g) and 4'-(bromomethyl)biphenyl-2-carbonitrile (6.64 g) in acetonitrile (50 mL) was added cesium carbonate (8.61 g), and the mixture was stirred at 50°C for 12 hr. The insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the title compound (2.09 g, 29%) as a colorless viscous substance.

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.2), 1.30-1.46 (2H, m), 1.61-1.74 (2H, m), 2.29 (3H, s), 2.68 (2H, t, J = 6.6), 5.36 (2H, s), 6.29 (1H, s), 7.23-7.32 (2H, m), 7.40-7.57 (4H, m), 7.59-7.69 (1H, m), 7.76 (1H, d, J = 7.8)

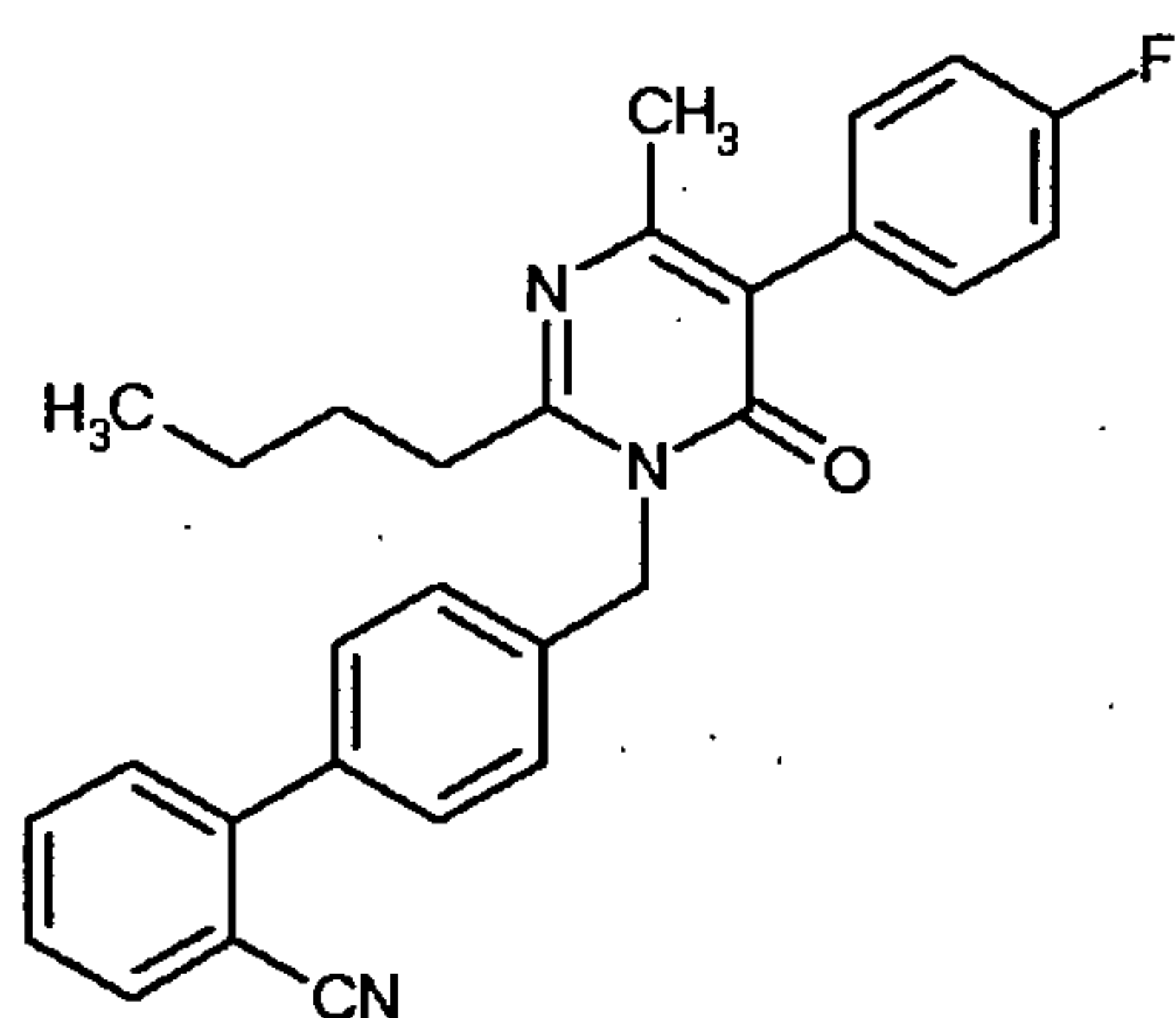


5b) 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[(2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.8 g) in acetic acid (40 mL) was added bromine (0.77 mL), and the mixture was stirred at 70°C for 2 hr. The reaction mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium

sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (1.96 g, 88%) as a colorless solid.

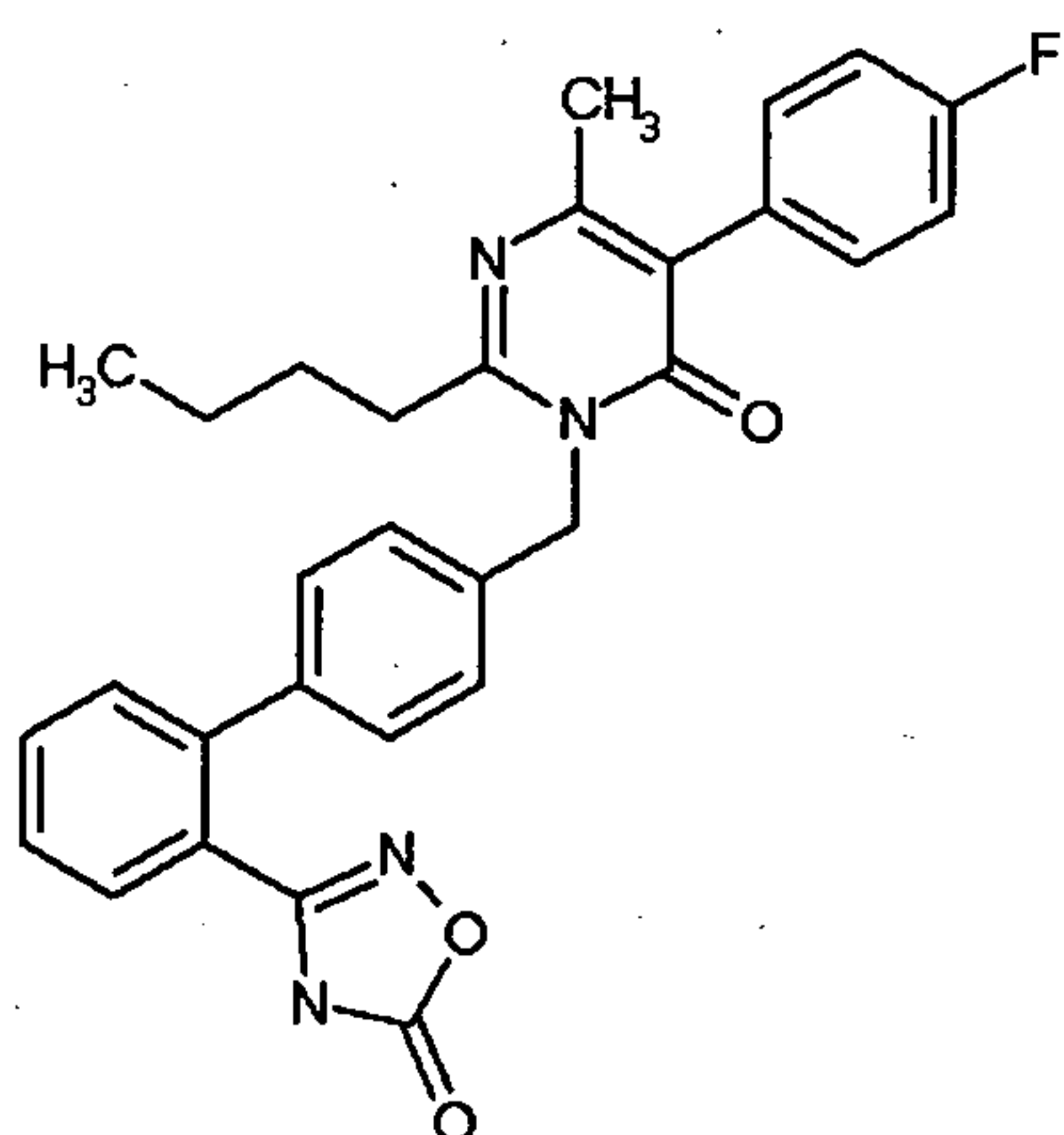
¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.5), 1.30-1.47 (2H, m), 1.60-1.75 (2H, m), 2.49 (3H, s), 2.69 (2H, t, J = 7.5), 5.39 (2H, s), 7.31 (2H, d, J = 8.1), 7.40-7.58 (4H, m), 7.60-7.70 (1H, m), 7.76 (1H, d, J = 6.9)



5c) 4'-{[2-butyl-5-(4-fluorophenyl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.0 g) and 4-fluorophenylboronic acid (0.48 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (1.0 g, 97%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.2), 1.34-1.52 (2H, m), 1.66-1.81 (2H, m), 2.22 (3H, s), 2.75 (2H, t, J = 7.8), 5.38 (2H, s), 7.09-7.17 (2H, m), 7.28-7.38 (4H, m), 7.40-7.58 (4H, m), 7.59-7.69 (1H, m), 7.76 (1H, d, J = 7.8)



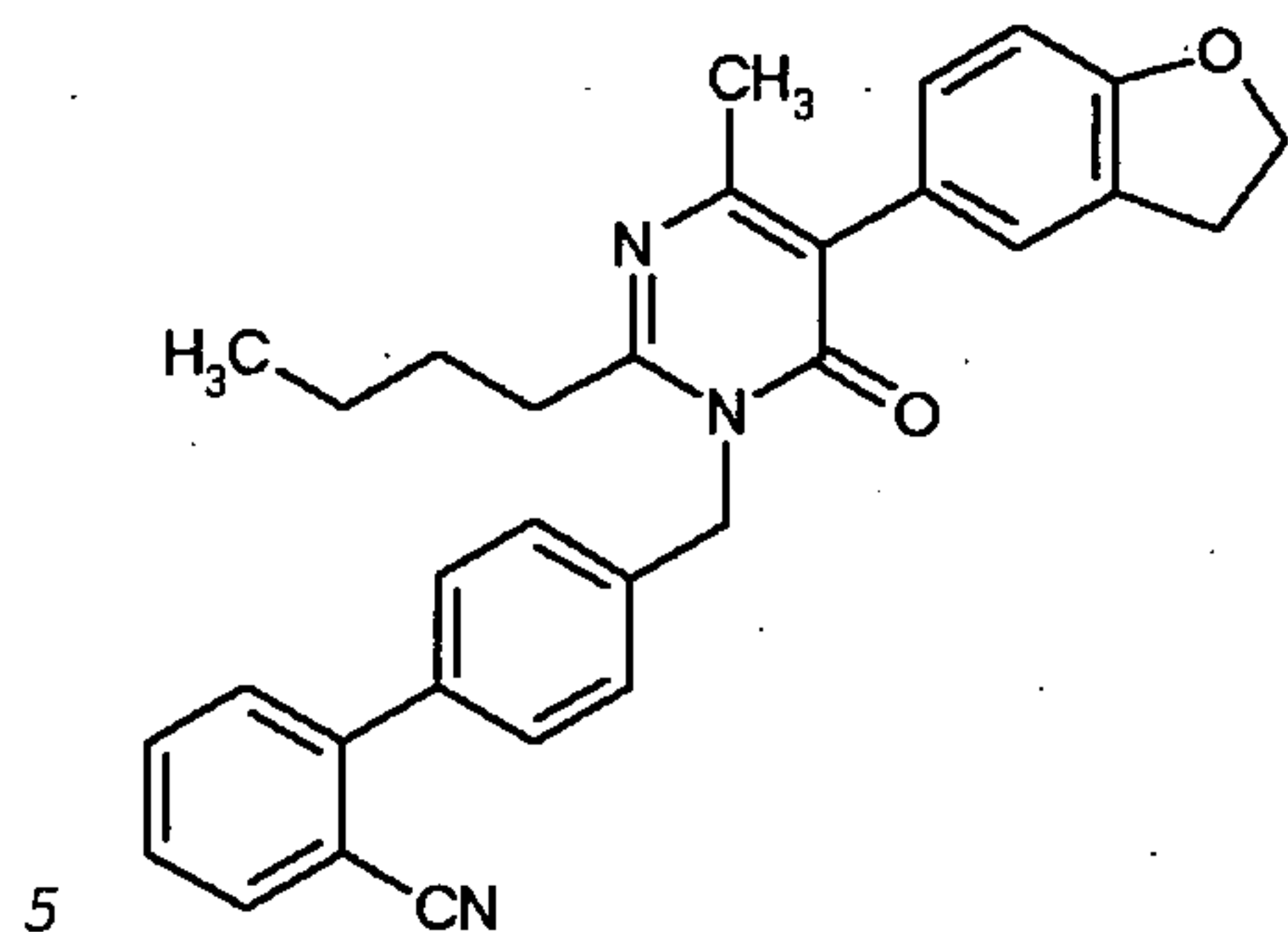
5d) 2-butyl-5-(4-fluorophenyl)-6-methyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (2.62 g), sodium hydrogen carbonate (3.72 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-{[2-butyl-5-(4-fluorophenyl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (1 g) was added, and the mixture was stirred at 90°C for 16 hr.
 10 The mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was
 15 evaporated. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.54 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1
 20 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.81 g, 72%).

25 ¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.2), 1.21-1.38 (2H, m), 1.50-1.66 (2H, m), 2.11 (3H, s), 2.69 (2H, t, J = 7.5), 5.36 (2H, s), 7.18-7.42 (8H, m), 7.47-7.62 (2H, m), 7.62-7.74 (2H, m), 12.41 (1H, s)

Example 6

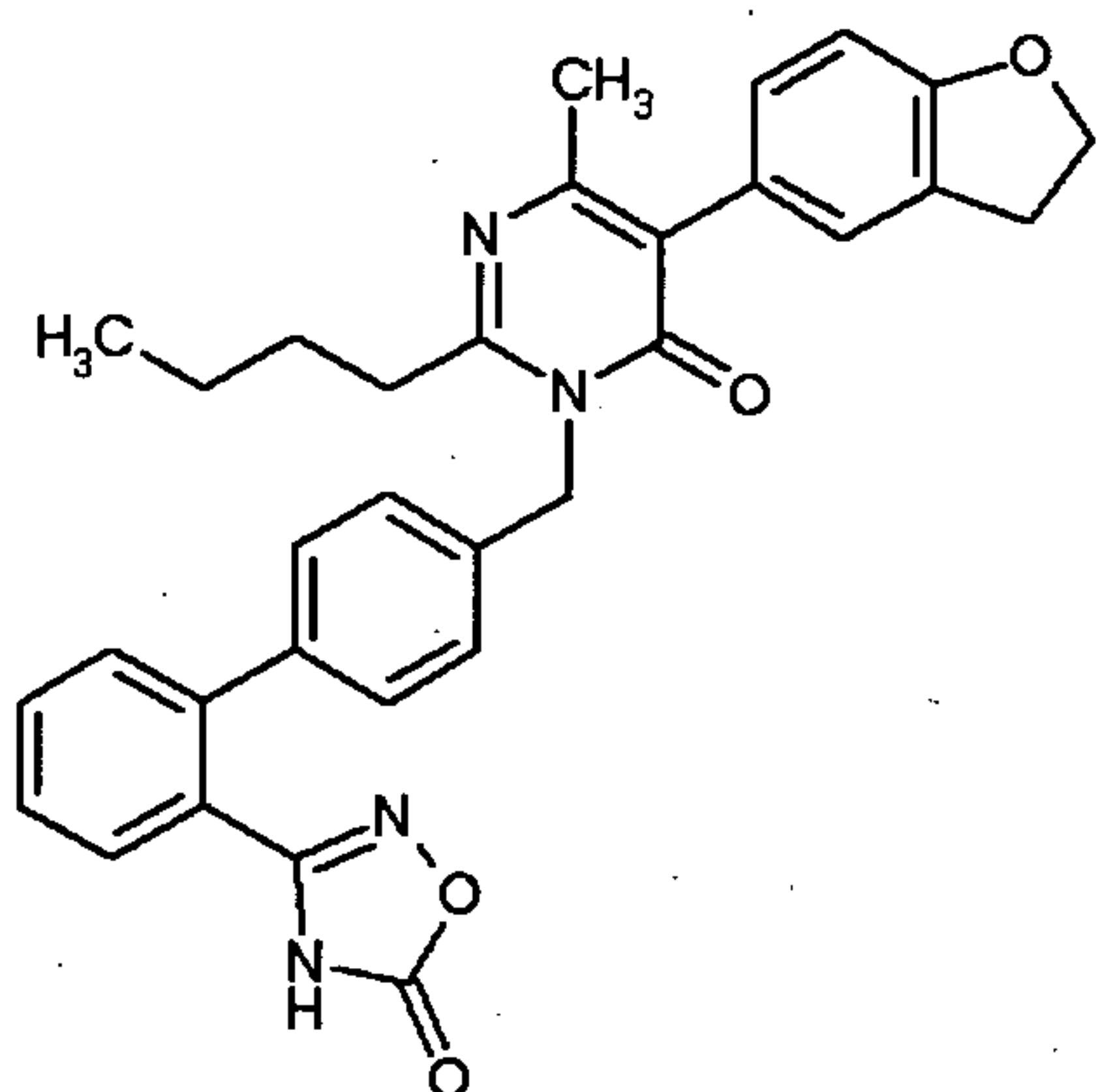
2-butyl-5-(2,3-dihydro-1-benzofuran-5-yl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



6a) 4'-{[2-butyl-5-(2,3-dihydro-1-benzofuran-5-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.96 g) and 2,3-dihydro-1-benzofuran-5-ylboronic acid (0.54 g) in 1,4-dioxane were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.09 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.75 g, 72%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.2), 1.33-1.51 (2H, m), 1.65-1.81 (2H, m), 2.24 (3H, s), 2.74 (2H, t, J = 7.8), 3.24 (2H, t, J = 8.4), 4.59 (2H, t, J = 8.4), 5.38 (2H, s), 6.83 (1H, d, J = 8.1), 7.05 (1H, d, J = 8.1), 7.19 (1H, s), 7.34 (2H, d, J = 8.1), 7.40-7.57 (4H, m), 7.59-7.69 (1H, m), 7.76 (1H, d, J = 7.8)



6b) 2-butyl-5-(2,3-dihydro-1-benzofuran-5-yl)-6-methyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

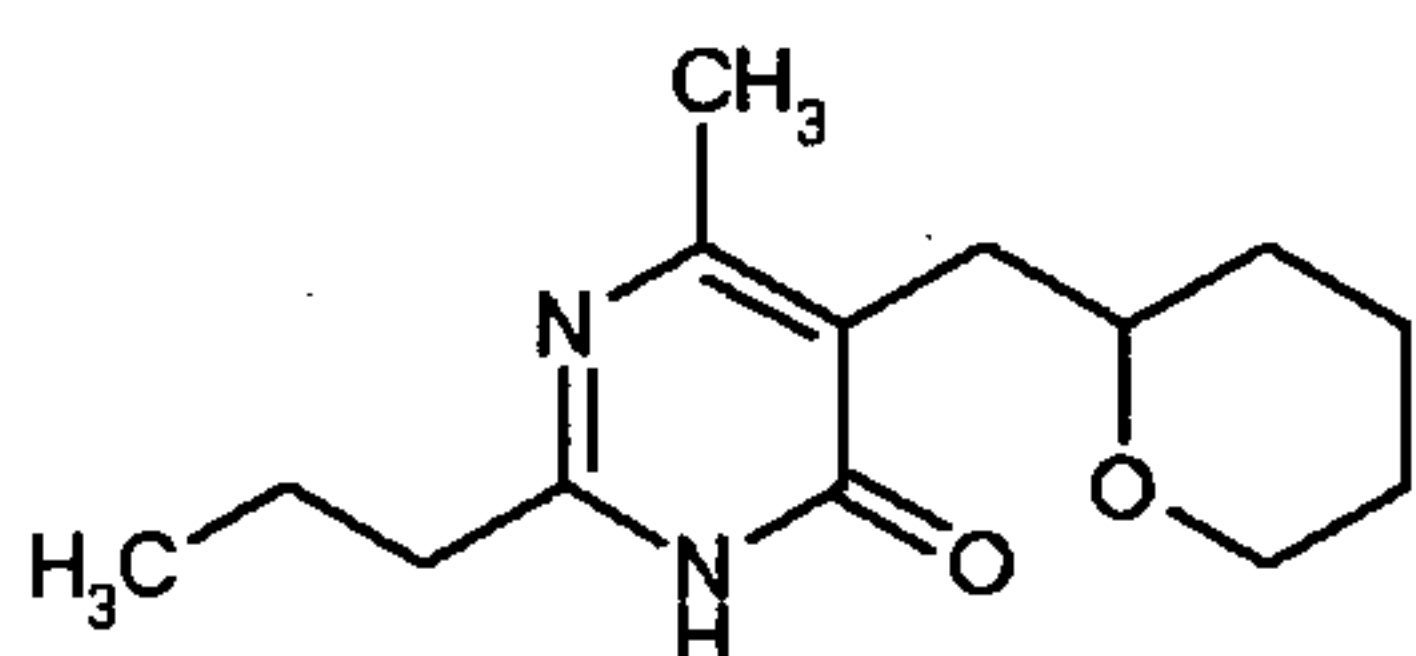
5 A mixture of hydroxylammonium chloride (1.86 g), sodium hydrogen carbonate (2.65 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-{[2-butyl-5-(2,3-dihydro-1-benzofuran-5-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.75 g) was added, and the
10 mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous
15 sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15 mL), N,N'-carbonyldiimidazole (0.38 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.35 mL) were added, and the mixture was stirred at room temperature for 30 min. The
20 reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless
25 crystals (0.63 g, 74%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.2), 1.21-1.38 (2H, m), 1.51-1.65 (2H, m), 2.12 (3H, s), 2.68 (2H, t, J = 7.2), 3.20 (2H, t, J = 8.4), 4.55 (2H, t, J = 8.4), 5.35 (2H,

s), 6.78 (1H, d, J = 8.1), 7.00 (1H, d, J = 8.1), 7.16 (1H, s), 7.25 (2H, d, J = 8.1), 7.32 (2H, d, J = 8.1), 7.48-7.61 (2H, m), 7.64-7.74 (2H, m), 12.41 (1H, s)

Example 7

- 5 6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one



- 7a) 6-methyl-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one

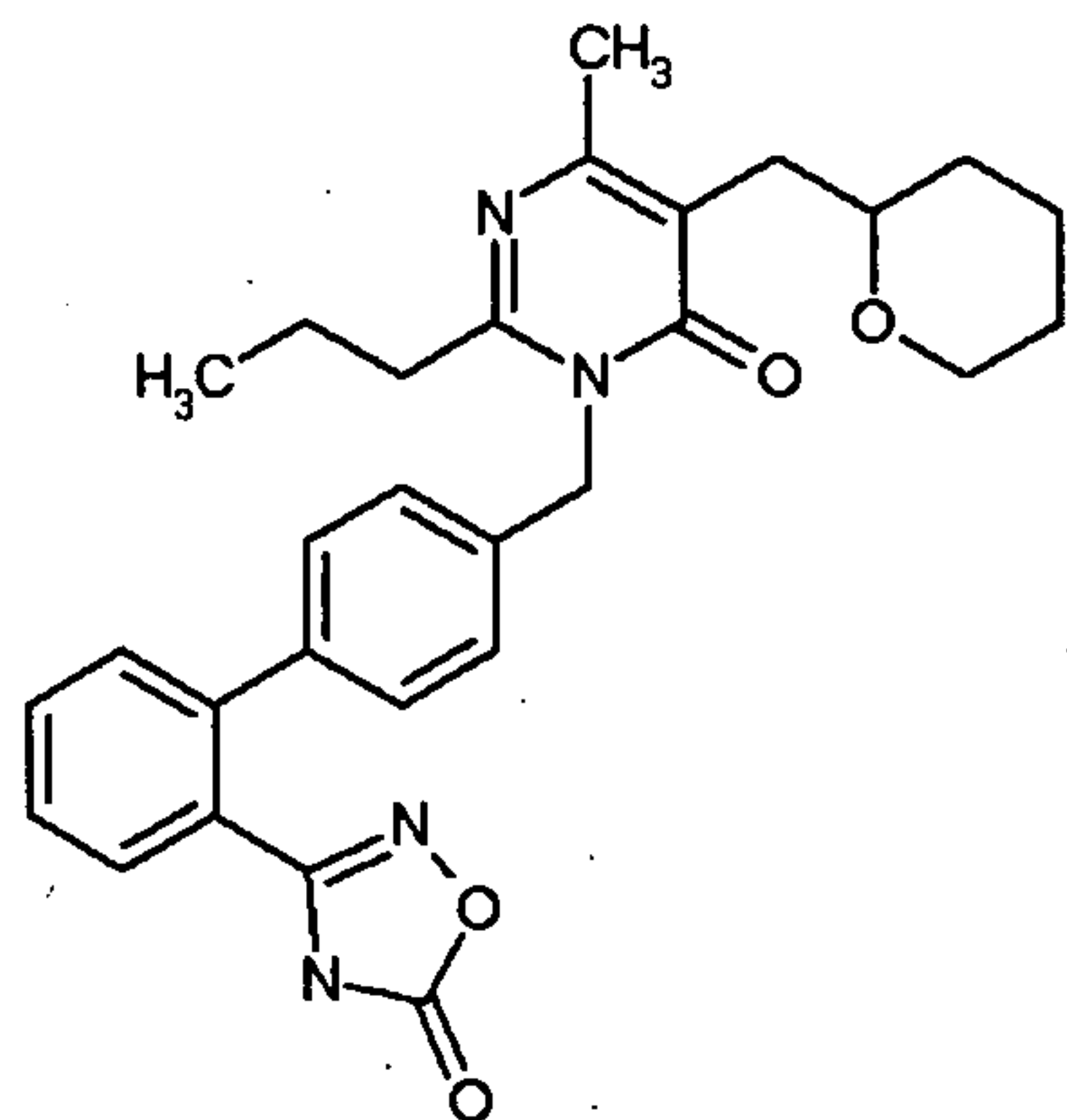
To a solution of ethyl 3-oxo-2-(tetrahydro-2H-pyran-2-ylmethyl)butyrate (0.73 g) and butylamidine hydrochloride (0.78 g) in methanol (50 mL) was added sodium methoxide (25 mL, 28% methanol solution), and the mixture was stirred for 12 hr.

15 The reaction mixture was concentrated, and the residue was dissolved in water and diethyl ether. The aqueous layer was separated, weakly acidified with 1 M hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium

20 sulfate to give the title compound (0.46 g, 57%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 0.88 (3H, t, J = 7.2), 1.08-1.80 (8H, m), 2.18 (3H, s), 2.41 (2H, t, J = 7.2), 2.48-2.50 (2H, m), 3.12-3.28 (1H, m), 3.33-3.47 (1H, m), 3.79 (1H, d, J = 10.8),

25 12.15 (1H, br)



7b) 6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one

To a solution of 6-methyl-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one (0.46 g) and 3-[4'-(bromomethyl)biphenyl-2-yl]-5-(trichloromethyl)-1,2,4-oxadiazole (0.95 g) in acetonitrile (20 mL) was added potassium carbonate (0.51 g), and the mixture was stirred for 12 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran-ethanol (1:1, 4 mL), 1 M sodium hydroxide (2 mL) was added and the mixture was stirred for 30 min. The reaction mixture was weakly acidified with 1 M hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.15 g, 17%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.2), 1.15-1.32 (1H, m), 1.32-1.49 (3H, m), 1.49-1.64 (3H, m), 1.75 (1H, m), 2.25 (3H, s), 2.54-2.66 (4H, m), 3.16-3.29 (1H, m), 3.37-3.51 (1H, m), 3.81 (1H, d, J = 10.2), 5.31 (2H, s), 7.17 (2H, d, J = 8.4), 7.29 (2H, d, J = 8.4), 7.46-7.62 (2H, m), 7.63-7.75 (2H, m), 12.38 (1H, br)

6-Methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one sodium salt

6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-

yl)biphenyl-4-yl)methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one potassium salt

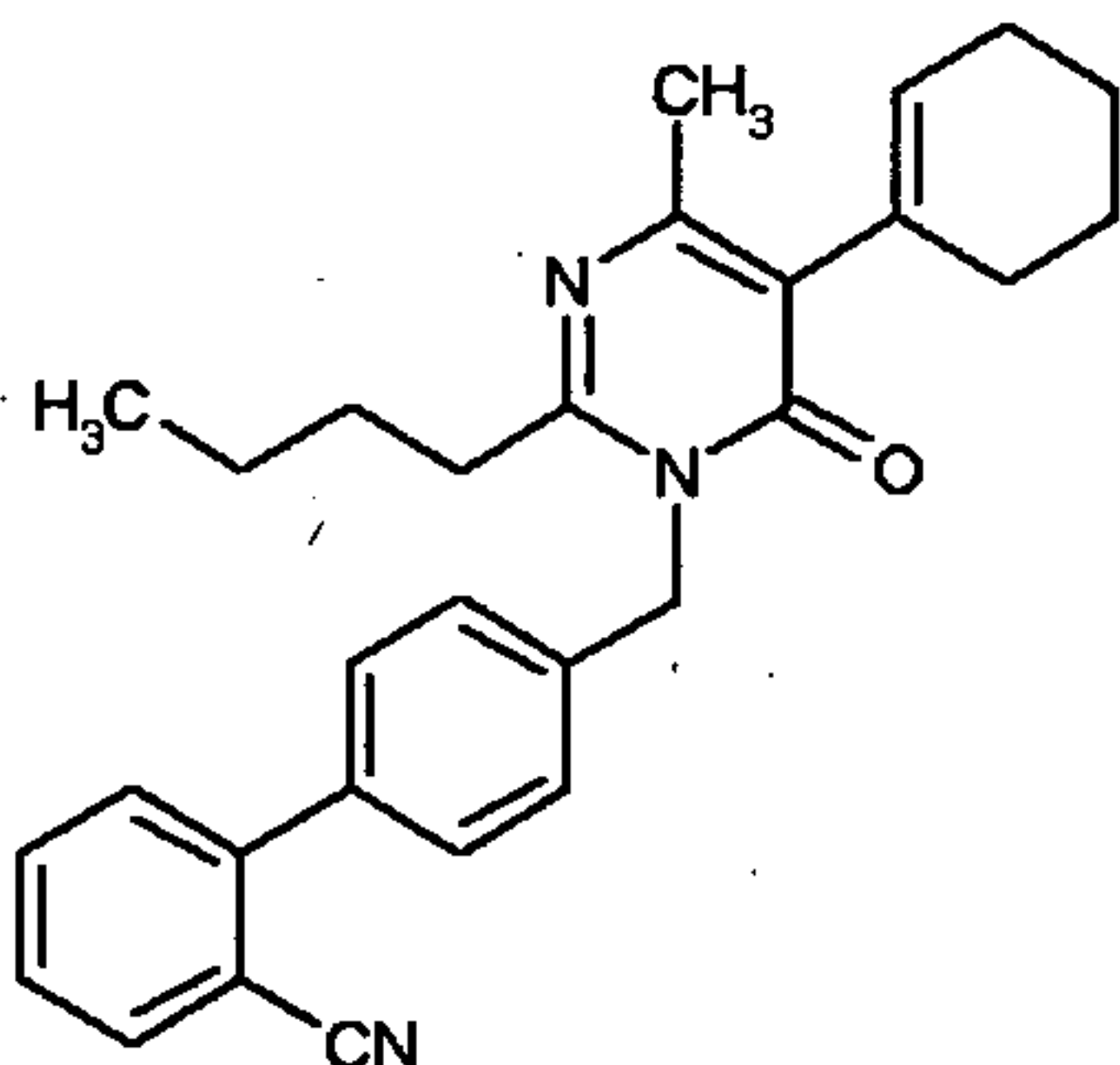
6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one 0.5 calcium salt

6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one hydrochloride

6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one hydrobromide

Example 8

2-butyl-5-cyclohex-1-en-1-yl-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one

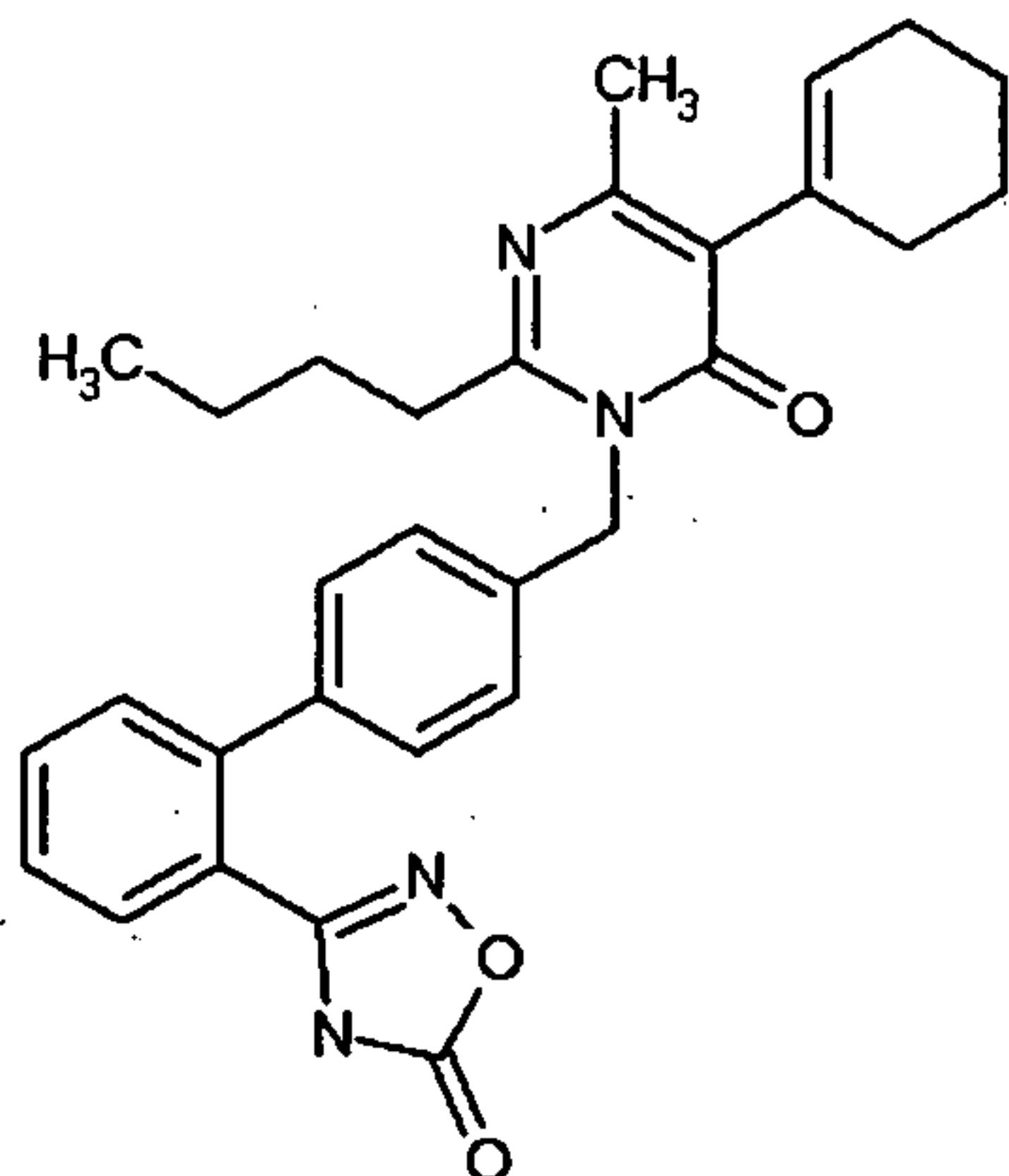


8a) 4'-[(2-butyl-5-cyclohex-1-en-1-yl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.67 g) and 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.48 g) in tetrahydrofuran (40 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.06 g), and the mixture was stirred at 70°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.58 g, 86%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.5), 1.31-1.46 (2H, m), 1.61-1.83 (6H, m), 2.11-2.24 (4H, m), 2.28 (3H, s), 2.67 (2H, t, J = 7.8), 5.33 (2H, s), 5.63 (1H, s), 7.27-7.34 (2H, m), 7.39-7.57 (4H, m), 7.58-7.69 (1H, m), 7.75 (1H, d, J = 7.8)



10 8b) 2-butyl-5-cyclohex-1-en-1-yl-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

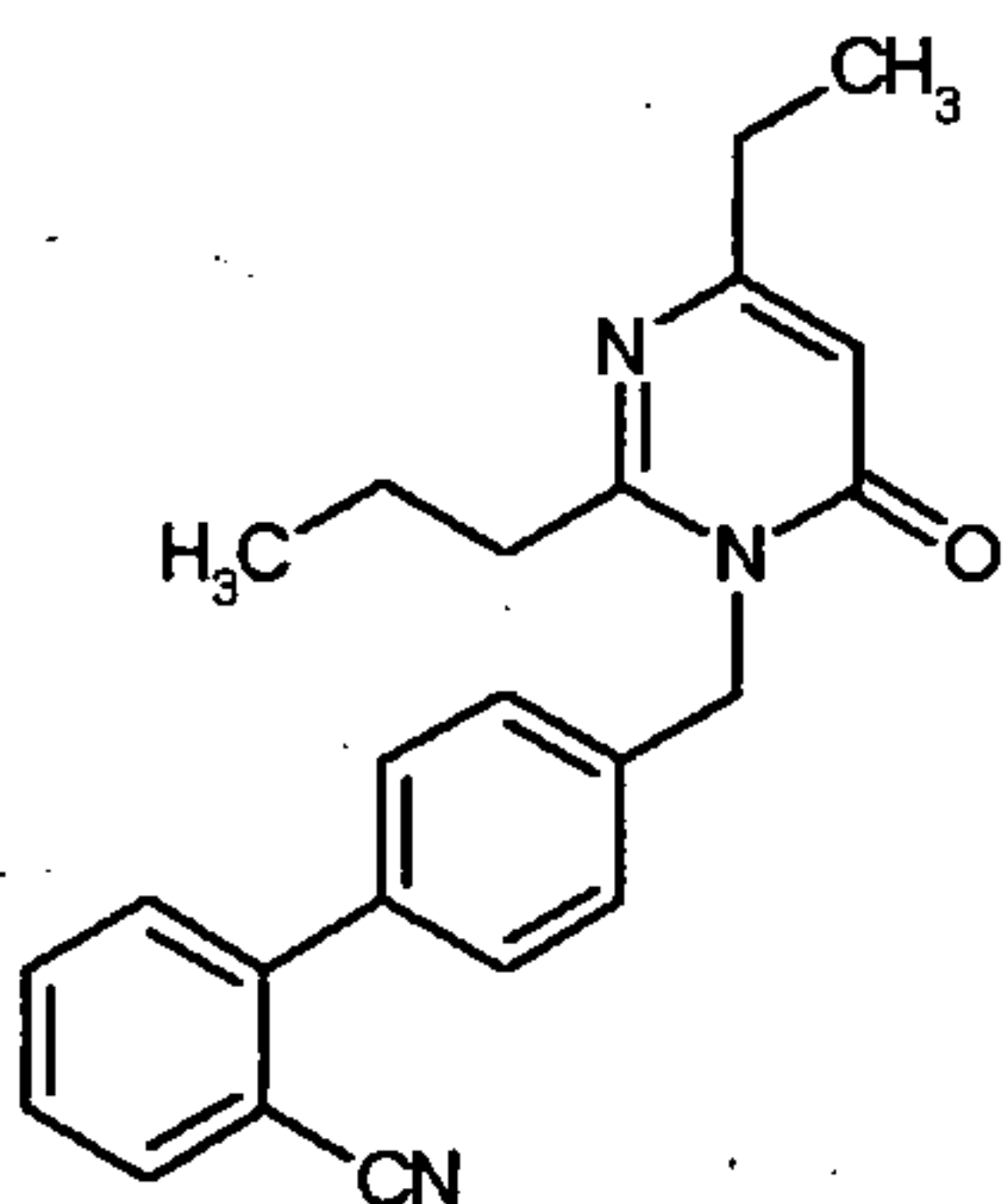
A mixture of hydroxylammonium chloride (0.78 g), sodium hydrogen carbonate (1.11 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-[(2-butyl-5-cyclohex-1-en-1-yl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.58 g) was added, and the mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15 mL), N,N'-carbonyldiimidazole (0.33 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and

dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.33 g, 49%).

- 5 ^1H NMR (300 MHz, DMSO- d_6) δ 0.80 (3H, t, $J = 7.5$), 1.18-1.35 (2H, m), 1.47-1.73 (6H, m), 2.11 (4H, br), 2.18 (3H, s), 2.62 (2H, t, $J = 7.5$), 5.29 (2H, s), 5.53 (1H, s), 7.20 (2H, d, $J = 8.4$), 7.30 (2H, d, $J = 8.4$), 7.47-7.61 (2H, m), 7.63-7.74 (2H, m), 12.41 (1H, br)

10 Example 9

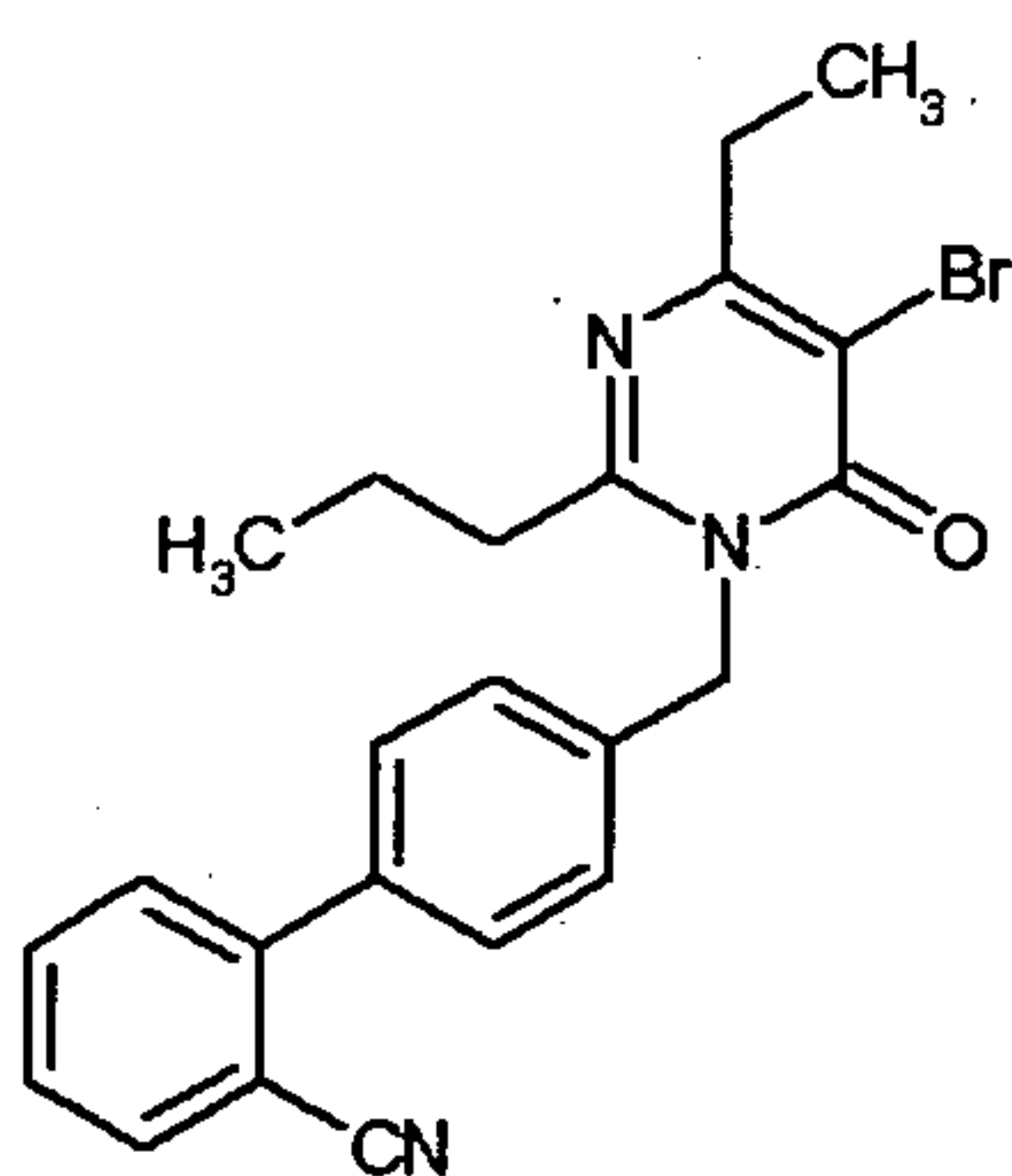
6-ethyl-5-(4-fluorophenyl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one



- 15 9a) 4'-[(4-ethyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 6-ethyl-2-propylpyrimidin-4(3H)-one (5.0 g) and 4'-(bromomethyl)biphenyl-2-carbonitrile (9.0 g) in acetonitrile (150 mL) was added potassium carbonate (8.32 g), and the mixture was stirred at 50°C for 12 hr. The insoluble material was filtered off, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give the title compound (4.95 g, 46%) as a colorless viscous substance.

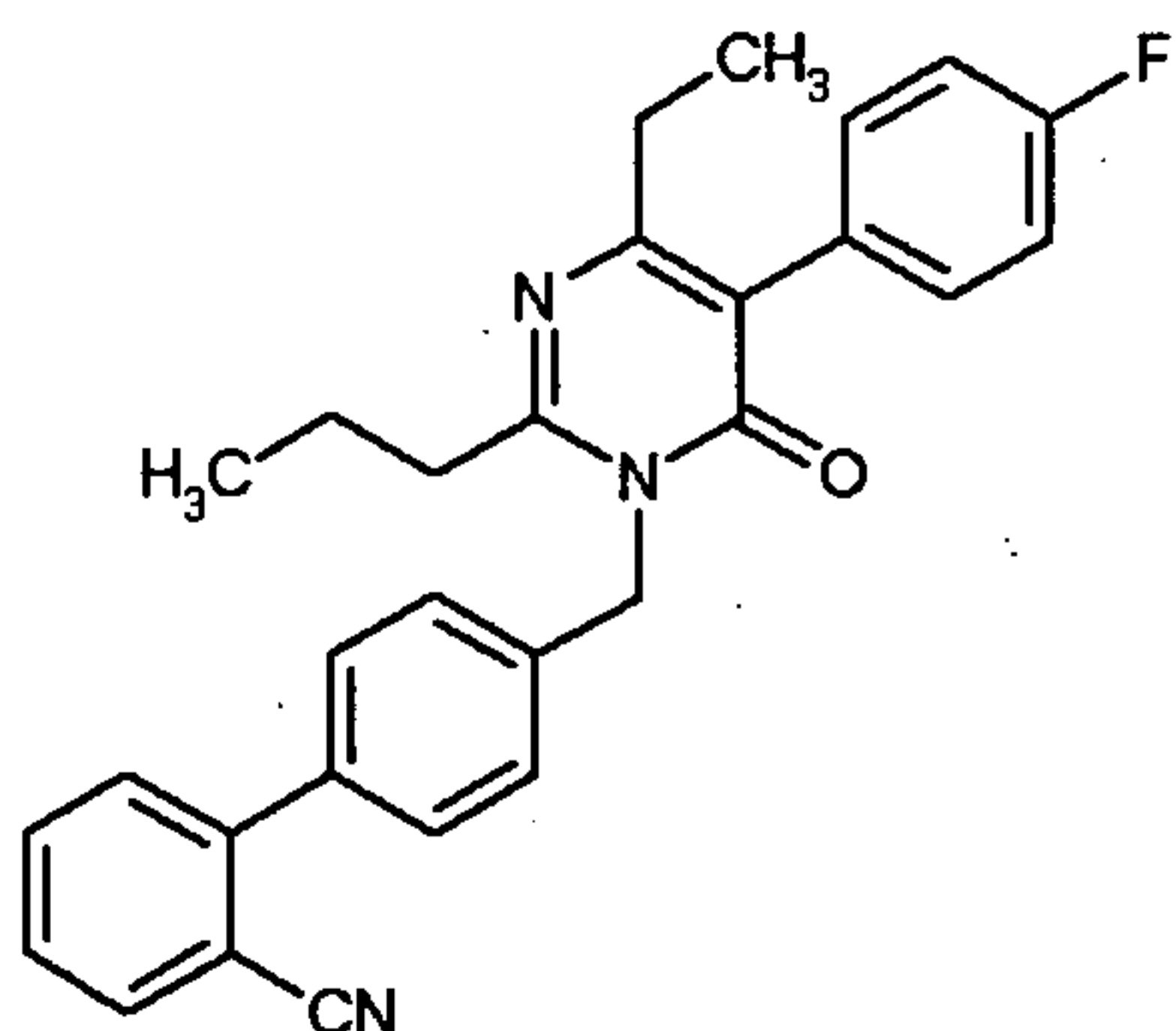
- 25 ^1H NMR (300 MHz, CDCl_3) δ 0.98 (3H, t, $J = 7.5$), 1.25 (3H, t, $J = 7.2$), 1.67-1.83 (2H, m), 2.56 (2H, q, $J = 7.2$), 2.66 (2H, t, $J = 7.5$), 5.36 (2H, br), 6.29 (1H, s), 7.29 (2H, d, $J = 8.1$), 7.40-7.59 (4H, m), 7.60-7.70 (1H, m), 7.76 (1H, d, $J = 7.8$)



9b) 4'-[4-ethyl-5-(4-cyanobiphenyl)-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[4-ethyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (4.95 g) and sodium acetate (1.25 g) in acetic acid (100 mL) was added bromine (0.78 mL), and the mixture was stirred for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (4.3 g, 71%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 0.98 (3H, t, J = 7.2), 1.26 (3H, t, J = 7.2), 1.70-1.83 (2H, m), 2.68 (2H, t, J = 7.2), 2.79 (2H, q, J = 7.2), 5.39 (2H, br), 7.32 (2H, d, J = 8.1), 7.42-7.55 (4H, m), 7.62-7.67 (1H, m), 7.76 (1H, d, J = 7.5)



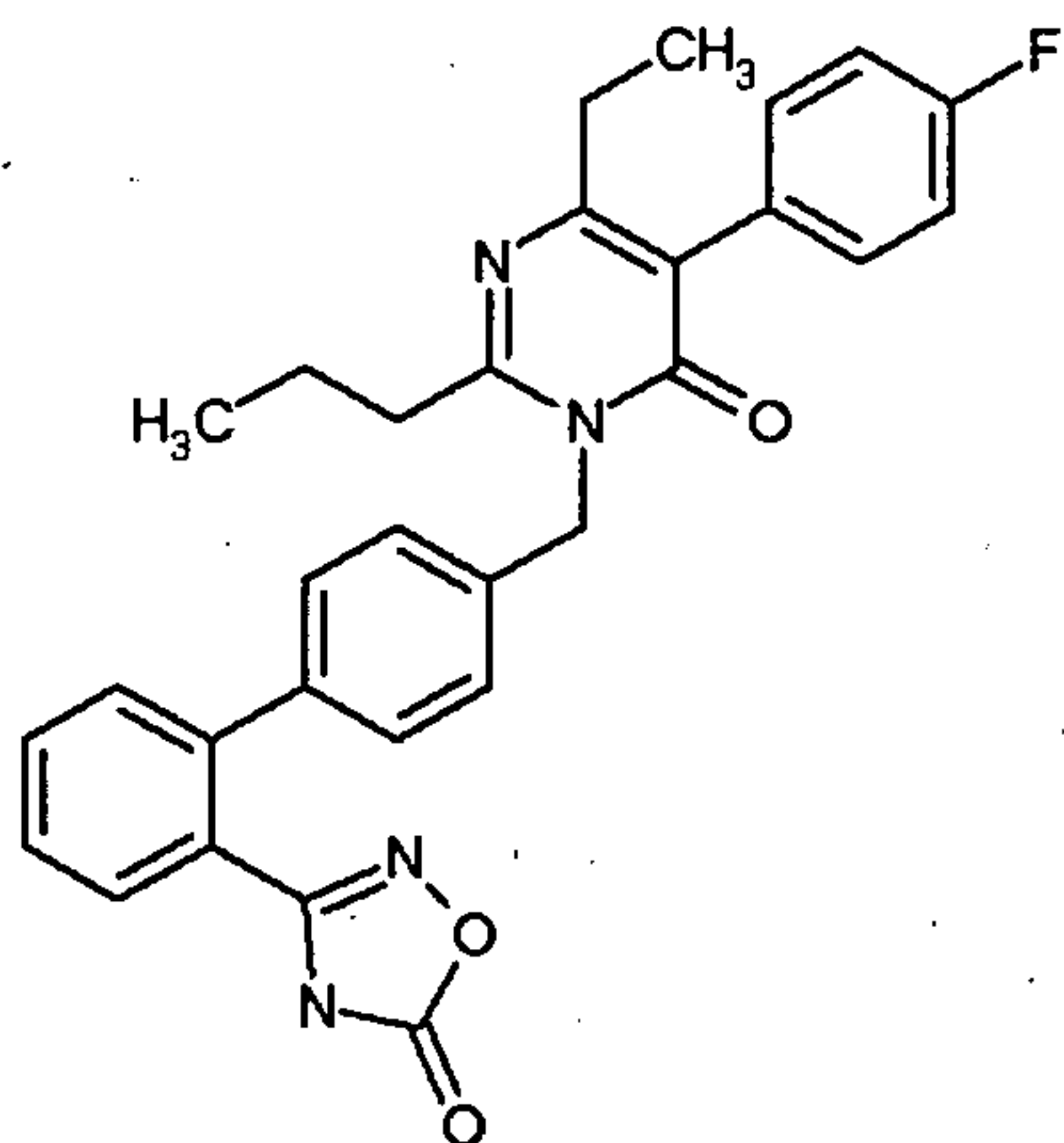
9c) 4'-{[4-ethyl-5-(4-fluorophenyl)-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[4-ethyl-5-(4-fluorophenyl)-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.0 g) and 4-fluorophenylboronic acid (0.48 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium

(0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M

5 hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.94 g, 91%) as a colorless solid.

10 ¹H NMR (300 MHz, CDCl₃) δ 1.02 (3H, t, J = 7.2), 1.18 (3H, t, J = 7.5), 1.73-1.90 (2H, m), 2.45 (2H, q, J = 7.5), 2.74 (2H, t, J = 7.2), 5.37 (2H, s), 7.04-7.16 (2H, m), 7.24-7.39 (4H, m), 7.40-7.57 (4H, m), 7.60-7.69 (1H, m), 7.76 (1H, d, J = 8.1)



15 9d) 6-ethyl-5-(4-fluorophenyl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (2.46 g), sodium hydrogen carbonate (3.5 g) and dimethyl sulfoxide (10 mL) was

20 stirred at 40°C for 30 min, 4'-{[4-ethyl-5-(4-fluorophenyl)-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.94 g) was added, and the mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the precipitate was

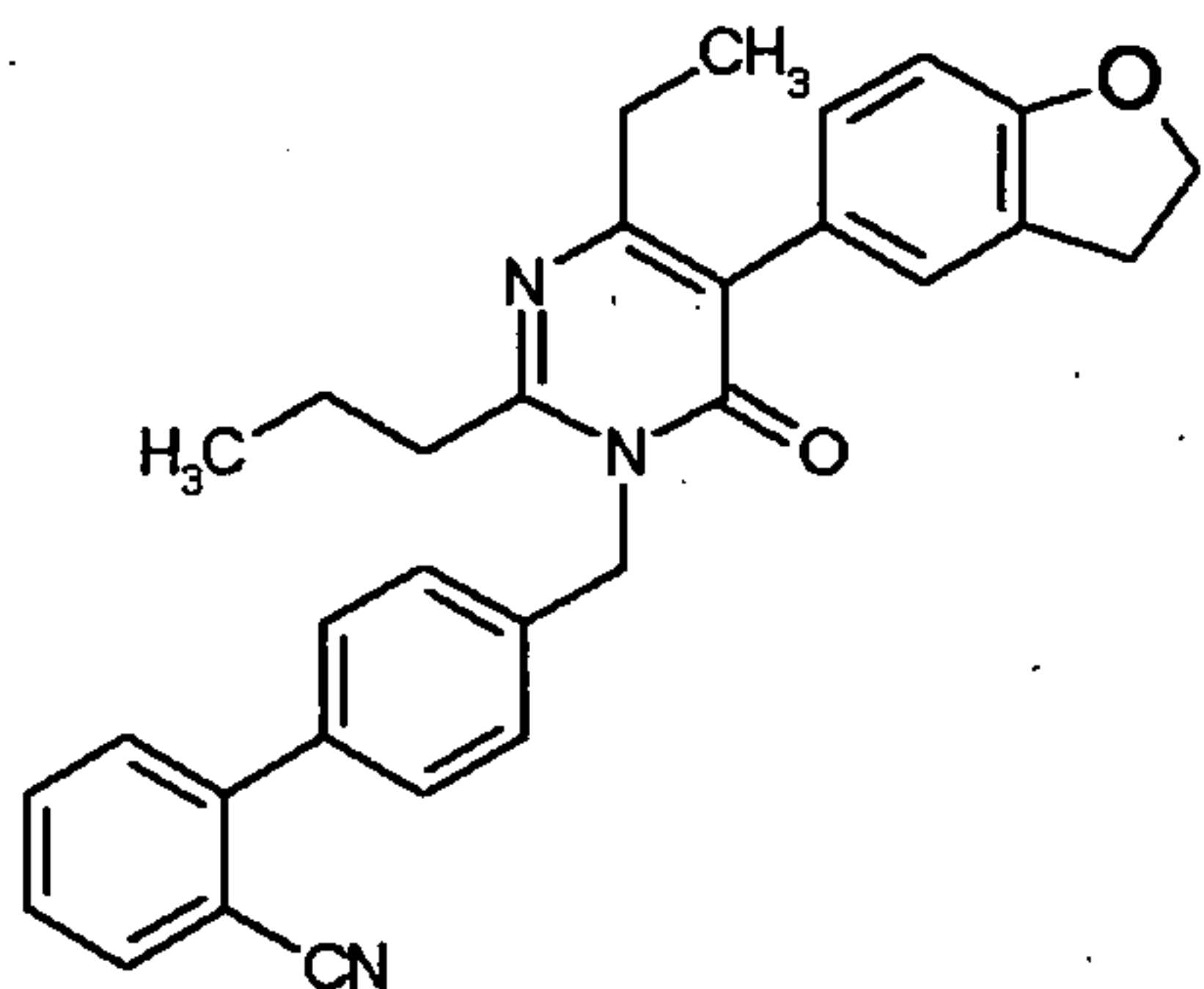
25 collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15

mL), N,N'-carbonyldiimidazole (0.51 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.47 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.77 g, 72%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.90 (3H, t, J = 7.5), 1.10 (3H, t, J = 7.2), 1.57-1.75 (2H, m), 2.34 (2H, q, J = 7.2), 2.69 (2H, t, J = 7.5), 5.35 (2H, s), 7.18-7.40 (8H, m), 7.48-7.62 (2H, m), 7.62-7.76 (2H, m), 12.40 (1H, br)

Example 10

5-(2,3-dihydro-1-benzofuran-5-yl)-6-ethyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one

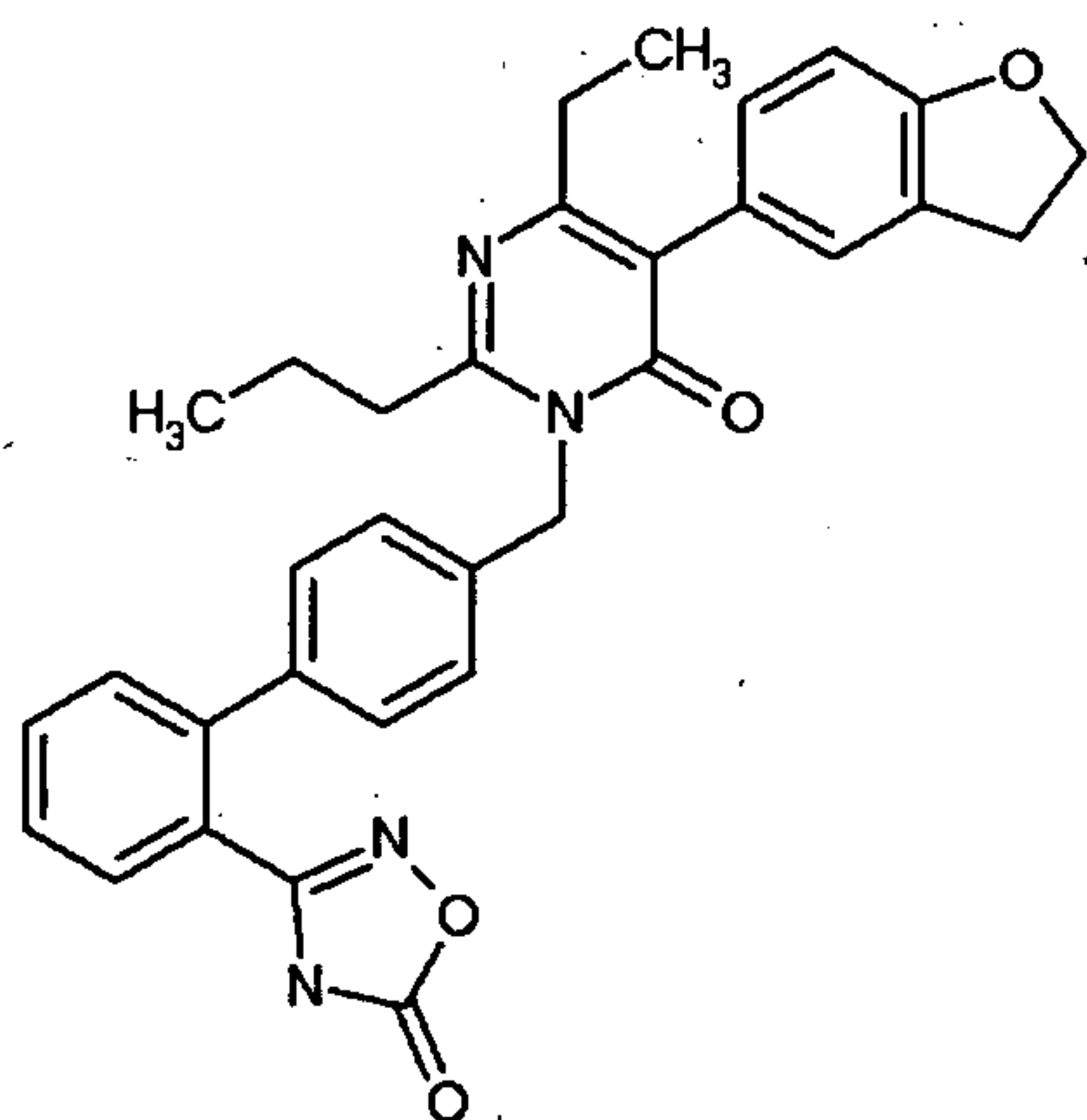


10a) 4'-{[5-(2,3-dihydro-1-benzofuran-5-yl)-4-ethyl-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-4-ethyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.0 g) and 2,3-dihydro-1-benzofuran-5-ylboronic acid (0.56 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.09 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M

hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.95 g, 87%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 1.02 (3H, t, J = 7.2), 1.18 (3H, t, J = 7.2), 1.71-1.91 (2H, m), 2.49 (2H, q, J = 7.2), 2.73 (2H, t, J = 8.1), 3.24 (2H, t, J = 8.4), 4.58 (2H, t, J = 8.4), 5.37 (2H, s), 6.83 (1H, d, J = 8.4), 6.98-7.06 (1H, m), 7.16 (1H, br), 7.35 (2H, d, J = 8.1), 7.41-7.57 (4H, m), 7.60-7.68 (1H, m), 7.76 (1H, d, J = 6.9)



10b) 5-(2,3-dihydro-1-benzofuran-5-yl)-6-ethyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (2.36 g), sodium hydrogen carbonate (3.36 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-{[5-(2,3-dihydro-1-benzofuran-5-yl)-4-ethyl-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.95 g) was added, and the mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15 mL), N,N'-carbonyldiimidazole (0.49 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.46 mL) were added,

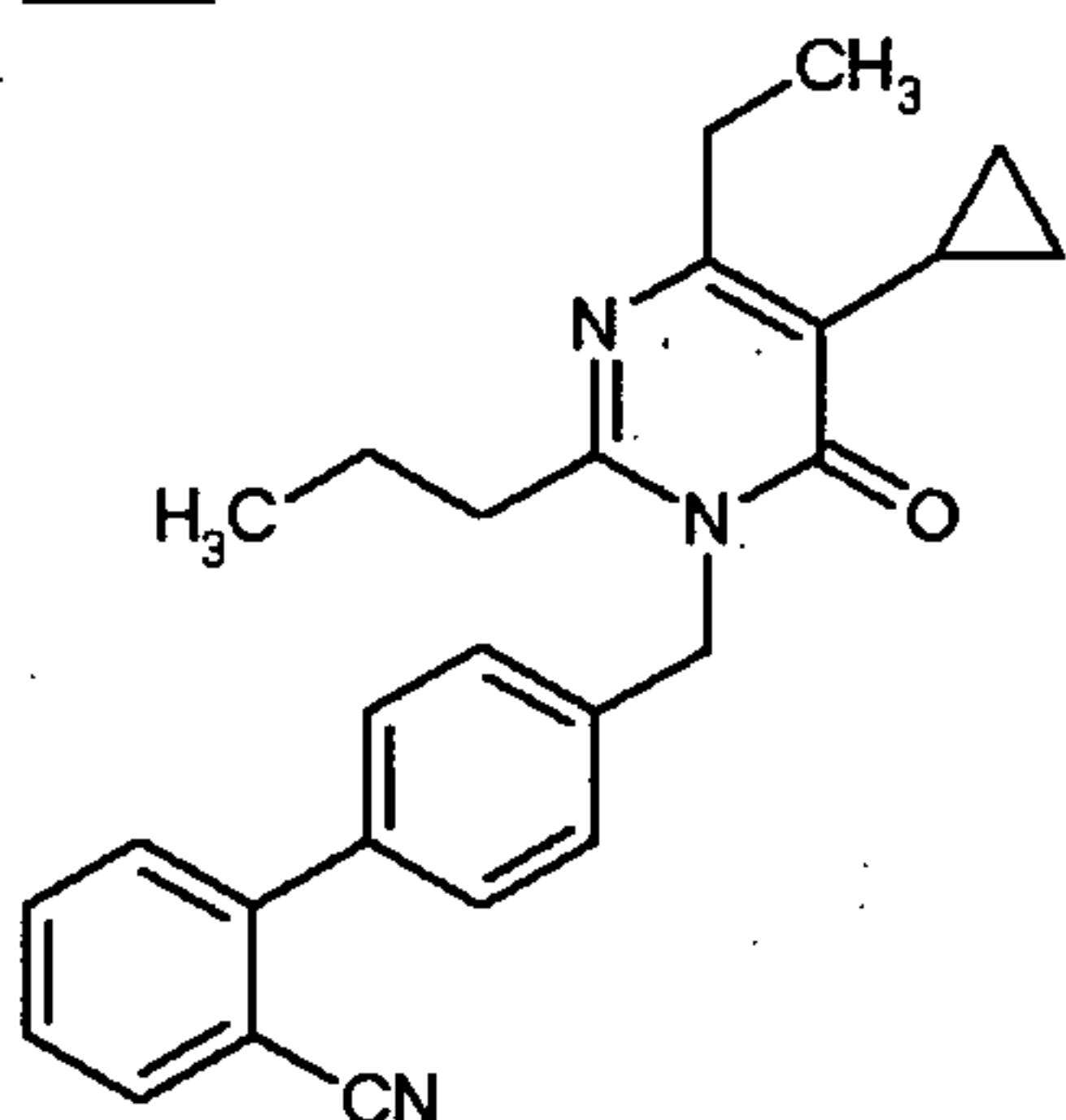
and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was

5 evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.69 g, 65%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.89 (3H, t, J = 7.5), 1.10 (3H, t, J = 7.5), 1.58-1.73 (2H, m), 2.36 (2H, q, J = 7.5), 2.68 (2H, t, J = 7.5), 3.20 (2H, t, J = 8.1), 4.55 (2H, t, J = 8.1), 5.33 (2H, s), 6.79 (1H, d, J = 8.1), 6.98 (1H, d, J = 8.1), 7.12 (1H, s), 7.21-7.35 (4H, m), 7.46-7.61 (2H, m), 7.62-7.76 (2H, m), 12.40 (1H, s)

Example 11

15 5-cyclopropyl-6-ethyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one

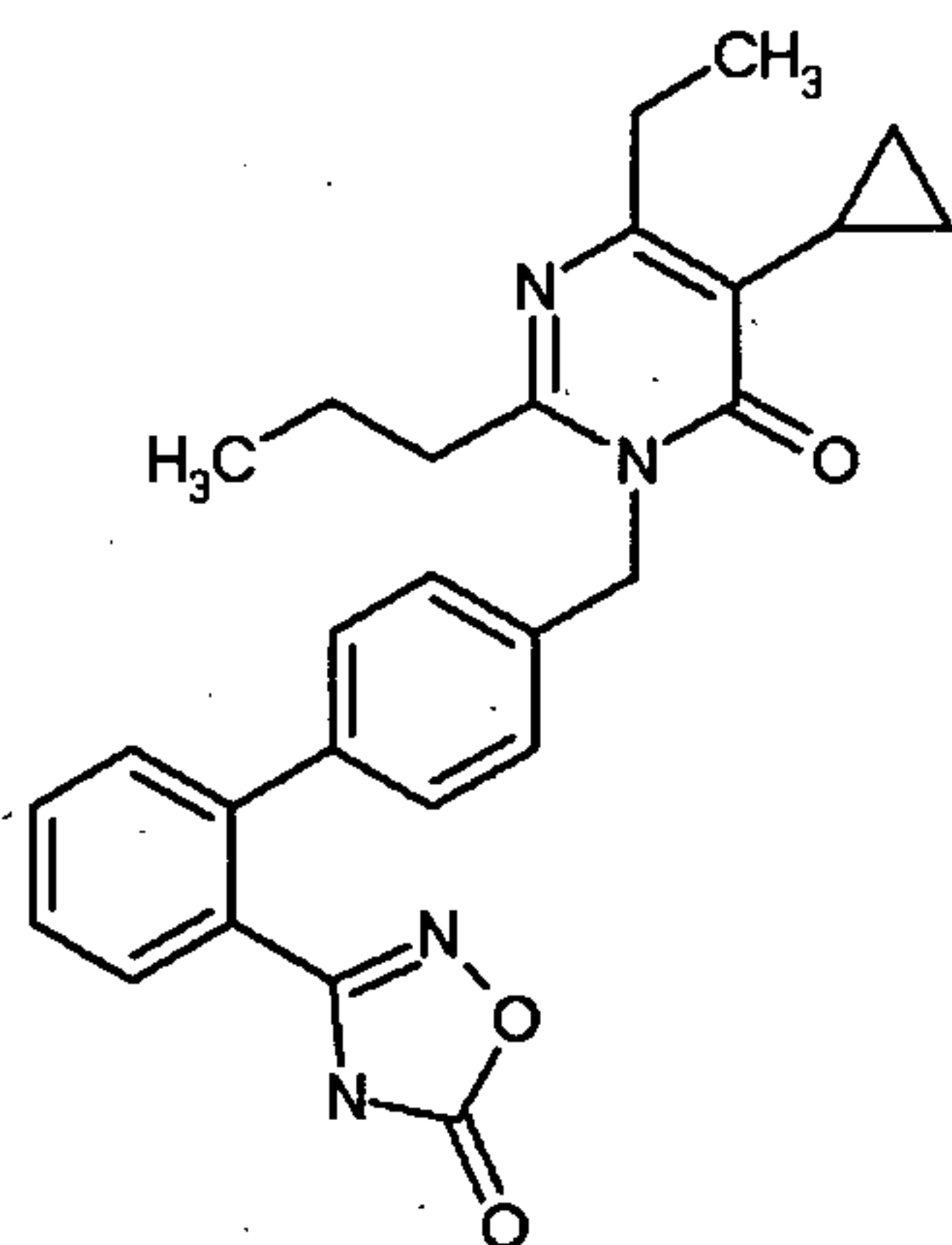


11a) 4'-[(5-cyclopropyl-4-ethyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-4-ethyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.0 g), cyclopropylboronic acid (0.26 g), potassium phosphate (1.7 g) and tricyclohexylphosphine (0.064 g) in toluene-water (20:1, 25 21 mL) was added palladium acetate (0.026 g), and the mixture was stirred at 100°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, 30 saturated aqueous sodium hydrogen carbonate and saturated

brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.79 g, 87%) as a colorless solid.

- 5 ¹H NMR (300 MHz, CDCl₃) δ 0.77-0.86 (2H, m), 0.89-1.04 (5H, m), 1.26 (3H, t, J = 7.2), 1.50-1.60 (1H, m), 1.65-1.82 (2H, m), 2.64 (2H, q, J = 7.2), 2.79 (2H, t, J = 7.2), 5.30 (2H, s), 7.27-7.37 (2H, m), 7.39-7.57 (4H, m), 7.59-7.69 (1H, m), 7.76 (1H, d, J = 7.8)



10

11b) 5-cyclopropyl-6-ethyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-2-propylpyrimidin-4(3H)-one

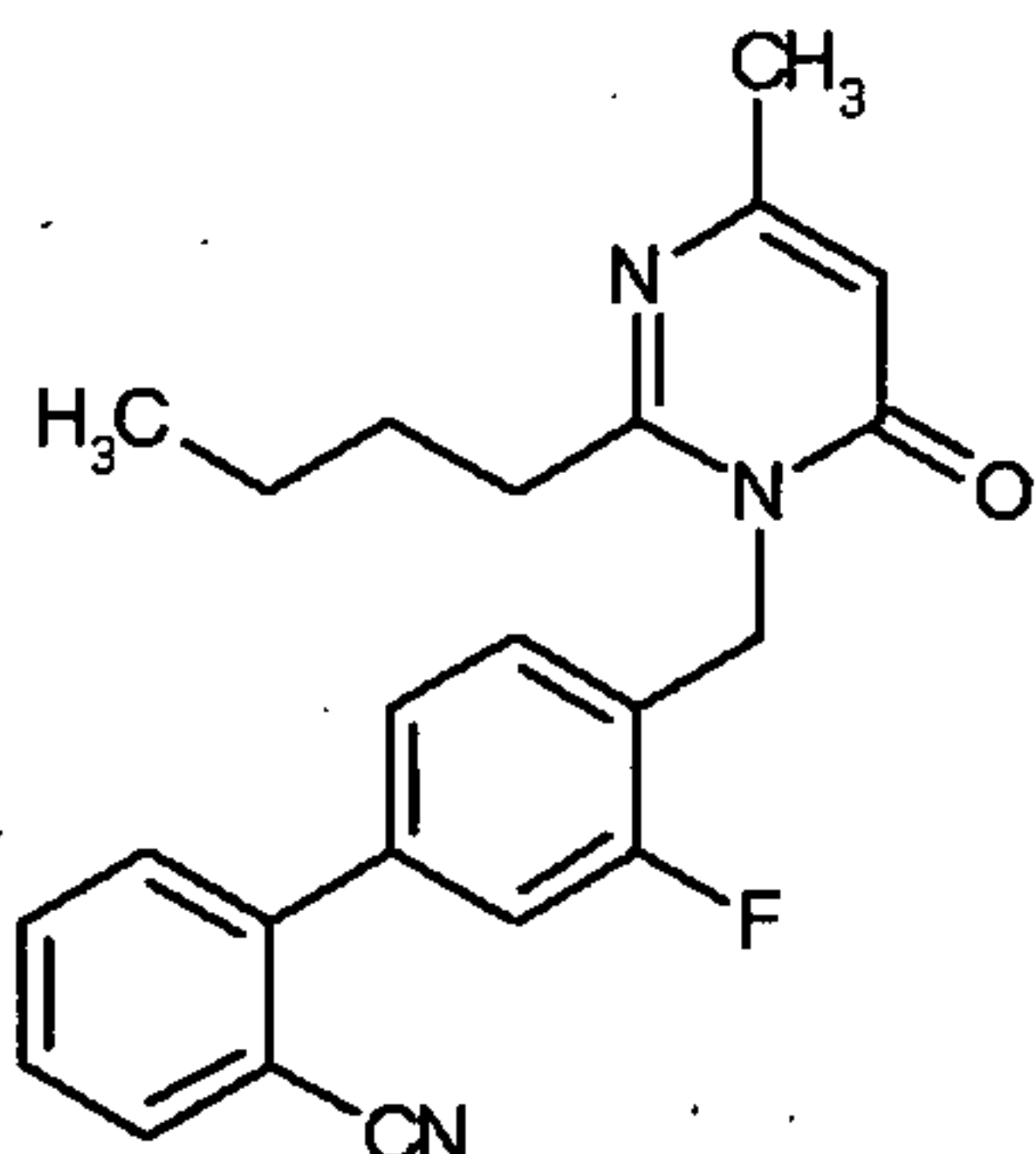
A mixture of hydroxylammonium chloride (2.35 g), sodium
 15 hydrogen carbonate (3.34 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-[(5-cyclopropyl-4-ethyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.79 g) was added, and the mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature, water was
 20 added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15
 25 mL), N,N'-carbonyldiimidazole (0.48 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.45 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1

M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.38 g, 42%).

^1H NMR (300 MHz, DMSO- d_6) δ 0.77-0.91 (7H, m), 1.18 (3H, t, J = 7.2), 1.51-1.66 (3H, m), 2.55 (2H, t, J = 7.2), 2.69 (2H, q, J = 7.5), 5.26 (2H, s), 7.17 (2H, d, J = 7.8), 7.29 (2H, d, J = 7.8), 7.49-7.60 (2H, m), 7.63-7.74 (2H, m), 12.39 (1H, br)

10 Example 12

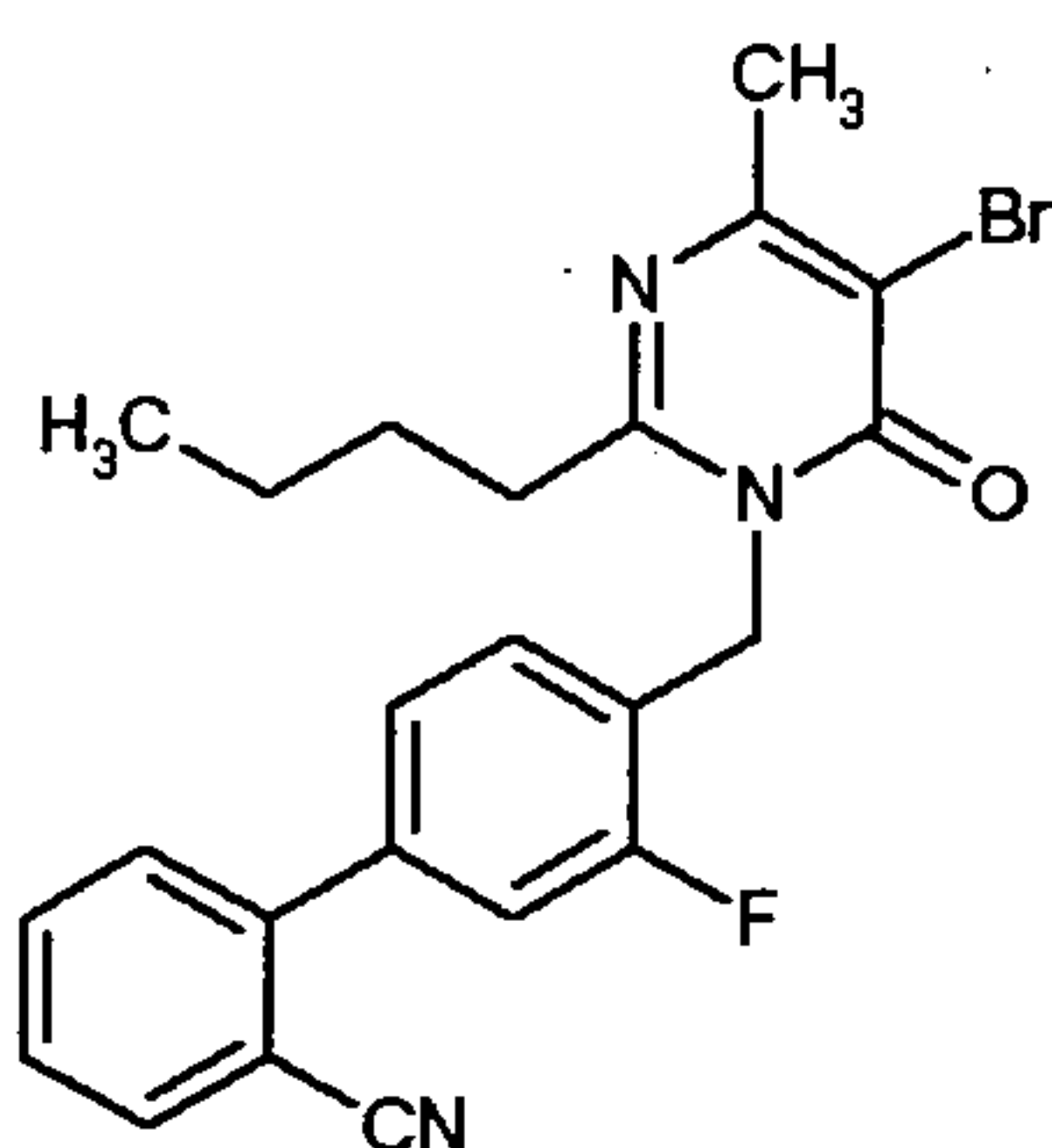
2-butyl-3-{[3-fluoro-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-5-(4-fluorophenyl)-6-methylpyrimidin-4(3H)-one



15 12a) 4'-[(2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]-3'-fluorobiphenyl-2-carbonitrile

To a solution of 2-butyl-6-methylpyrimidin-4(3H)-one (2.24 g) and 4'-(bromomethyl)-3'-fluorobiphenyl-2-carbonitrile (4.3 g) in acetonitrile (30 mL) was added potassium carbonate (3.72 g), and the mixture was stirred at 50°C for 12 hr. The insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the title compound (1.48 g, 29%) as a colorless viscous substance.

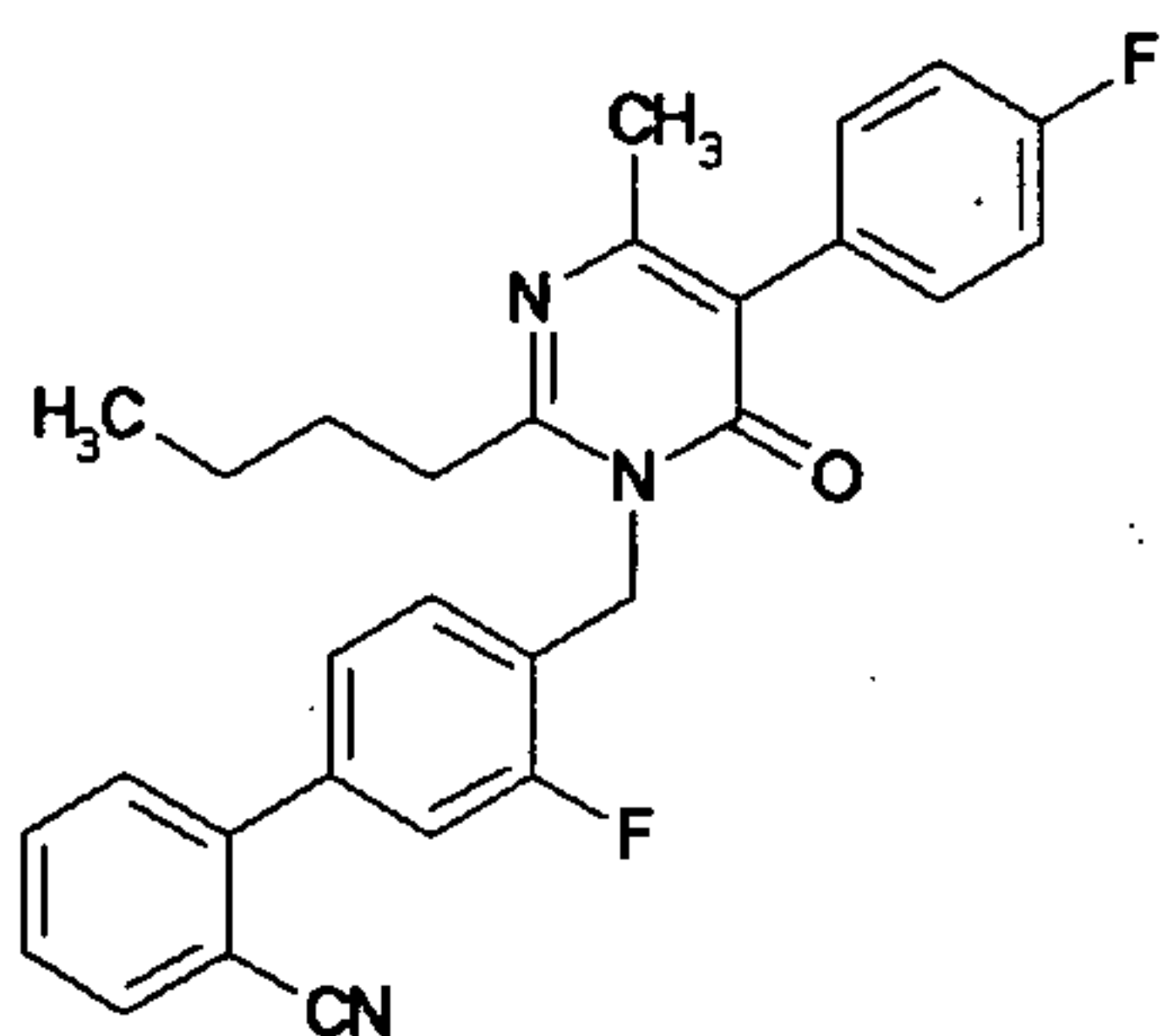
^1H NMR (300 MHz, CDCl_3) δ 0.91 (3H, t, J = 7.2), 1.31-1.47 (2H, m), 1.63-1.76 (2H, m), 2.29 (3H, s), 2.68 (2H, t, J = 7.2), 5.39 (2H, s), 6.29 (1H, s), 7.08-7.19 (1H, m), 7.24-7.35 (2H, m), 7.42-7.52 (2H, m), 7.60-7.71 (1H, m), 7.77 (1H, d, J = 8.1)



12b) 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]-3'-fluorobiphenyl-2-carbonitrile

To a solution of 4'-[(2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]-3'-fluorobiphenyl-2-carbonitrile (1.48 g) and sodium acetate (0.36 g) in acetic acid (20 mL) was added bromine (0.22 mL), and the mixture was stirred for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (1.07 g, 60%) as a colorless solid.

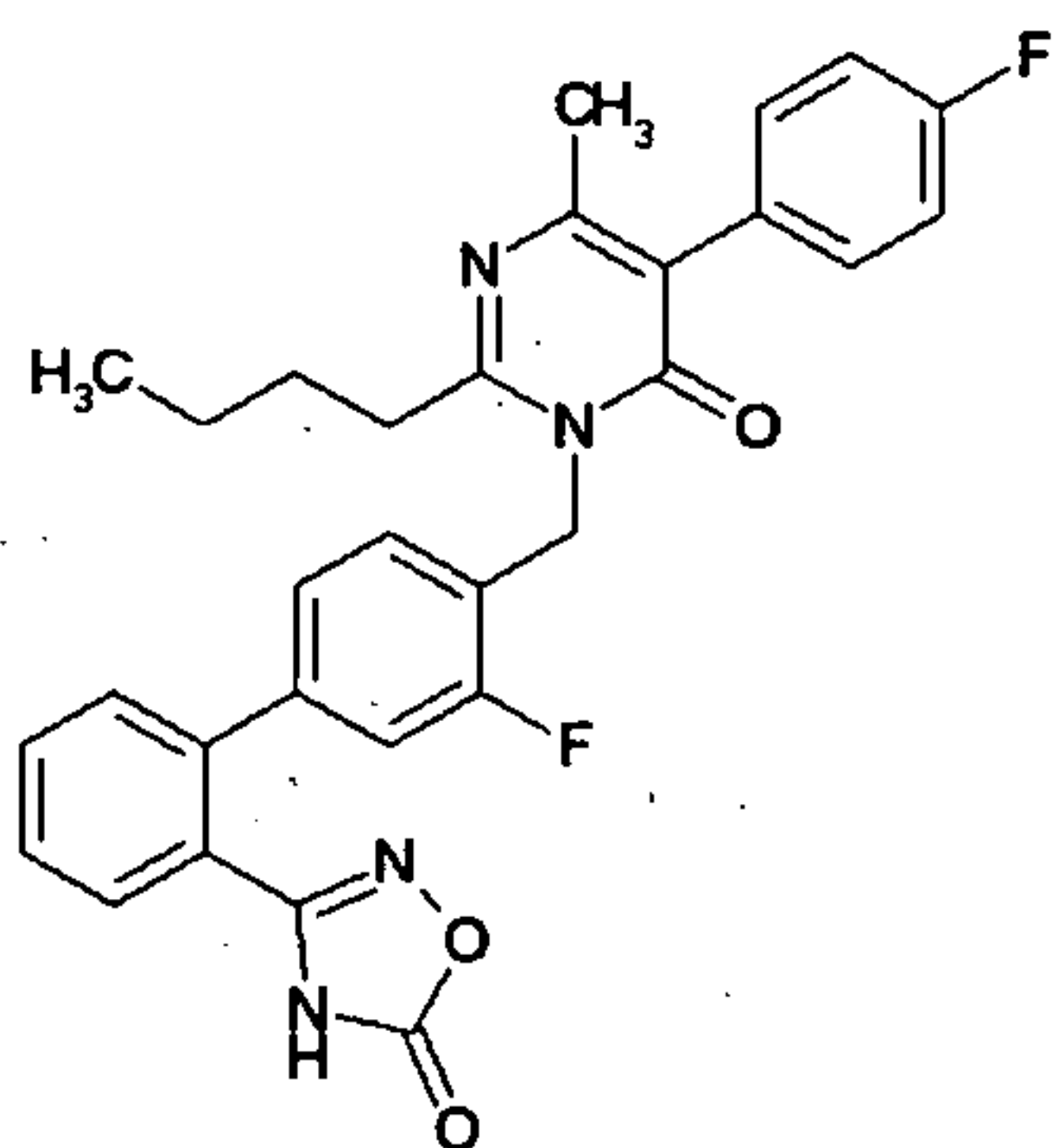
¹H NMR (300 MHz, CDCl₃) δ 0.92 (3H, t, J = 7.2), 1.32-1.48 (2H, m), 1.63-1.76 (2H, m), 2.50 (3H, s), 2.69 (2H, t, J = 7.2), 5.42 (2H, s), 7.15-7.36 (3H, m), 7.48 (2H, t, J = 7.5), 7.60 - 7.71 (1H, m), 7.77 (1H, d, J = 8.1)



12c) 4'-{[2-butyl-5-(4-fluorophenyl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-3'-fluorobiphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]-3'-fluorobiphenyl-2-carbonitrile (0.5 g) and 4-fluorophenylboronic acid (0.23 g) in 1,4-dioxane (10 mL) were added 2 M aqueous cesium carbonate solution (2 mL) and [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium (0.05 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through
 5 celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to
 10 give the title compound (0.51 g, 98%) as a colorless solid.
¹H NMR (300 MHz, CDCl₃) δ 0.94 (3H, t, J = 7.2), 1.37-1.51 (2H, m), 1.67-1.81 (2H, m), 2.23 (3H, s), 2.74 (2H, t, J = 7.8), 5.41 (2H, s), 7.06-7.16 (2H, m), 7.21-7.36 (5H, m), 7.43-7.53 (2H, m), 7.61-7.71 (1H, m), 7.77 (1H, d, J = 6.9)



15

12d) 2-butyl-3-([3-fluoro-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-5-(4-fluorophenyl)-6-methylpyrimidin-4(3H)-one

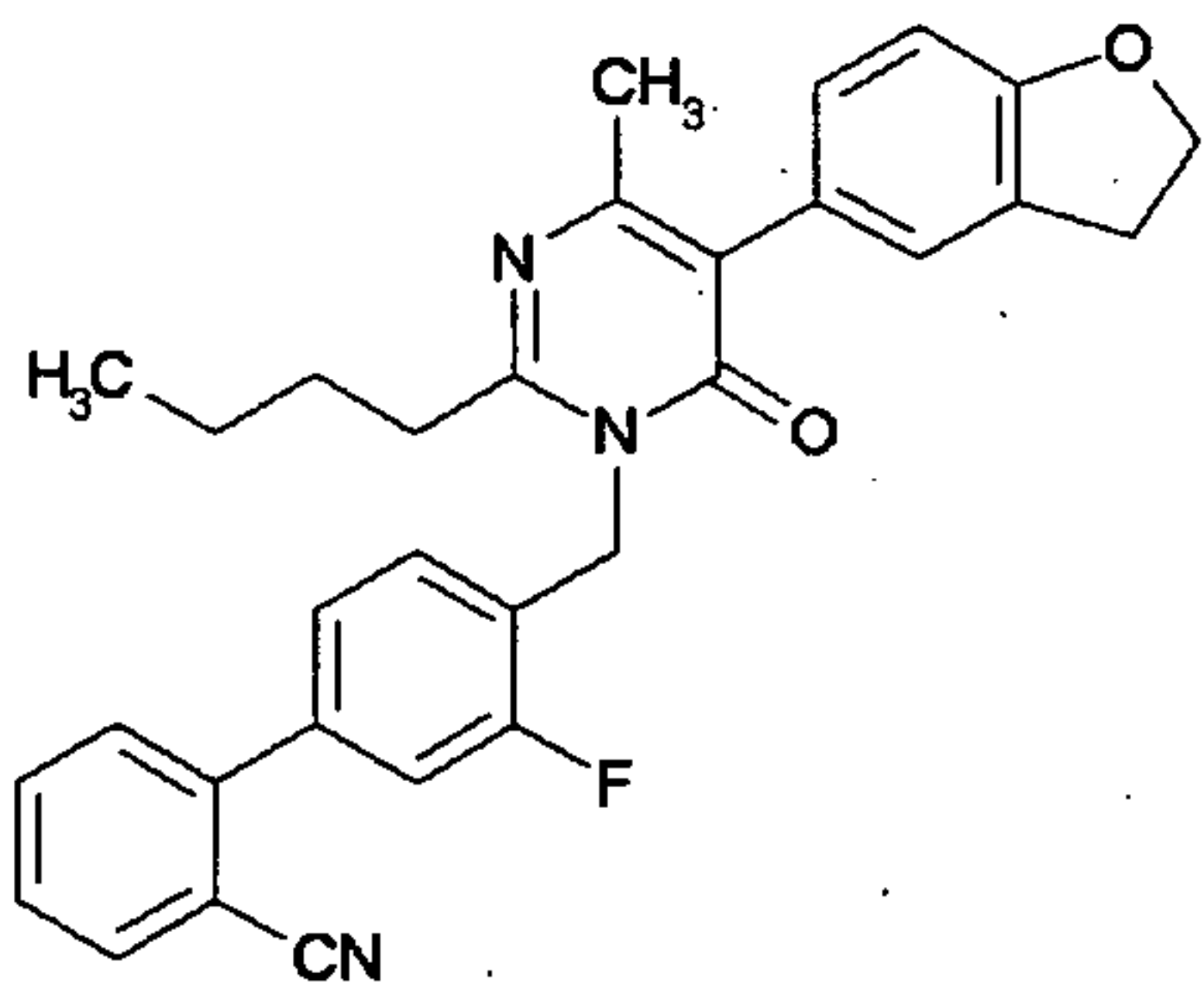
A mixture of hydroxylammonium chloride (1.02 g), sodium
 20 hydrogen carbonate (1.45 g) and dimethyl sulfoxide (5 mL) was stirred at 40°C for 30 min, 4'-{[2-butyl-5-(4-fluorophenyl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-3'-fluorobiphenyl-2-carbonitrile (0.51 g) was added, and the mixture was stirred
 at 90°C for 16 hr. The mixture was allowed to cool to room
 25 temperature, water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in

tetrahydrofuran (15 mL), N,N'-carbonyldiimidazole (0.26 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.24 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed
 5 with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.41 g, 73%).

10 ¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.5), 1.24-1.41 (2H, m), 1.52-1.70 (2H, m), 2.13 (3H, s), 2.71 (2H, t, J = 7.5), 5.36 (2H, s), 6.96-7.14 (2H, m), 7.18-7.29 (3H, m), 7.30-7.39 (2H, m), 7.50-7.64 (2H, m), 7.65-7.75 (2H, m), 12.49 (1H, br)

15 Example 13

2-butyl-5-(2,3-dihydro-1-benzofuran-5-yl)-3-{[3-fluoro-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-methylpyrimidin-4(3H)-one



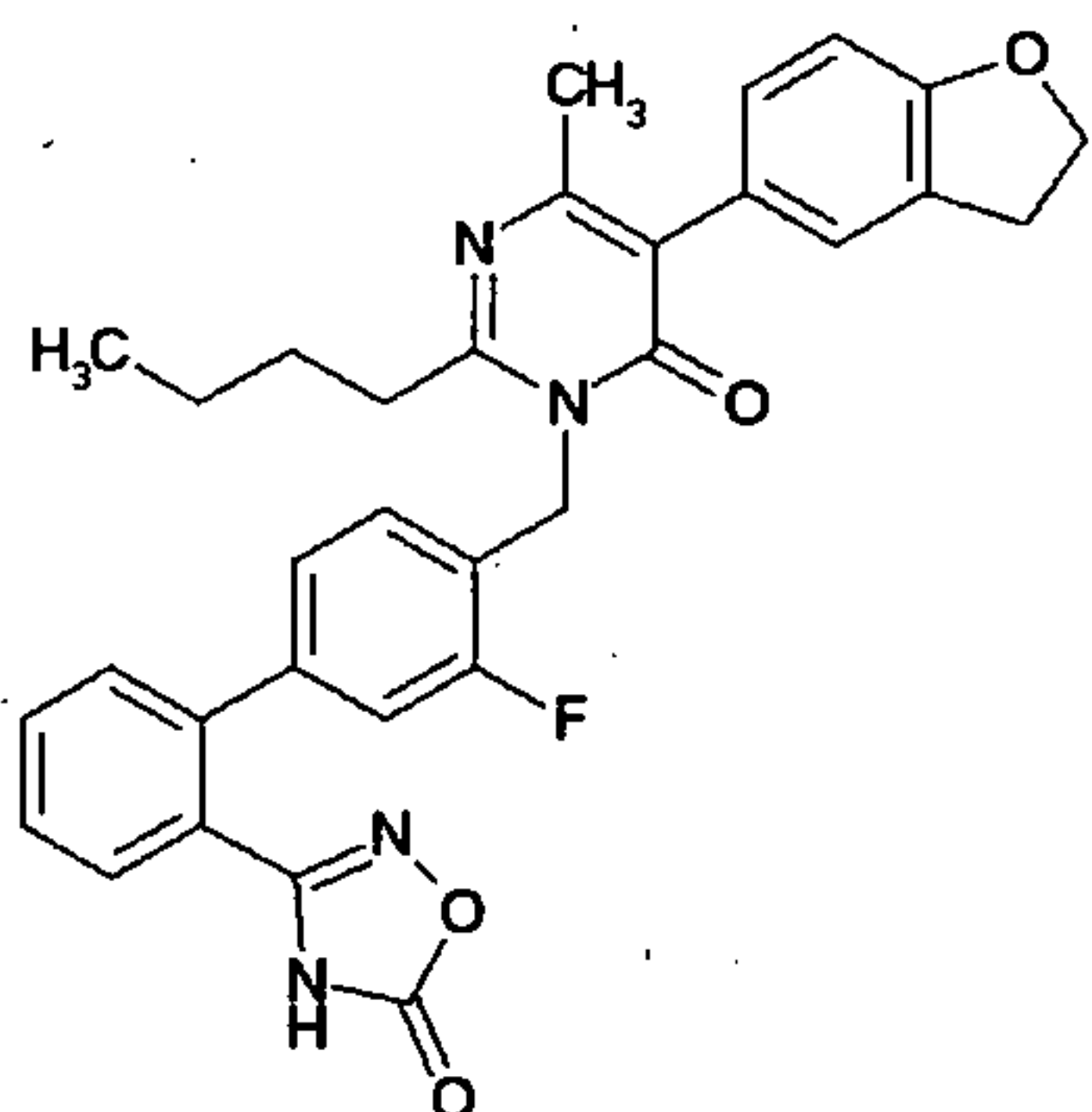
20 13a) 4'-{[2-butyl-5-(2,3-dihydro-1-benzofuran-5-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-3'-fluorobiphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]-3'-fluorobiphenyl-2-carbonitrile
 25 (0.5 g) and 2,3-dihydro-1-benzofuran-5-ylboronic acid (0.27 g) in 1,4-dioxane (10 mL) were added 2 M aqueous cesium carbonate solution (2 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.05 g), and the mixture was stirred at 90°C for 12 hr under an argon
 30 atmosphere. The reaction mixture was diluted with ethyl

acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate.

5. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.43 g, 79%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 0.94 (3H, t, J = 7.2), 1.35-1.51 (2H, m), 1.66-1.82 (2H, m), 2.25 (3H, s), 2.73 (2H, t, J = 8.1),
 10 3.25 (2H, t, J = 8.7), 4.59 (2H, t, J = 8.7), 5.41 (2H, s), 6.83 (1H, d, J = 8.1), 7.05 (1H, d, J = 8.4), 7.19 (1H, s), 7.24-7.36 (3H, m), 7.43-7.53 (2H, m), 7.61-7.71 (1H, m), 7.77 (1H, d, J = 7.2)



- 15 13b) 2-butyl-5-(2,3-dihydro-1-benzofuran-5-yl)-3-([3-fluoro-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-methylpyrimidin-4(3H)-one

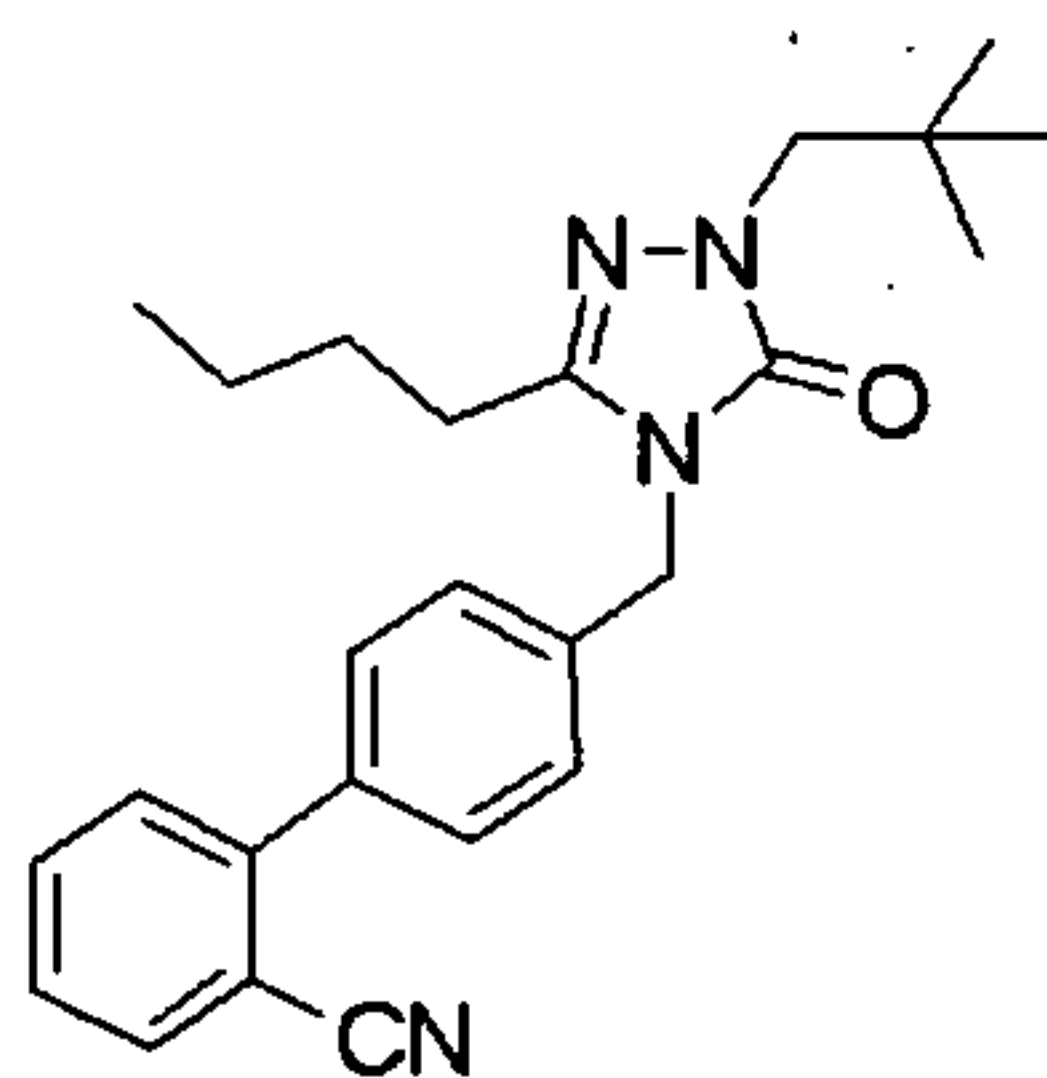
A mixture of hydroxylammonium chloride (1.02 g), sodium hydrogen carbonate (1.45 g) and dimethyl sulfoxide (5 mL) was
 20 stirred at 40°C for 30 min, 4'-{[2-butyl-5-(2,3-dihydro-1-benzofuran-5-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-3'-fluorobiphenyl-2-carbonitrile (0.43 g) was added, and the mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature, water was added to the reaction
 25 mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (5 mL), N,N'-

carbonyldiimidazole (0.21 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.19 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.38 g, 84%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.5), 1.24-1.40 (2H, m), 1.53-1.70 (2H, m), 2.13 (3H, s), 2.70 (2H, t, J = 7.5), 3.19 (2H, t, J = 8.7), 4.55 (2H, t, J = 8.7), 5.34 (2H, s), 6.78 (1H, d, J = 8.4), 6.94-7.17 (4H, m), 7.19-7.29 (1H, m), 7.50-7.64 (2H, m), 7.65-7.75 (2H, m), 12.49 (1H, br)

Example 14

3-(4'-{[3-butyl-1-(2,2-dimethylpropyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one

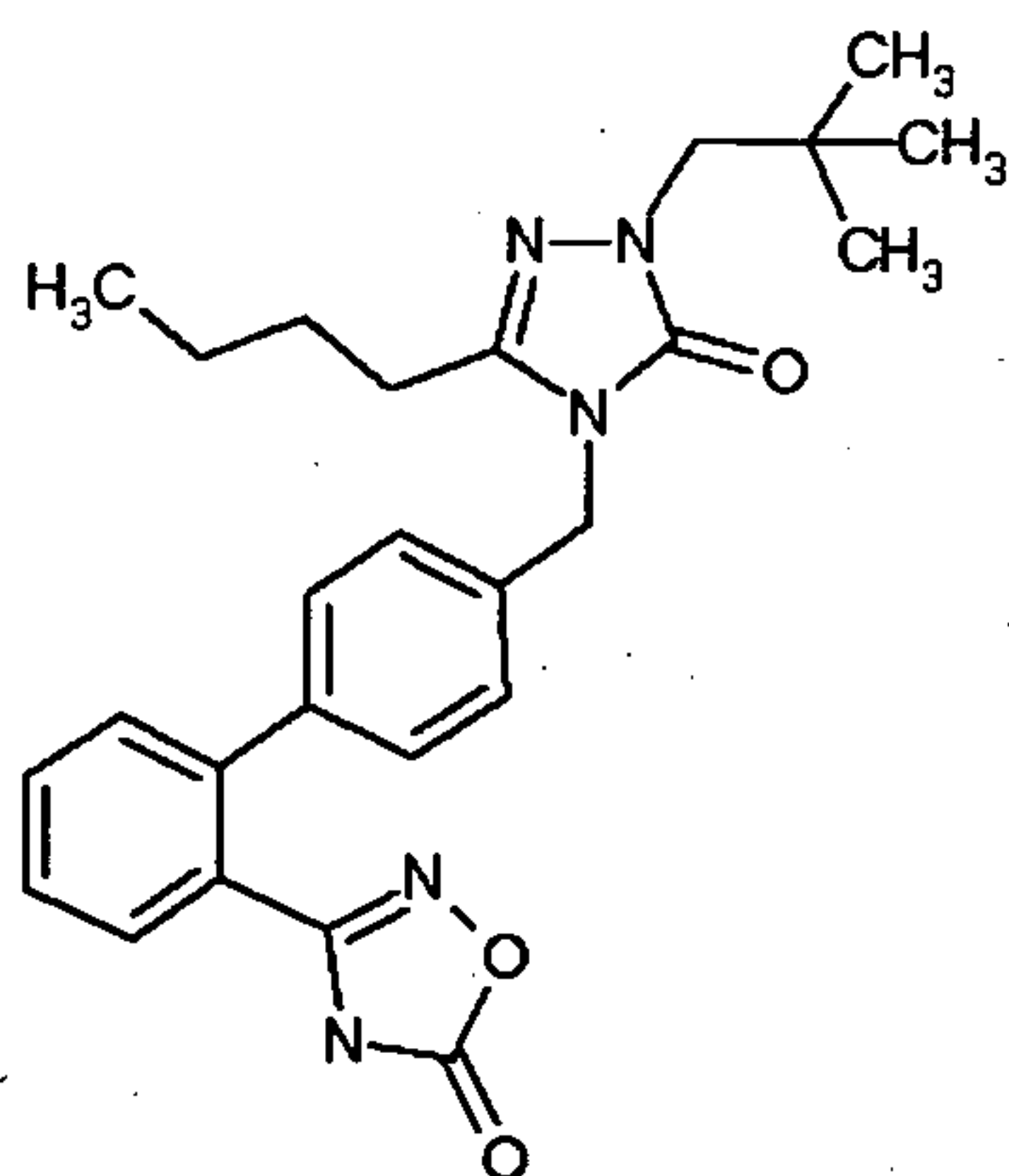


14a) 4'-{[3-butyl-1-(2,2-dimethylpropyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-{[3-butyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-carbonitrile (1 g), sodium hydride (0.24 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-iodo-2,2-dimethylpropane (2 mL) was added, and the mixture was stirred at 40°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and

the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.6 g, 50%).

¹H NMR (300 MHz, CDCl₃) δ 0.88 (3H, t, J = 7.3), 1.01 (9H, s), 1.35 (2H, dq, J = 7.5, 7.3), 1.52-1.65 (2H, m), 2.39-2.46 (2H, m), 3.61 (2H, s), 4.90 (2H, s), 7.35 (2H, d, J = 8.5), 7.42-7.57 (4H, m), 7.65 (1H, dt, J = 7.7, 1.3), 7.77 (1H, dd, J = 7.6, 0.8)



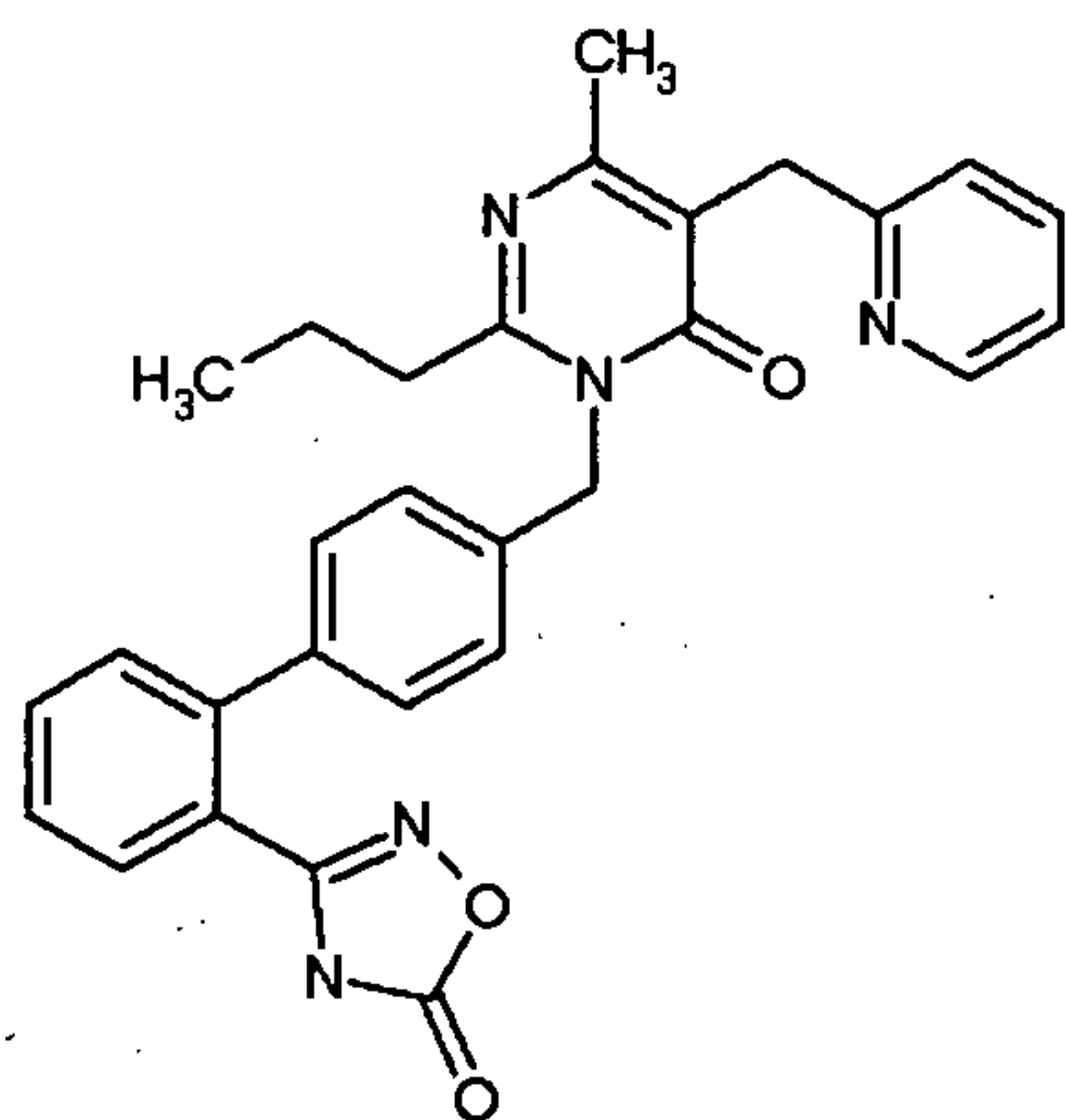
14b) 3-(4'-{[3-butyl-1-(2,2-dimethylpropyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one

A mixture of hydroxylammonium chloride (1.24 g), sodium hydrogen carbonate (1.88 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[3-butyl-1-(2,2-dimethylpropyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-carbonitrile (0.6 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.29 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.25 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the

residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.46 g, 72%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.80 (3H, t, J = 7.3), 0.93 (9H, s), 1.17-1.33 (2H, m), 1.37-1.54 (2H, m), 2.43 (2H, t, J = 7.4), 3.48 (2H, s), 4.88 (2H, s), 7.20-7.36 (4H, m), 7.47-7.61 (2H, m), 7.64-7.76 (2H, m), 12.40 (1H, s)

Example 15



6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propyl-5-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one

To a solution of 6-methyl-2-propyl-5-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one (0.51 g) and 3-[4'-(bromomethyl)biphenyl-2-yl]-5-(trichloromethyl)-1,2,4-oxadiazole (1.0 g) in acetonitrile (20 mL) was added potassium carbonate (0.58 g), and the mixture was stirred for 12 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran-ethanol (1:1, 4 mL), 1 M sodium hydroxide (2 mL) was added and the mixture was stirred for 30 min. The reaction mixture was weakly acidified with 1 M hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.043 g, 4%) as a pale-yellow

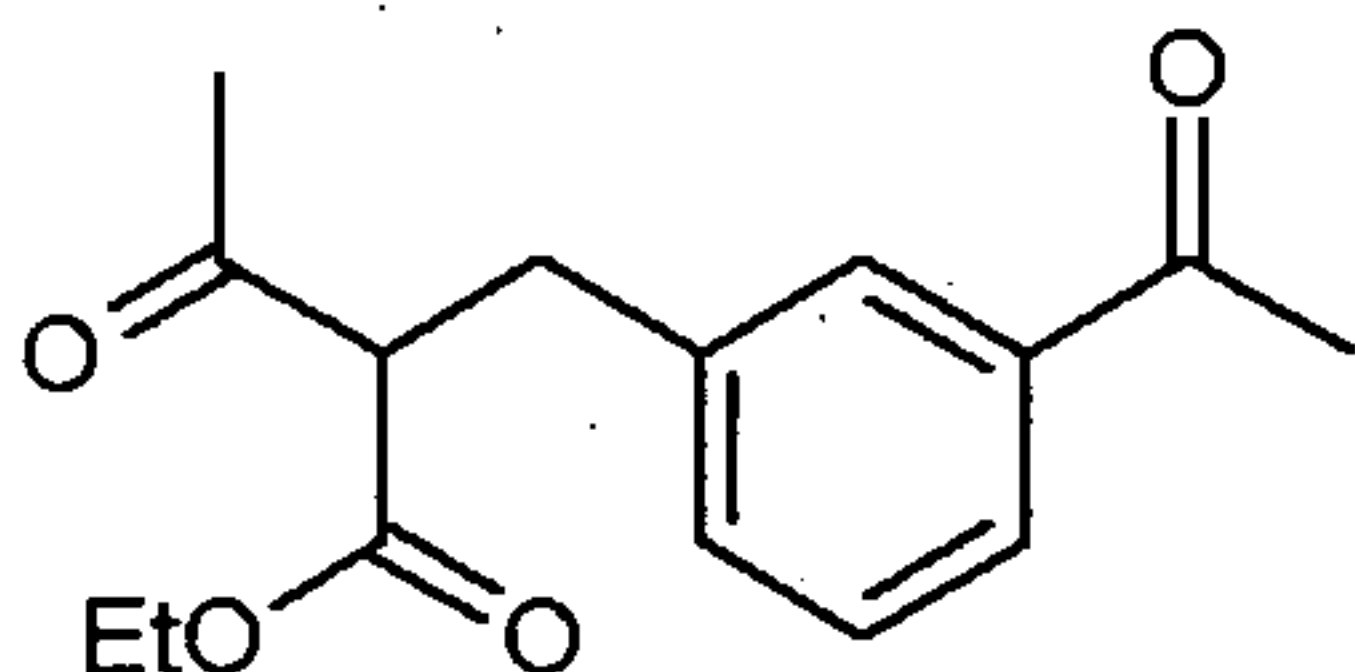
solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.86 (3H, t, J = 7.2), 1.52-1.67 (2H, m), 2.27 (3H, s), 2.62 (2H, t, J = 7.2), 4.00 (2H, s), 5.33 (2H, s), 7.15-7.27 (4H, m), 7.30 (2H, d, J = 8.1), 7.49-7.61 (2H, m), 7.63-7.75 (3H, s), 8.44 (1H, d, J = 3.6), 12.41 (1H, br)

Example 16

5-(3-acetylbenzyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-

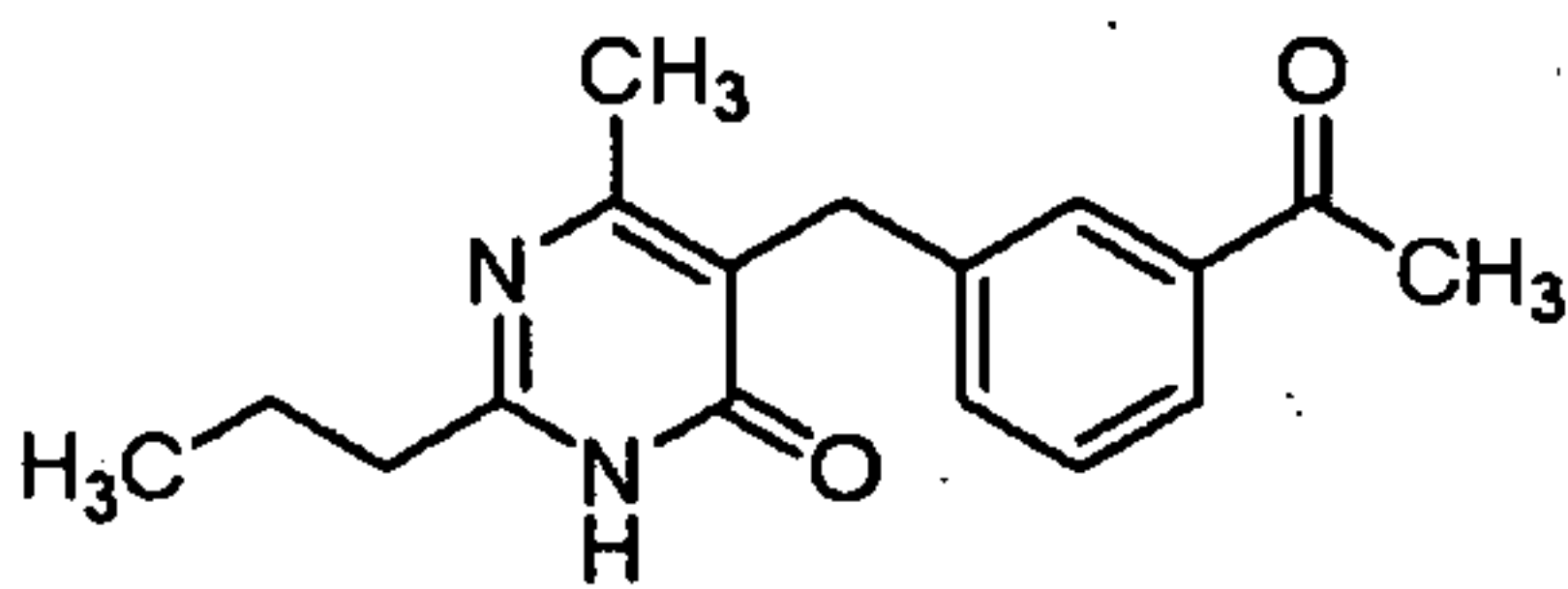
10 one



16a) ethyl 2-(3-acetylbenzyl)-3-oxobutanoate

A solution of 3-acetylbenzyl bromide (4 g) and ethyl acetoacetate sodium salt (3.42 g) in tetrahydrofuran (50 mL) was stirred for 12 hr. The insoluble material was filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the title compound (2.42 g, 49%) as a colorless viscous oil.

¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, t, J = 7.2), 2.20 (3H, s), 2.59 (3H, s), 3.21 (2H, d, J = 7.2), 3.80 (1H, d, J = 7.2), 4.15 (2H, q, J = 7.2), 7.31-7.47 (2H, m), 7.74-7.86 (2H, m)

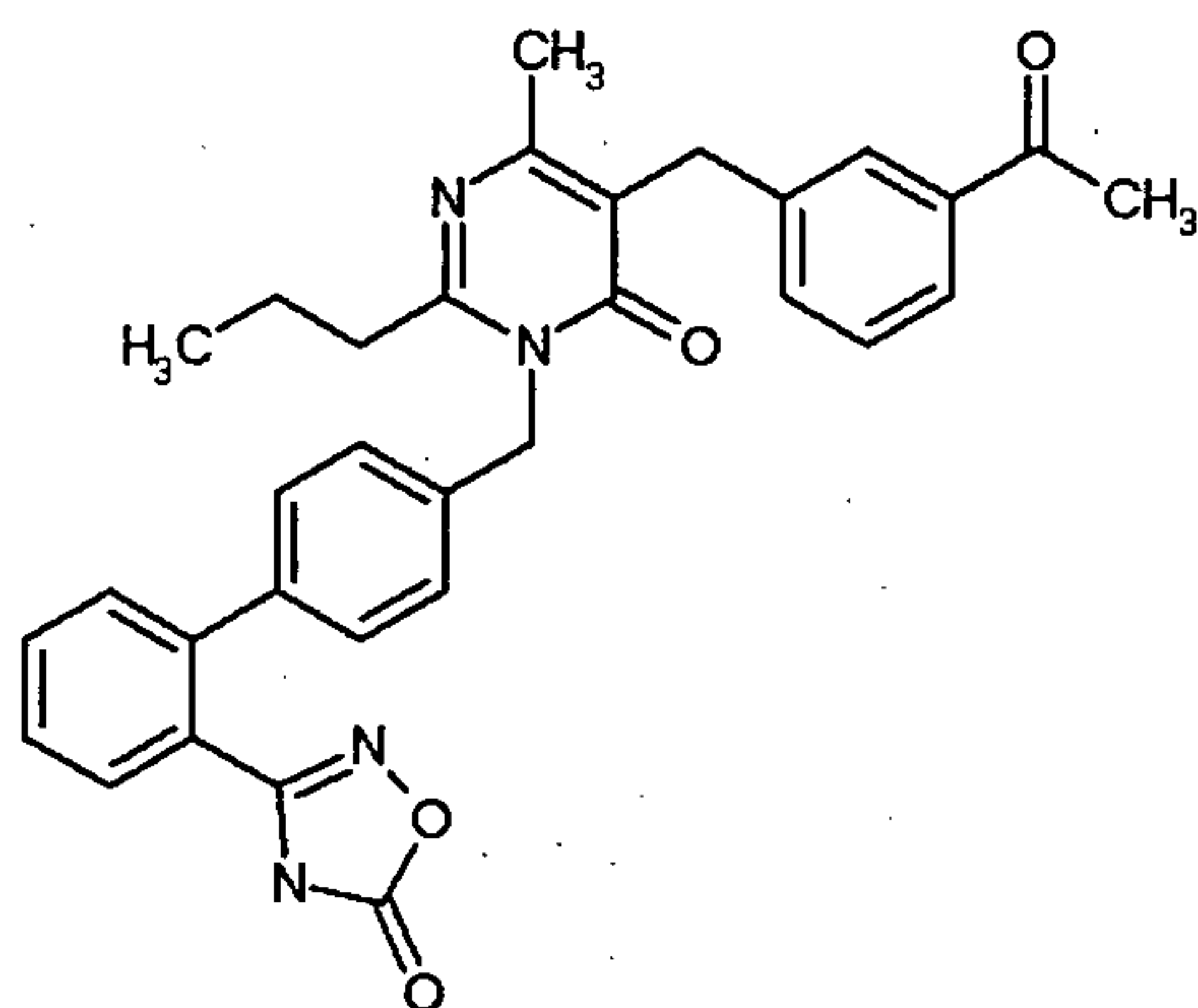


16b) 5-(3-acetylbenzyl)-6-methyl-2-propylpyrimidin-4(3H)-one

To a solution of ethyl 2-(3-acetylbenzyl)-3-oxobutanoate (2.39 g) and butanimidamide hydrochloride (1.68 g) in methanol (20 mL) was added 28% sodium methoxide-methanol solution (5.27 mL), and the mixture was stirred for 12 hr. The reaction mixture was concentrated, and the residue was dissolved in water and diethyl ether. The aqueous layer was separated, and weakly acidified with 1 M hydrochloric acid. The precipitate was collected by filtration and dried under reduced pressure

to give the title compound (2.02 g, 78%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.89 (3H, t, J = 7.5), 1.55-1.74 (2H, m), 2.18 (3H, s), 2.45 (2H, t, J = 7.5), 2.54 (3H, s), 3.83 (2H, s), 7.33-7.52 (2H, m), 7.68-7.86 (2H, m), 12.31 (1H, br)



16c) 5-(3-acetylbenzyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one

To a solution of 5-(3-acetylbenzyl)-6-methyl-2-propylpyrimidin-4(3H)-one (1 g) and 3-[4'-(bromomethyl)biphenyl-2-yl]-5-(trichloromethyl)-1,2,4-oxadiazole (1.68 g) in acetonitrile (30 mL) was added potassium carbonate (0.98 g), and the mixture was stirred for 12 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran-ethanol (1:1, 8 mL), 1 M sodium hydroxide (2 mL) was added, and the mixture was stirred for 30 min. The reaction mixture was weakly acidified with 1 M hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.40 g, 21%) as a colorless solid.

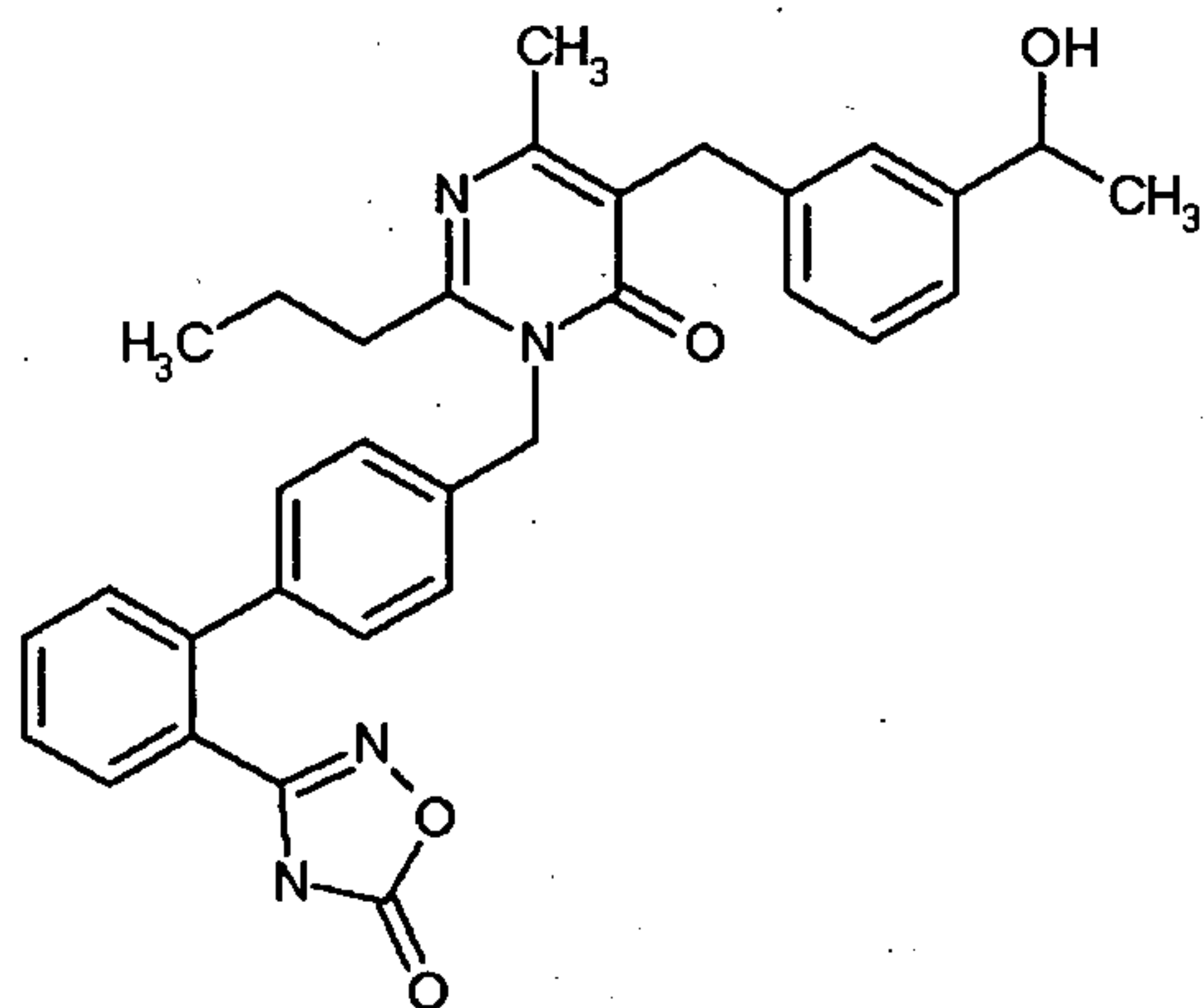
¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.2), 1.51-1.66 (2H, m), 2.25 (3H, s), 2.54 (3H, s), 2.62 (2H, t, J = 7.2),

WO 2008/062905

PCT/JP2007/073004

3.93 (2H, s), 5.36 (2H, s), 7.20 (2H, d, J = 8.4), 7.31 (2H, d, J = 8.4), 7.39-7.61 (4H, m), 7.63-7.74 (2H, m), 7.75-7.83 (2H, m), 12.40 (1H, s)

Example 17



5

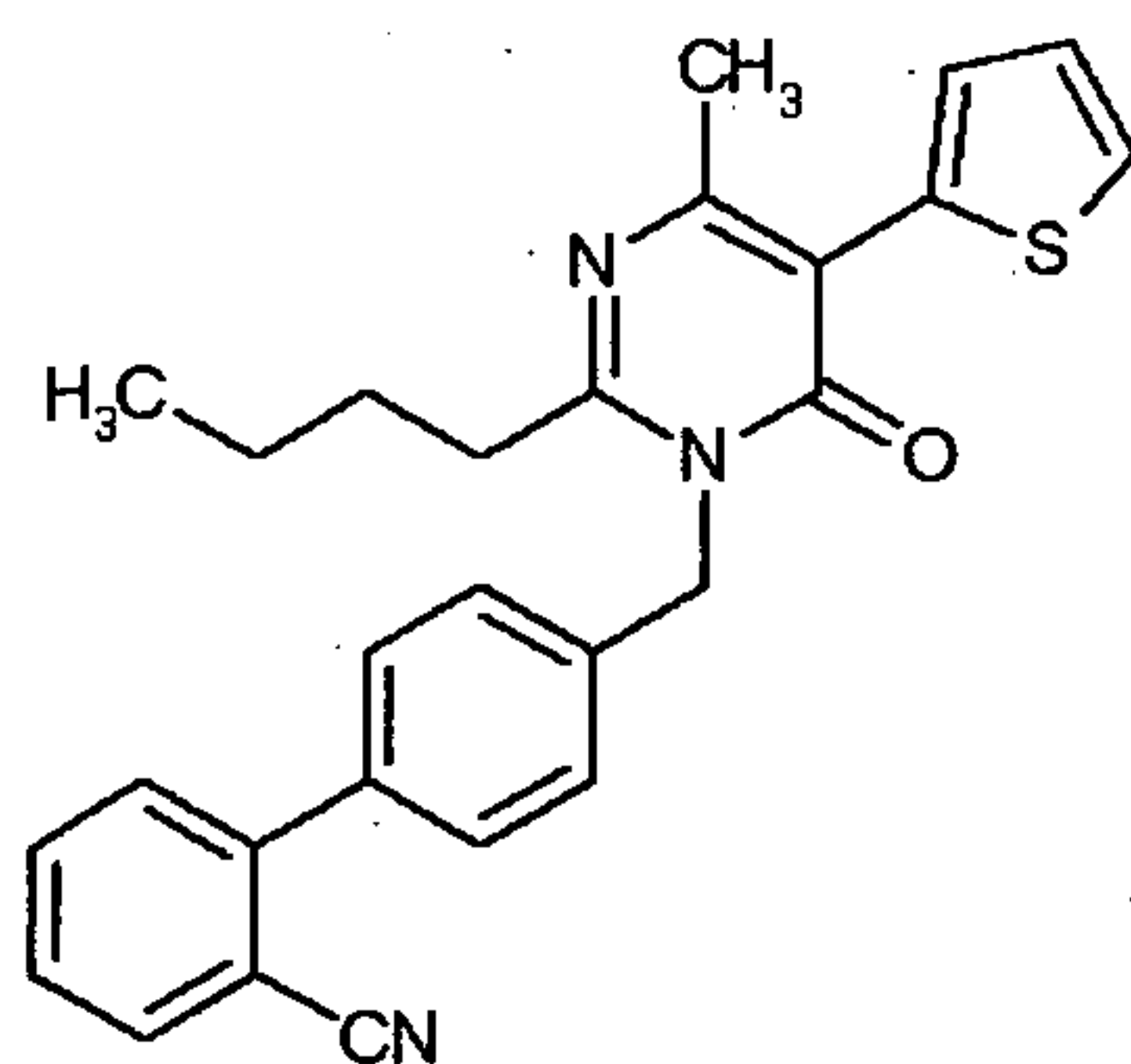
5-[3-(1-hydroxyethyl)benzyl]-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one

To a solution of 5-(3-acetylbenzyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one (0.20 g) in tetrahydrofuran-methanol (1:1, 4 mL) was added sodium borohydride (0.014 g), and the mixture was stirred for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.14 g, 69%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.2), 1.27 (3H, d, J = 6.6), 1.52-1.65 (2H, m), 2.23 (3H, s), 2.61 (2H, t, J = 7.2), 3.85 (2H, s), 4.58-4.71 (1H, m), 5.10 (1H, d, J = 4.2), 5.36 (2H, s), 7.01-7.25 (6H, m), 7.29 (2H, d, J = 8.1), 7.48-7.61 (2H, m), 7.63-7.74 (2H, m), 12.40 (1H, s)

25 Example 18

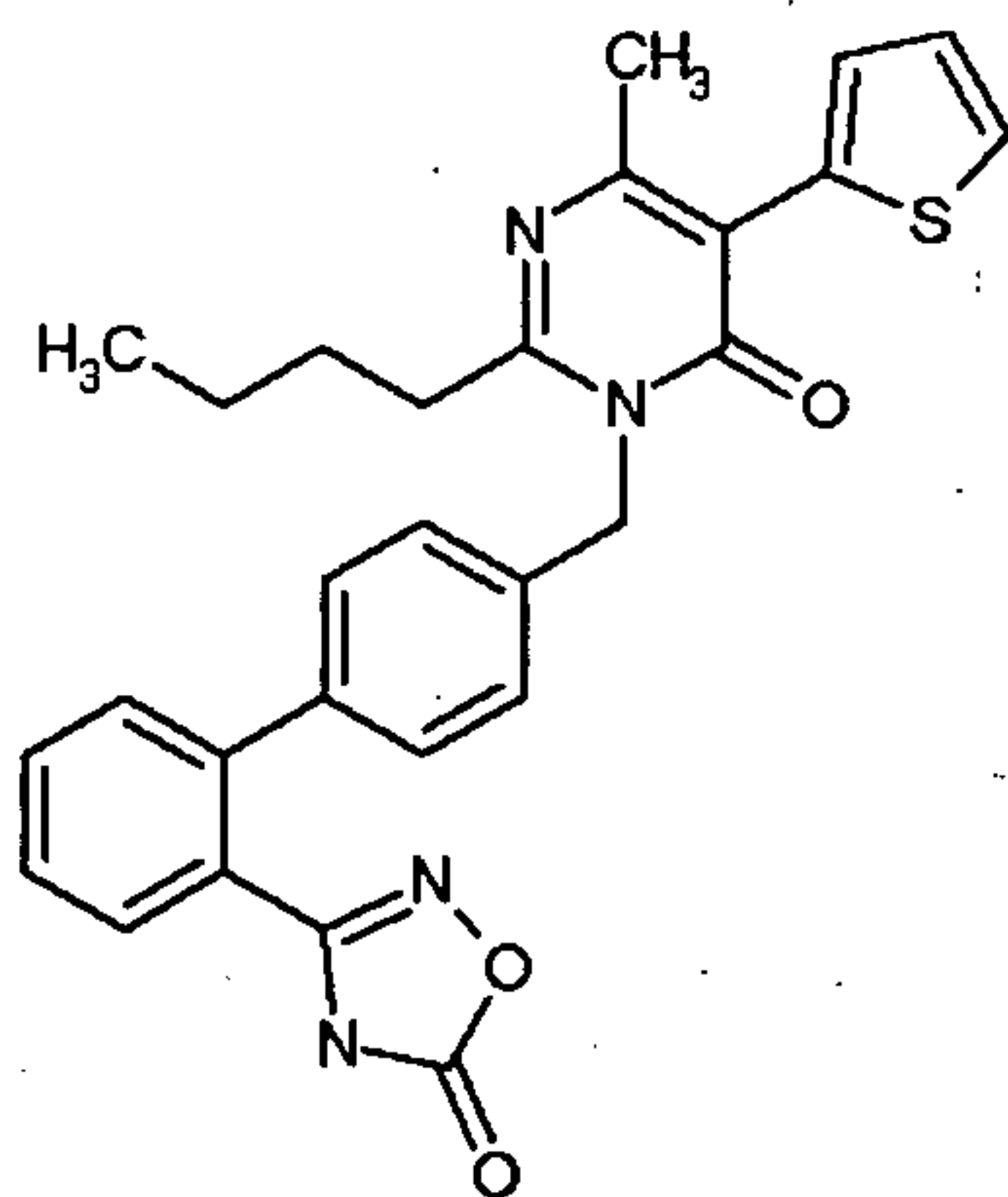
2-butyl-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-5-(2-thienyl)pyrimidin-4(3H)-one



18a) 4'-{[2-butyl-4-methyl-6-oxo-5-(2-thienyl)pyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.5 g), tributyl(2-thienyl)tin (0.64 g) and lithium chloride (0.15 g) in N,N-dimethylformamide (10 mL) was added dichlorobis(triphenylphosphine)palladium (0.04 g), and the mixture was stirred for 12 hr under an argon atmosphere. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate. A 20% aqueous potassium fluoride solution was added, and the mixture was stirred for 2 hr. The insoluble material was filtered off through celite. The organic layer of the filtrate was separated, washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.38 g, 75%) as a colorless viscous oil.

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.2), 1.33-1.49 (2H, m), 1.67-1.79 (2H, m), 2.45 (3H, s), 2.74 (2H, t, J = 8.1), 5.41 (2H, s), 7.07-7.14 (1H, m), 7.16-7.22 (1H, m), 7.34 (2H, d, J = 8.1), 7.40-7.57 (5H, m), 7.60-7.59 (1H, m), 7.75 (1H, d, J = 7.5)



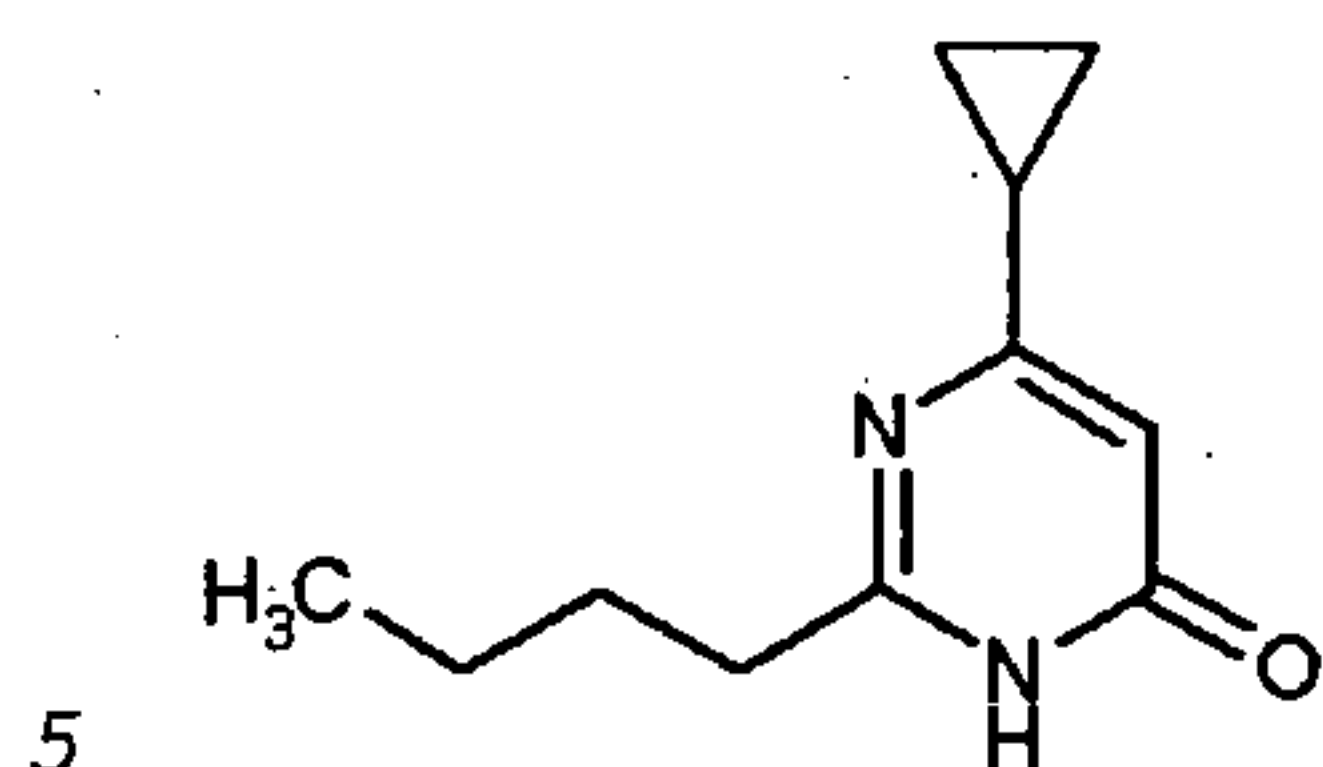
18b) 2-butyl-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-5-(2-thienyl)pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (0.54 g), sodium hydrogen carbonate (0.76 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-{[2-butyl-4-methyl-6-oxo-5-(2-thienyl)pyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.38 g) was added, and the mixture was stirred at 90°C for 16
10 hr. The mixture was allowed to cool to room temperature. Water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was
15 evaporated. The residue was dissolved in tetrahydrofuran (5 mL), N,N'-carbonyldiimidazole (0.21 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.19 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1
20 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.38 g, 78%).

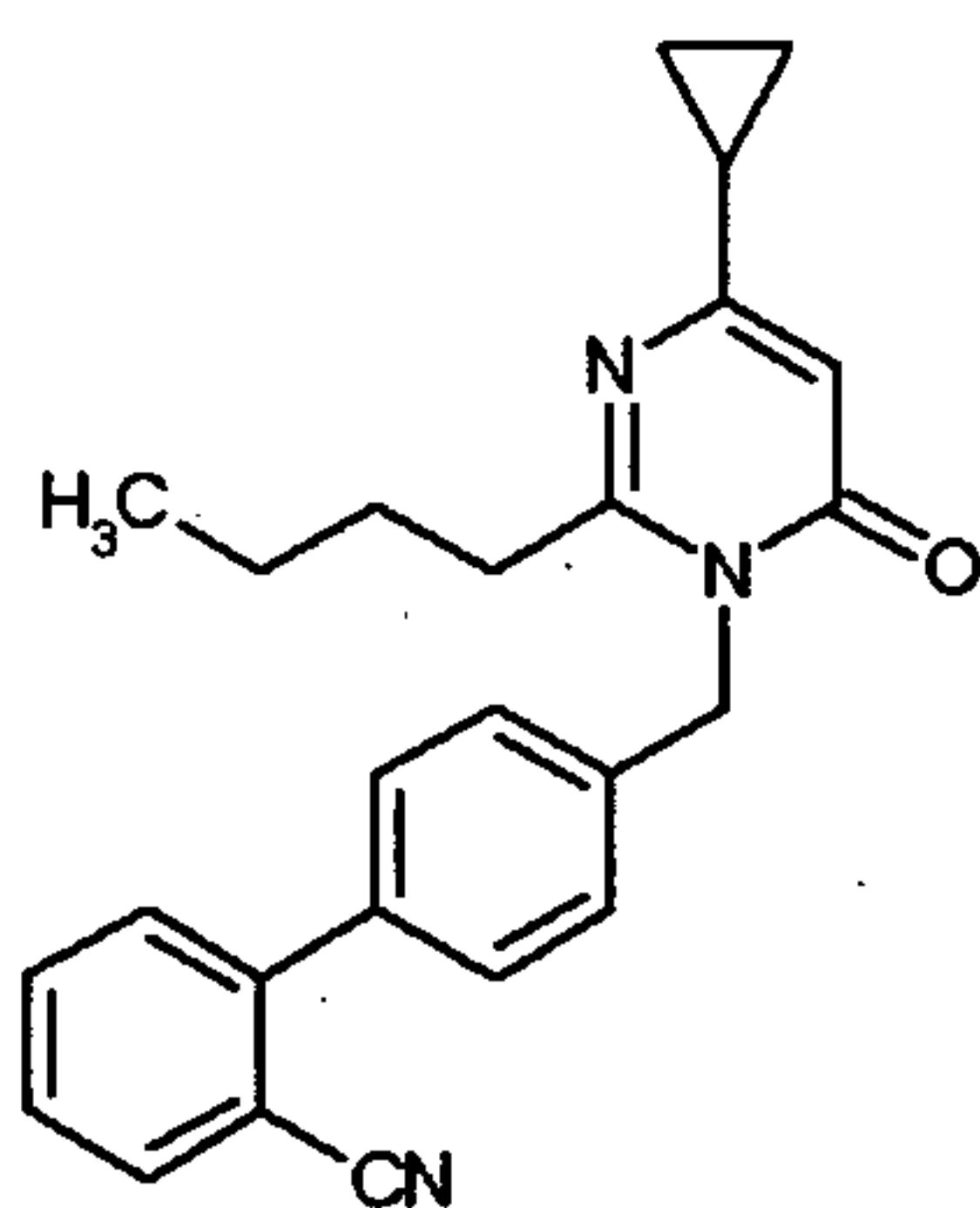
25 ¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.2), 1.22-1.38 (2H, m), 1.51-1.66 (2H, m), 2.38 (3H, s), 2.71 (2H, t, J = 7.2), 5.38 (2H, s), 7.09-7.16 (1H, m), 7.20-7.28 (3H, m), 7.31 (2H, d, J = 8.4), 7.48-7.74 (5H, m), 12.42 (1H, br)

Example 19

2-butyl-6-cyclopropyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-3-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one

19a) 2-butyl-6-cyclopropylpyrimidin-4(3H)-one

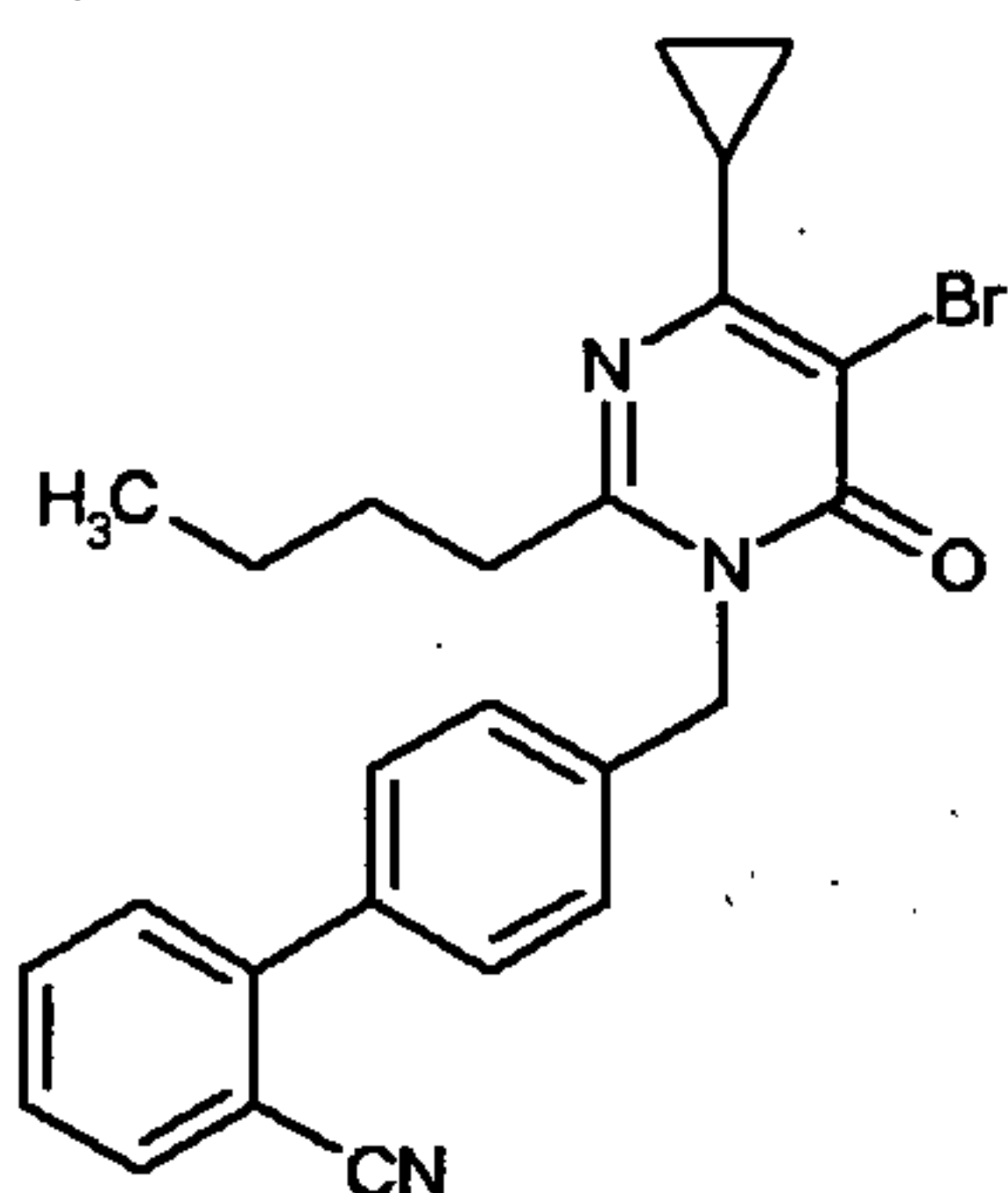
To a solution of methyl 3-cyclopropyl-3-oxopropionate (2.39 g) and pentylamidine hydrochloride (1.68 g) in methanol (20 mL) was added 28% sodium methoxide-methanol solution (5.27 mL), and the mixture was stirred for 12 hr. The reaction mixture was concentrated, and the residue was dissolved in water and diethyl ether. The aqueous layer was separated, and weakly acidified with 1 M hydrochloric acid. The precipitate was collected by filtration and dried under reduced pressure to give the title compound (2.02 g, 78%) as a colorless solid. ¹H NMR (300 MHz, CDCl₃) δ 0.87-0.99 (5H, m), 1.01-1.10 (2H, m), 1.29-1.46 (2H, m), 1.61-1.85 (3H, m), 2.61 (2H, t, J = 7.5), 6.15 (1H, s), 12.89 (1H, br)

19b) 4'-[(2-butyl-4-cyclopropyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 2-butyl-6-cyclopropylpyrimidin-4(3H)-one (6 g) and 4'-(bromomethyl)biphenyl-2-carbonitrile (9.34 g) in acetonitrile (180 mL) was added potassium carbonate (8.63 g), and the mixture was stirred at 50°C for 12 hr. The insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography

to give the title compound (5.23 g, 44%) as a colorless viscous substance.

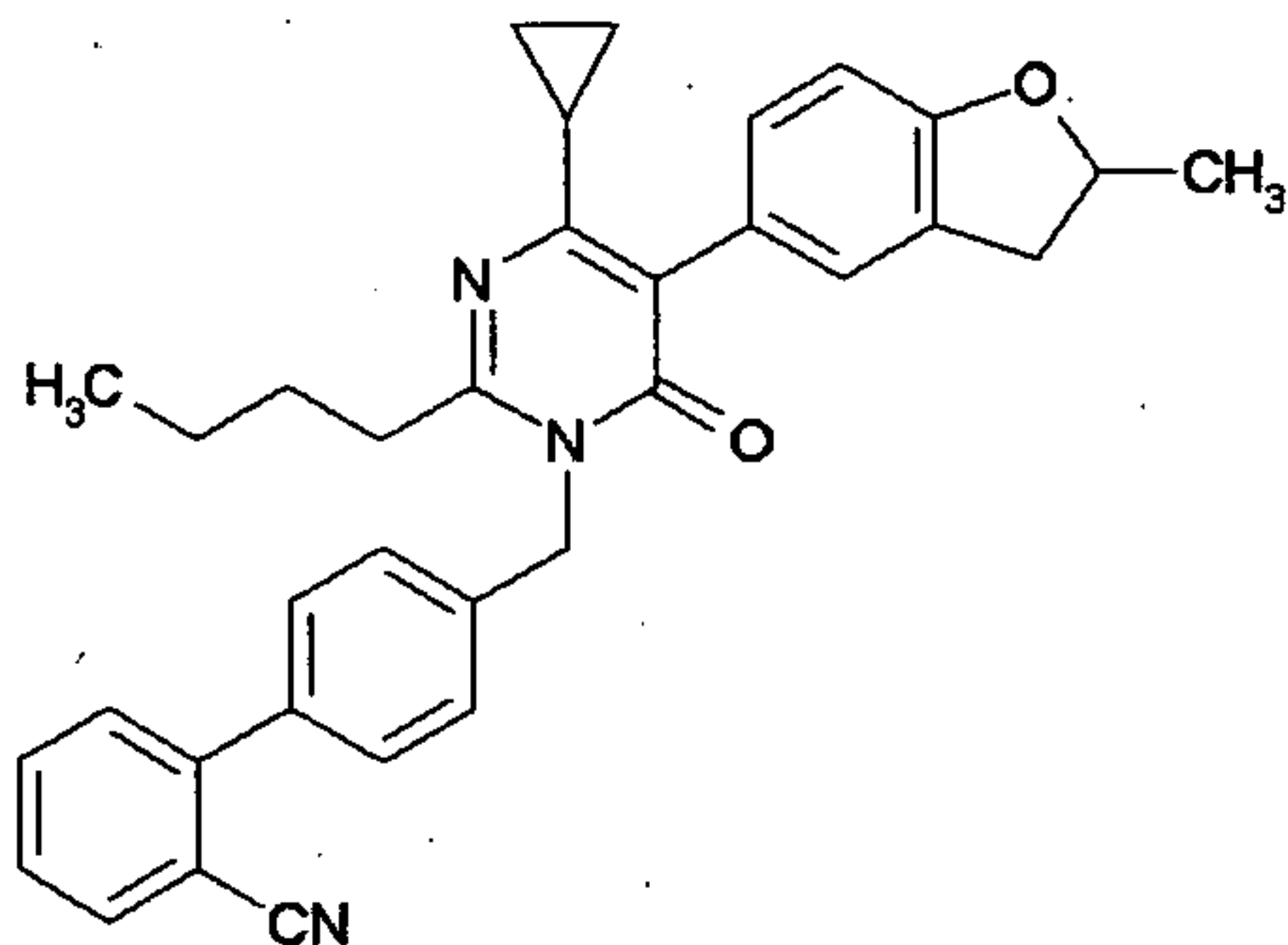
¹H NMR (300 MHz, CDCl₃) δ 0.88 (3H, t, J = 7.2), 0.90-1.00 (2H, m), 1.03-1.12 (2H, m), 1.24-1.42 (2H, m), 1.57-1.70 (2H, m), 1.73-1.84 (1H, m), 2.62 (2H, t, J = 7.5), 5.33 (2H, s), 6.32 (1H, s), 7.28 (2H, d, J = 8.1), 7.40-7.56 (4H, m), 7.60-7.68 (1H, m), 7.76 (1H, d, J = 7.8)



19c) 4'-[(5-bromo-2-butyl-4-cyclopropyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

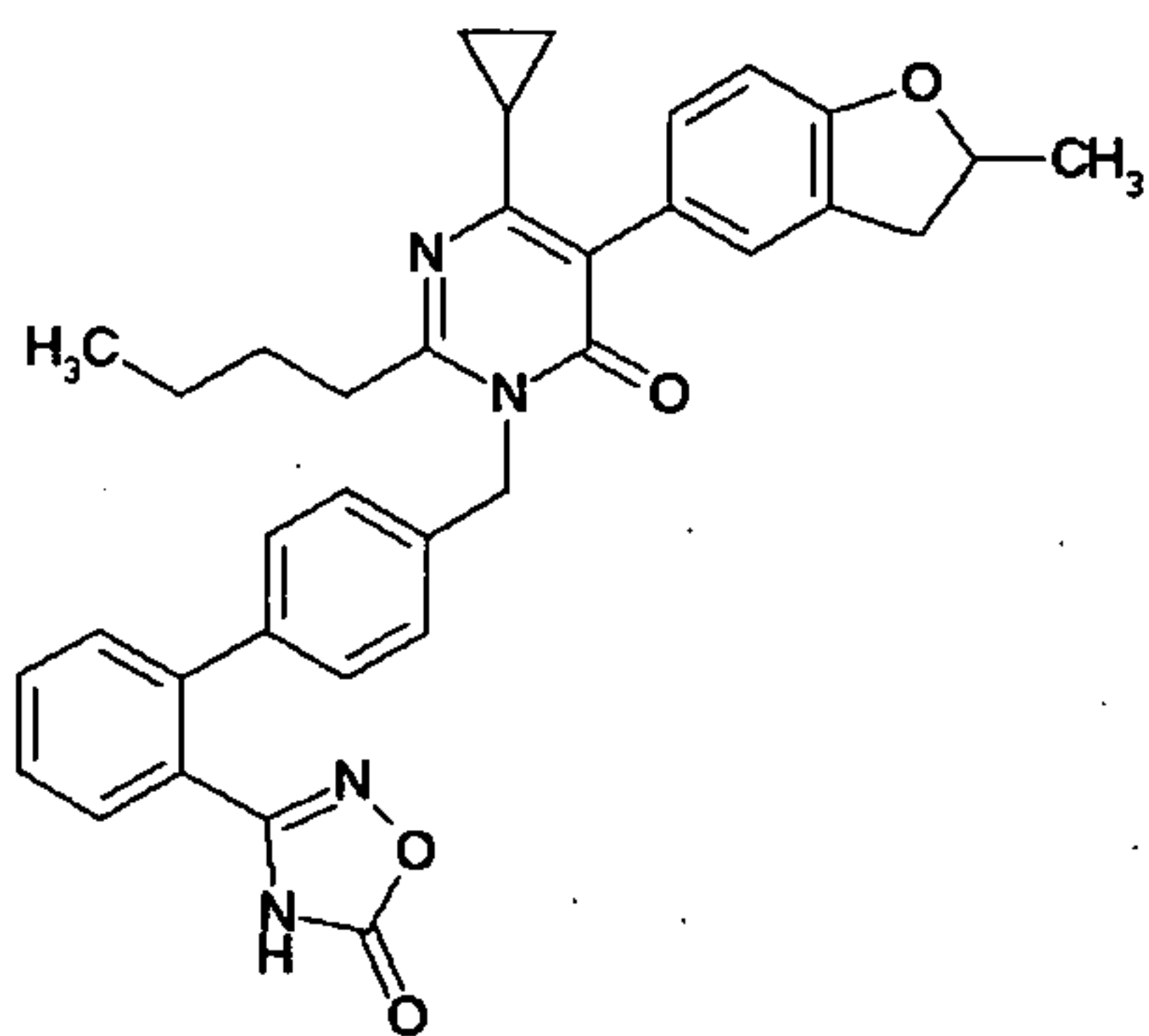
To a solution of 4'-[(2-butyl-4-cyclopropyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (5.22 g) in acetic acid (60 mL) was added bromine (1.39 mL), and the mixture was stirred at 70°C for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous sodium thiosulfate solution, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (5.4 g, 80%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.79 (3H, t, J = 7.5), 1.06 (4H, d, J = 6.0), 1.16-1.32 (2H, m), 1.46-1.61 (2H, m), 2.29-2.41 (1H, m), 2.66 (2H, t, J = 7.5), 5.38 (2H, s), 7.30 (2H, d, J = 8.4), 7.53-7.65 (4H, m), 7.74-7.84 (1H, m), 7.95 (1H, d, J = 7.2)



19d) 4'-{[2-butyl-4-cyclopropyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-cyclopropyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.5 g) and 2-methyl-2,3-dihydro-1-benzofuran-5-ylboronic acid (0.29 g) in 1,4-dioxane (10 mL) were added 2 M aqueous cesium carbonate solution (2 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.05 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.47 g, 84%) as a pale-yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 0.78-0.87 (2H, m), 0.91 (3H, t, J = 7.2), 1.10-1.19 (2H, m), 1.30-1.44 (2H, m), 1.48 (3H, d, J = 6.3), 1.62-1.76 (2H, m), 1.86-1.97 (1H, m), 2.67 (2H, t, J = 7.2), 2.86 (1H, dd, J = 15.3, 7.8), 3.25 (1H, dd, J = 15.3, 8.7), 4.87-5.01 (1H, m), 5.34 (2H, s), 6.80 (1H, d, J = 8.1), 7.17 (1H, d, J = 8.1), 7.25-7.78 (1H, m), 7.35 (2H, d, J = 8.1), 7.40-7.55 (4H, m), 7.60-7.58 (1H, m), 7.76 (1H, d, J = 8.1)



19e) 2-butyl-6-cyclopropyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-

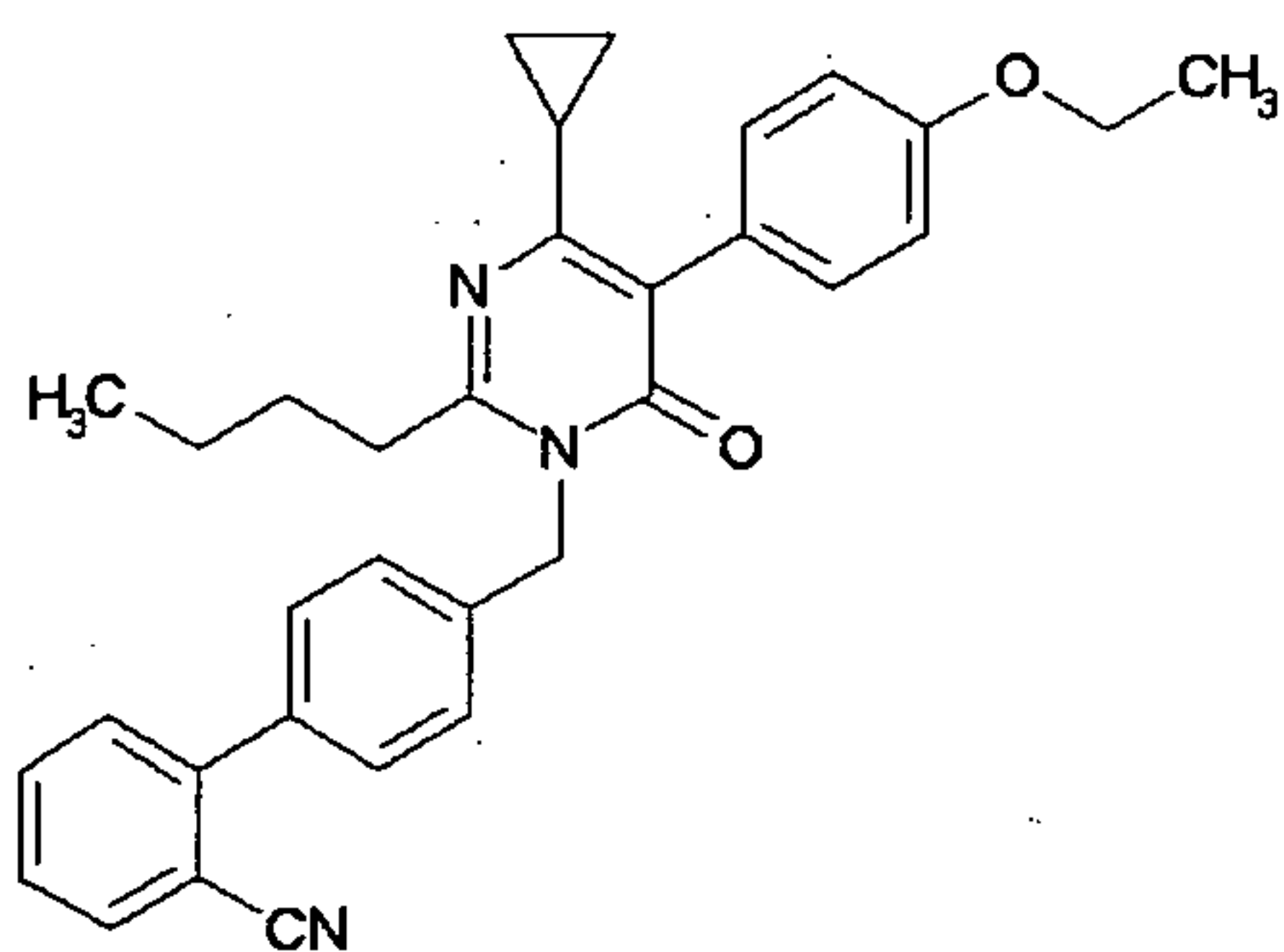
yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.54 g), sodium hydrogen carbonate (0.76 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-{[2-butyl-4-cyclopropyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-6-oxopyrimidin-1(6H)-yl)methyl}biphenyl-2-carbonitrile (0.46 g) was added, and the mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (5 mL), N,N'-carbonyldiimidazole (0.22 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.2 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.43 g, 82%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.75-0.87 (5H, m), 0.96-1.17 (2H, m), 1.18-1.34 (2H, m), 1.40 (3H, d, J = 6.0), 1.48-1.62 (2H, m), 1.72-1.85 (1H, m), 2.64 (2H, t, J = 7.2), 2.75-2.87 (1H, m), 3.25-3.41 (1H, m), 4.85-5.01 (1H, m), 5.31 (2H, s), 6.77 (1H, d, J = 8.1), 7.06 (1H, d, J = 8.1), 7.18 (1H, s), 7.24 (2H, d, J = 8.4), 7.31 (2H, d, J = 8.4), 7.48-7.61 (2H, m), 7.63-7.74 (2H, m), 12.41 (1H, s)

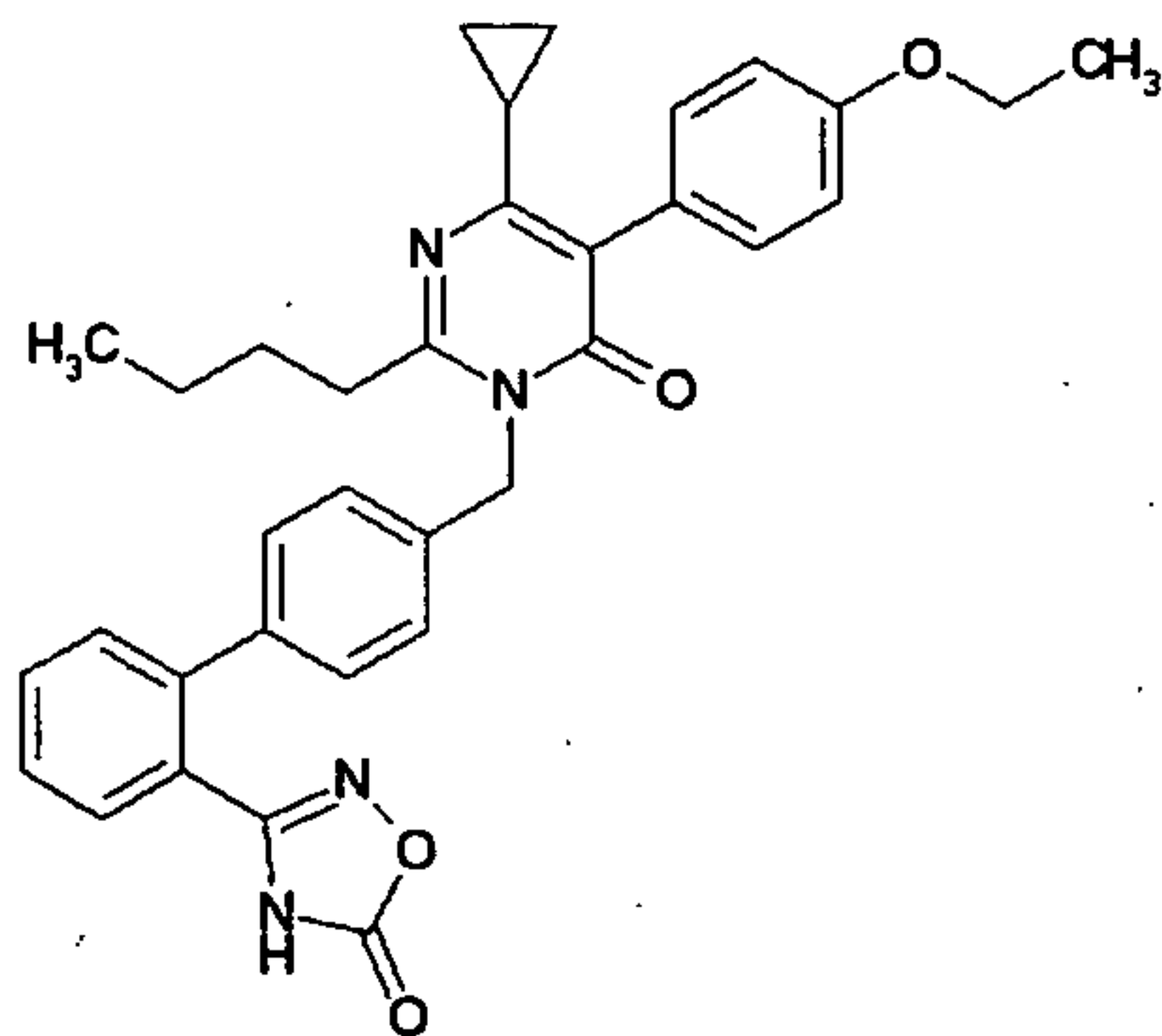
Example 20

2-butyl-6-cyclopropyl-5-(4-ethoxyphenyl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one



20a) 4'-{[2-butyl-4-cyclopropyl-5-(4-ethoxyphenyl)-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-cyclopropyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.5 g) and 4-ethoxyphenylboronic acid (0.27 g) in 1,4-dioxane (10 mL) were added 2 M aqueous cesium carbonate solution (2 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.05 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.38 g, 70%) as a colorless solid. ¹H NMR (300 MHz, CDCl₃) δ 0.76-0.87 (2H, m), 0.91 (3H, t, J = 7.5), 1.10-1.20 (2H, m), 1.31-1.47 (5H, m), 1.61-1.75 (2H, m), 1.83-1.96 (1H, m), 2.67 (2H, t, J = 7.5), 4.06 (2H, q, J = 7.5), 5.35 (2H, s), 6.96 (2H, d, J = 8.1), 7.31-7.56 (8H, m), 7.60-7.69 (1H, m), 7.76 (1H, d, J = 7.5)



20b) 2-butyl-6-cyclopropyl-5-(4-ethoxyphenyl)-3-{[2'-(5-oxo-

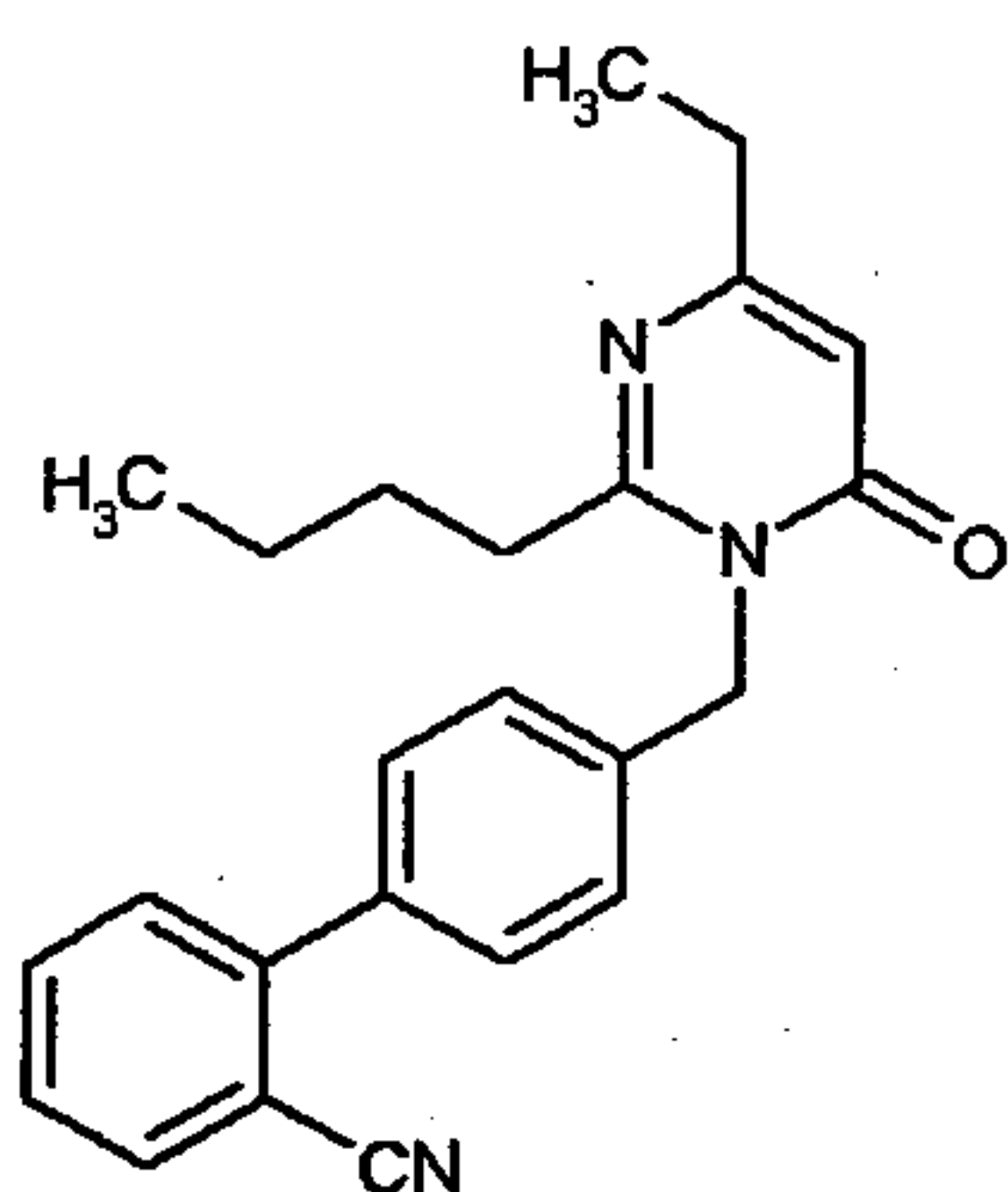
4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.54 g), sodium hydrogen carbonate (0.76 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-{[2-butyl-4-cyclopropyl-5-(4-ethoxyphenyl)-6-oxopyrimidin-1(6H)-yl)methyl}biphenyl-2-carbonitrile (0.38 g) was added, and the mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature. Water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (5 mL), N,N'-carbonyldiimidazole (0.18 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.17 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.38 g, 90%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.76-1.89 (5H, m), 0.97-1.09 (2H, m), 1.19-1.39 (5H, m), 1.47-1.62 (2H, m), 1.70-1.82 (1H, m), 2.64 (2H, t, J = 7.2), 4.05 (2H, q, J = 7.2), 5.32 (2H, s), 6.98 (2H, d, J = 8.4), 7.19-7.36 (6H, m), 7.47-7.62 (2H, m), 7.63-7.75 (2H, m), 12.41 (1H, s)

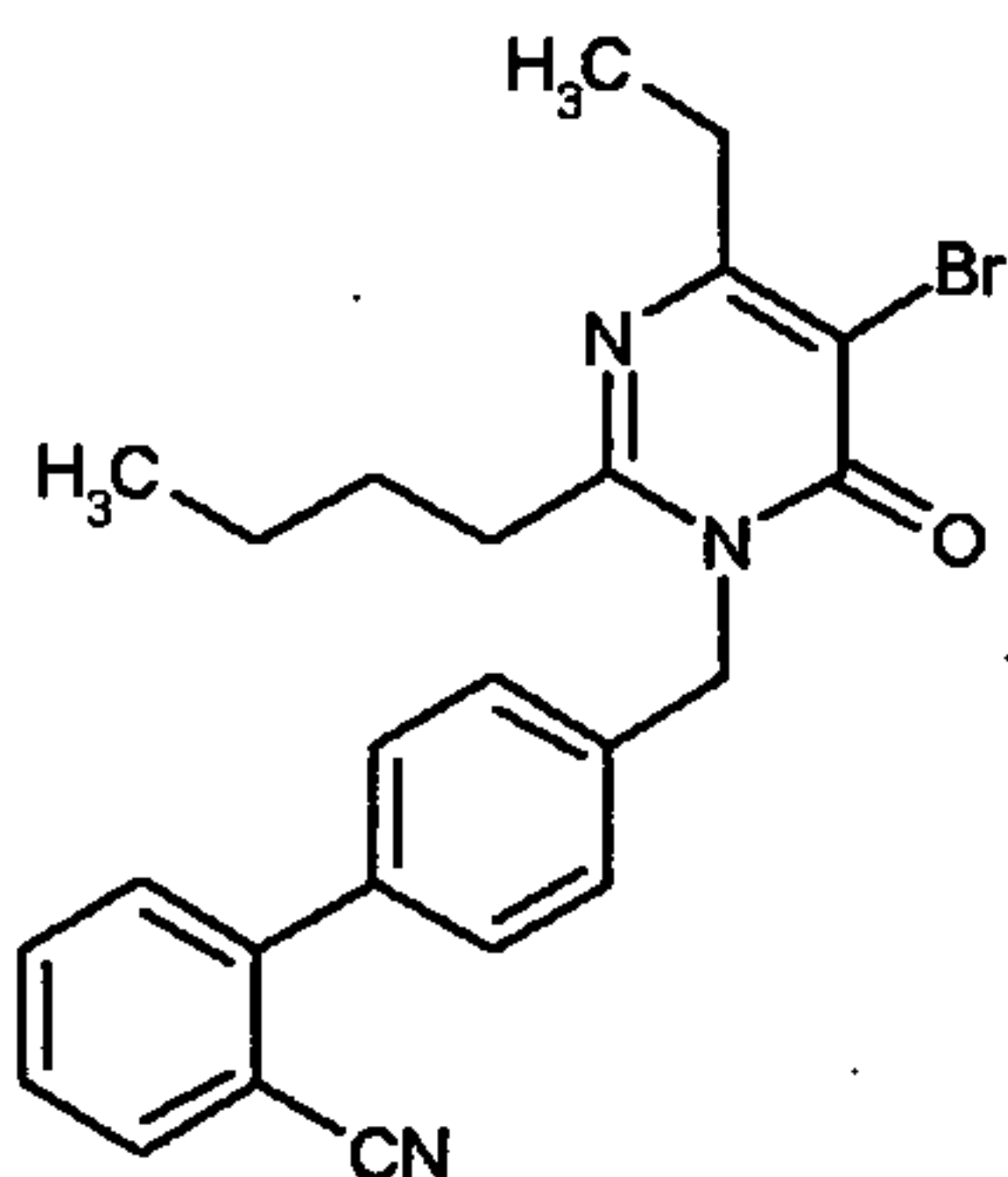
Example 21

2-butyl-6-ethyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one



21a) 4'-[(2-butyl-4-ethyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 2-butyl-6-ethylpyrimidin-4(3H)-one (4 g) and 4'-(bromomethyl)biphenyl-2-carbonitrile (6.64 g) in acetonitrile (120 mL) was added potassium carbonate (6.1 g), and the mixture was stirred at 50°C for 12 hr. The insoluble material was filtered off, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give the title compound (2.09 g, 25%) as a colorless solid. ¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.2), 1.25 (3H, t, J = 7.5), 1.31-1.46 (2H, m), 1.61-1.76 (2H, m), 2.56 (2H, q, J = 7.5), 2.68 (2H, t, J = 7.2), 5.36 (2H, s), 6.29 (1H, s), 7.29 (2H, d, J = 8.1), 7.40-7.57 (4H, m), 7.60-7.69 (1H, m), 7.76 (1H, d, J = 7.8)

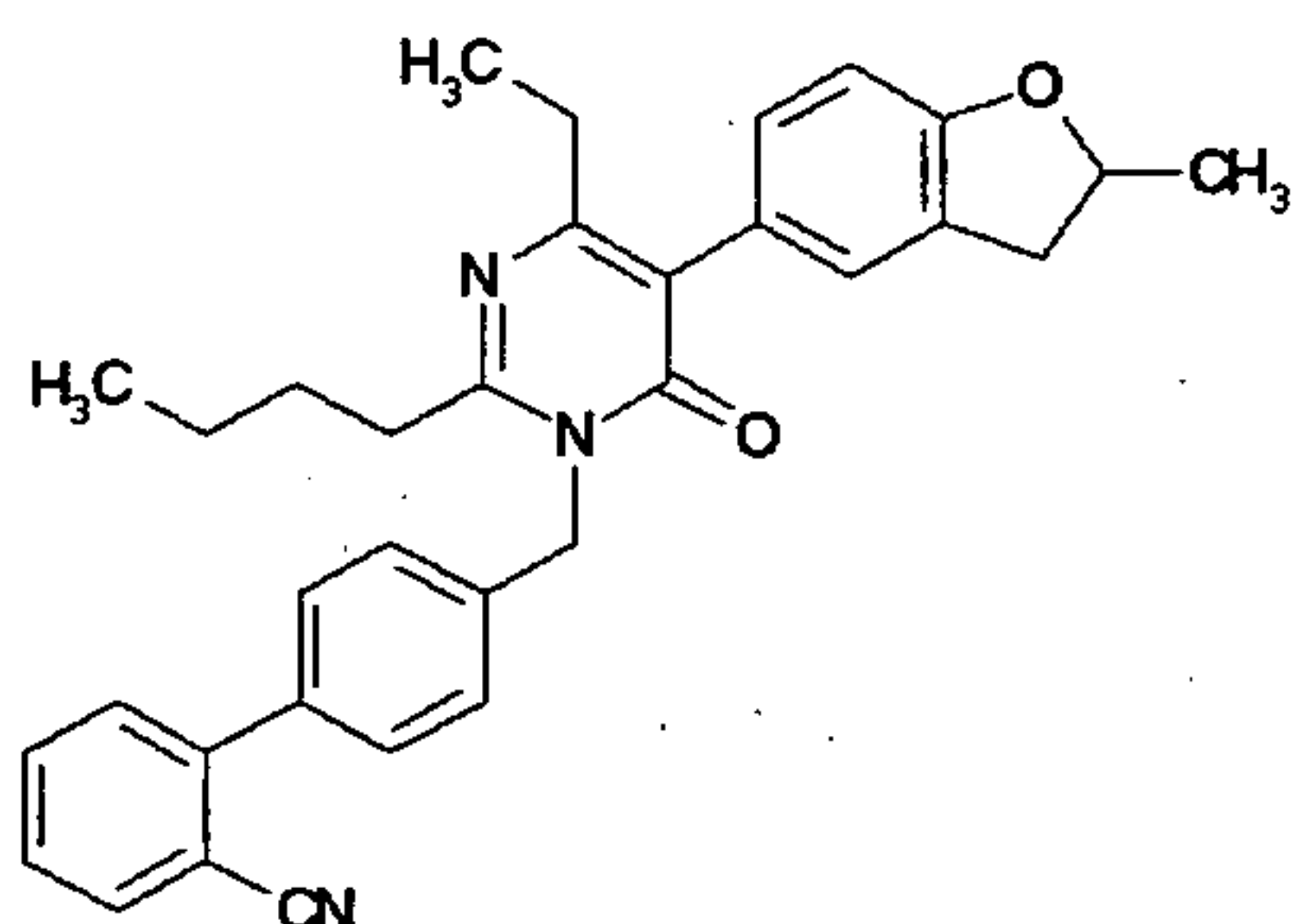


21b) 4'-[(5-bromo-2-butyl-4-ethyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[(2-butyl-4-ethyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.67 g) in acetic acid (20 mL) was added bromine (0.46 mL), and the mixture was stirred at 70°C for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous sodium thiosulfate solution, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The

solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (1.26 g, 62%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.81 (3H, t, J = 7.2), 1.19 (3H, t, J = 7.5), 1.23-1.36 (2H, m), 1.52-1.67 (2H, m), 2.65-2.78 (4H, m), 5.41 (2H, s), 7.32 (2H, d, J = 8.4), 7.53-7.64 (4H, m), 7.74-7.84 (1H, m), 7.95 (1H, d, J = 7.5)

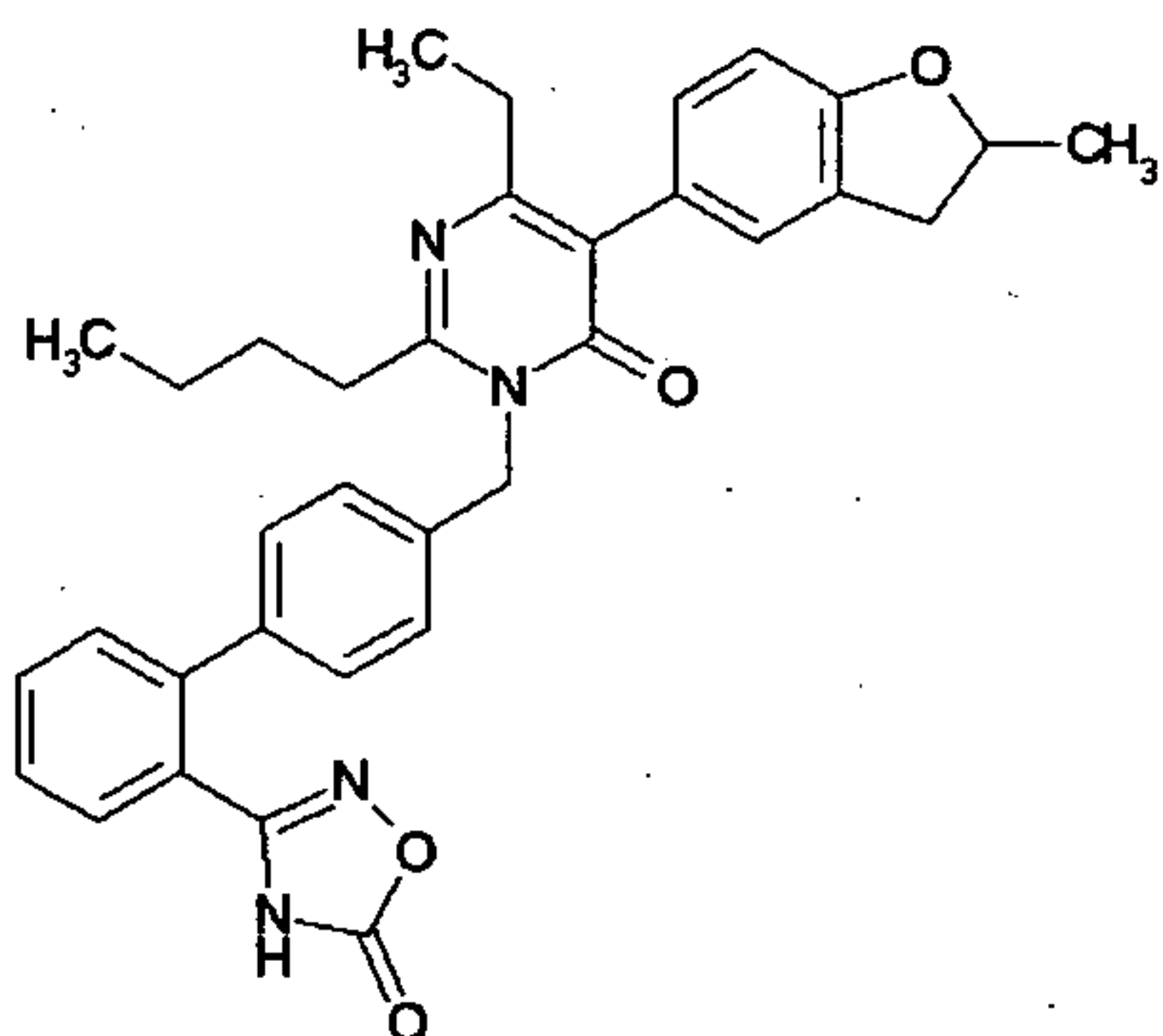


21c) 4'-{[2-butyl-4-ethyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-ethyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.5 g) and 2-methyl-2,3-dihydro-1-benzofuran-5-ylboronic acid (0.30 g) in 1,4-dioxane (10 mL) were added 2 M aqueous cesium carbonate solution (2 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.05 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.46 g, 82%) as a pale-yellow solid.

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.2), 1.18 (3H, t, J = 7.5), 1.35-1.52 (5H, m), 1.68-1.83 (2H, m), 2.49 (2H, q, J = 7.5), 2.75 (2H, t, J = 7.2), 2.86 (1H, dd, J = 15.6, 8.1), 3.34 (1H, dd, J = 15.6, 8.7), 4.86-5.02 (1H, m), 5.36 (2H, s),

6.79 (1H, d, J = 8.4), 7.01 (1H, d, J = 8.4), 7.12 (1H, s),
 7.36 (2H, d, J = 8.1), 7.40-7.57 (4H, m), 7.60-7.69 (1H, m),
 7.76 (1H, d, J = 7.8)



5 21d) 2-butyl-6-ethyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

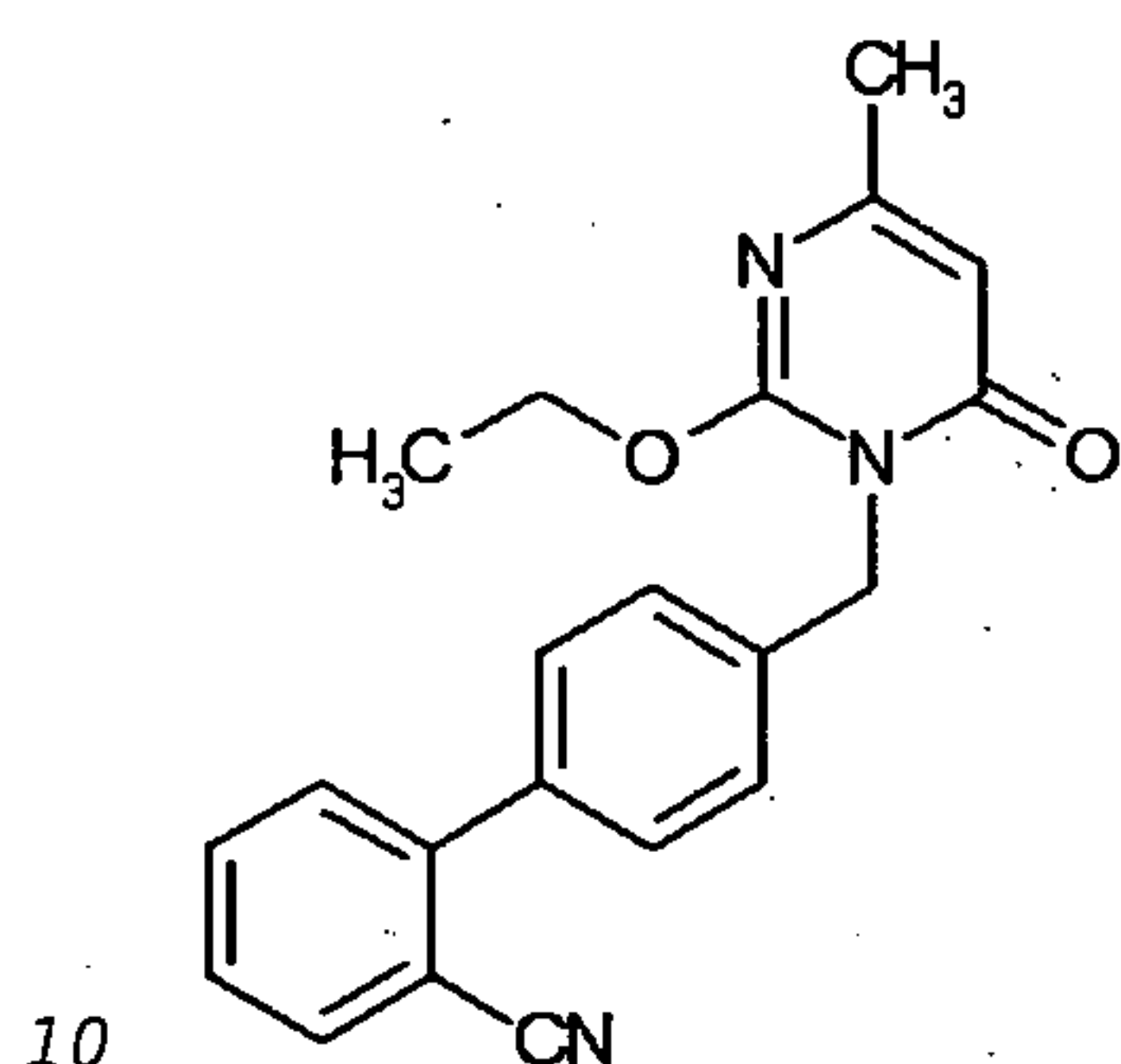
A mixture of hydroxylammonium chloride (0.54 g), sodium hydrogen carbonate (0.76 g) and dimethyl sulfoxide (10 mL) was
 10 stirred at 40°C for 30 min, 4'-{[2-butyl-4-ethyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.46 g) was added, and the mixture was stirred at 90°C for 16 hr. The mixture was allowed to cool to room temperature. Water was added to the reaction
 15 mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (5 mL), N,N'-
 20 carbonyldiimidazole (0.22 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.20 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried
 25 over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.45 g, 88%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.5), 1.10 (3H, t,

J = 7.5), 1.38-1.45 (2H, m), 1.40 (3H, d, J = 6.0), 1.53-1.68 (2H, m), 2.36 (2H, q, J = 7.5), 2.69 (2H, t, J = 7.5), 2.74-2.86 (1H, m), 3.26-3.40 (1H, m), 4.86-5.00 (1H, m), 5.33 (2H, s), 6.75 (1H, d, J = 8.1), 6.96 (1H, d, J = 8.1), 7.09 (1H, s), 7.25 (2H, d, J = 8.1), 7.32 (2H, d, J = 8.1), 7.48-7.62 (2H, m), 7.64-7.74 (2H, m), 12.41 (1H, s)

Example 22

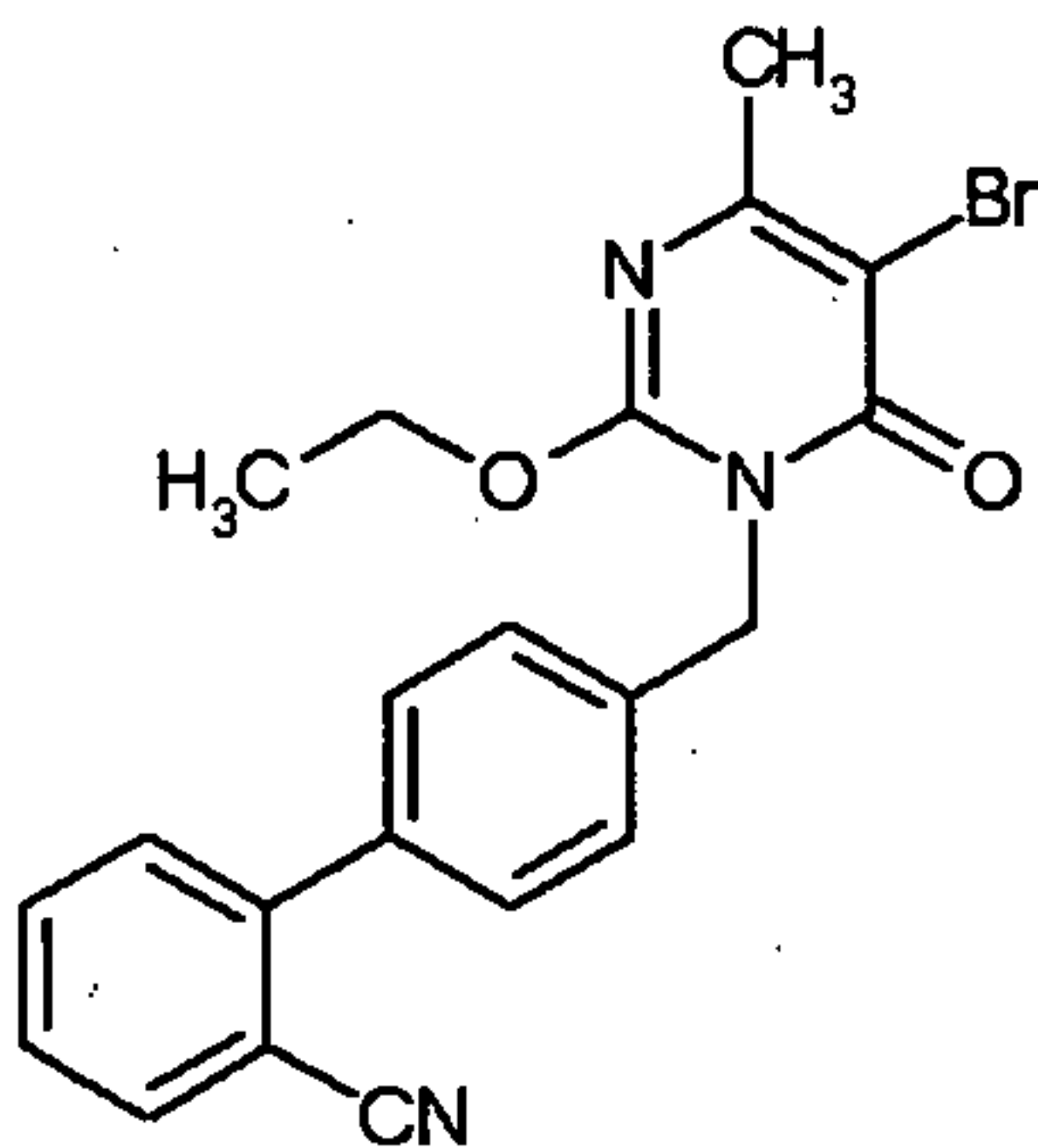
2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-5-phenylpyrimidin-4(3H)-one



22a) 4'-[(2-ethoxy-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 2-ethoxy-6-methylpyrimidin-4(3H)-one (4.9 g) and 4'-(bromomethyl)biphenyl-2-carbonitrile (10.3 g) in acetonitrile (120 mL) was added potassium carbonate (5.24 g), and the mixture was stirred at 50°C for 12 hr. The insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the title compound (6.15 g, 56%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 1.37 (3H, t, J = 7.2), 2.18 (3H, s), 4.43 (2H, q, J = 7.2), 5.21 (2H, s), 6.03 (1H, s), 7.39-7.56 (6H, m), 7.58-7.69 (1H, m), 7.75 (1H, d, J = 7.8)

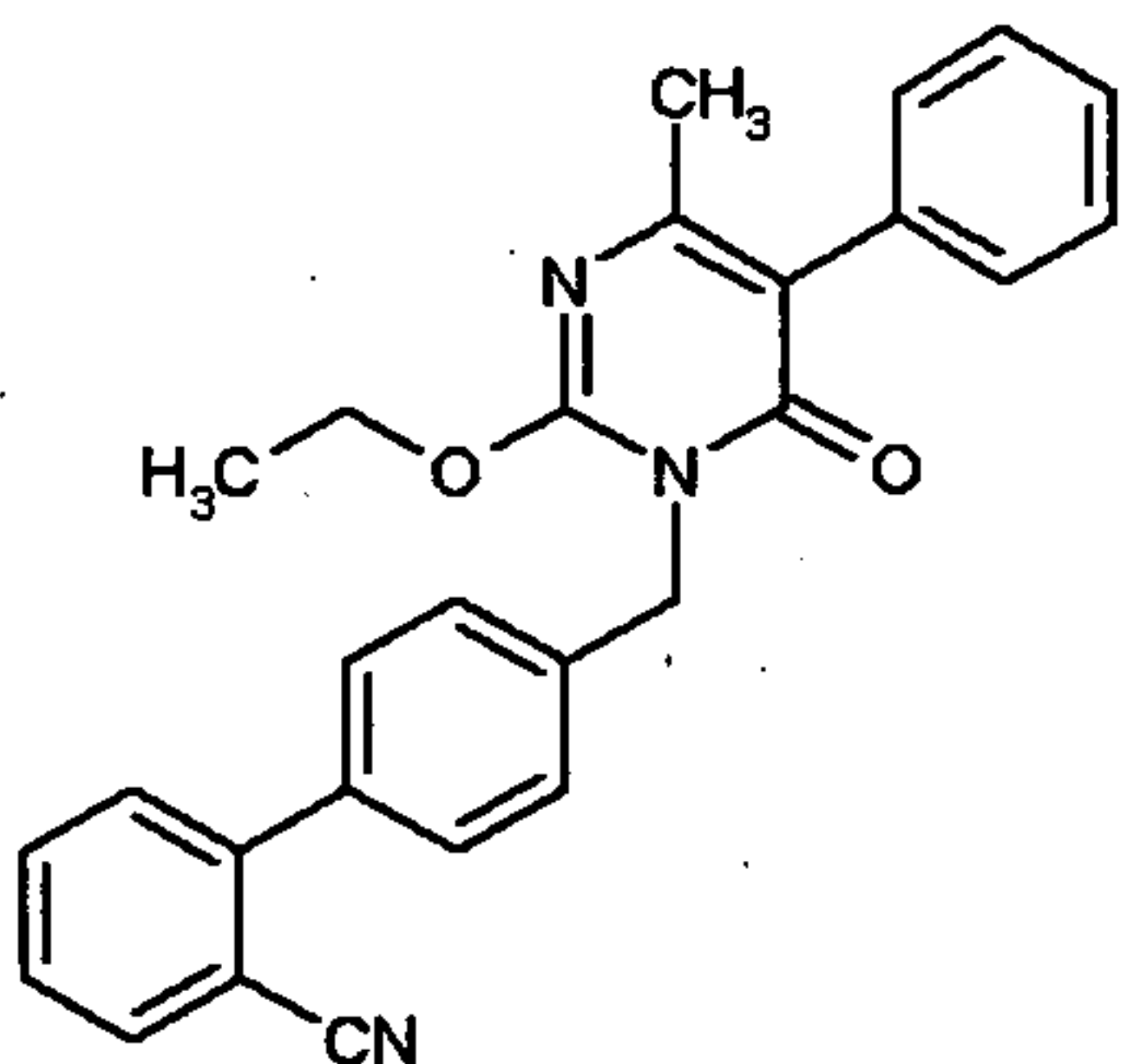


22b) 4'-[(5-bromo-2-ethoxy-4-methyl-6-oxopyrimidin-1(6H)-

yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[(2-ethoxy-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (6.15 g) and sodium acetate (1.46 g) in acetic acid (100 mL) was added bromine (0.91 mL), and the mixture was stirred for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous sodium thiosulfate solution, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (7.12 g, 94%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 1.30 (3H, t, J = 7.2), 2.36 (3H, s), 4.42 (2H, q, J = 7.2), 5.19 (2H, s), 7.43 (2H, d, J = 8.1), 7.51-7.66 (4H, m), 7.74-7.85 (1H, m), 7.95 (1H, d, J = 7.8)

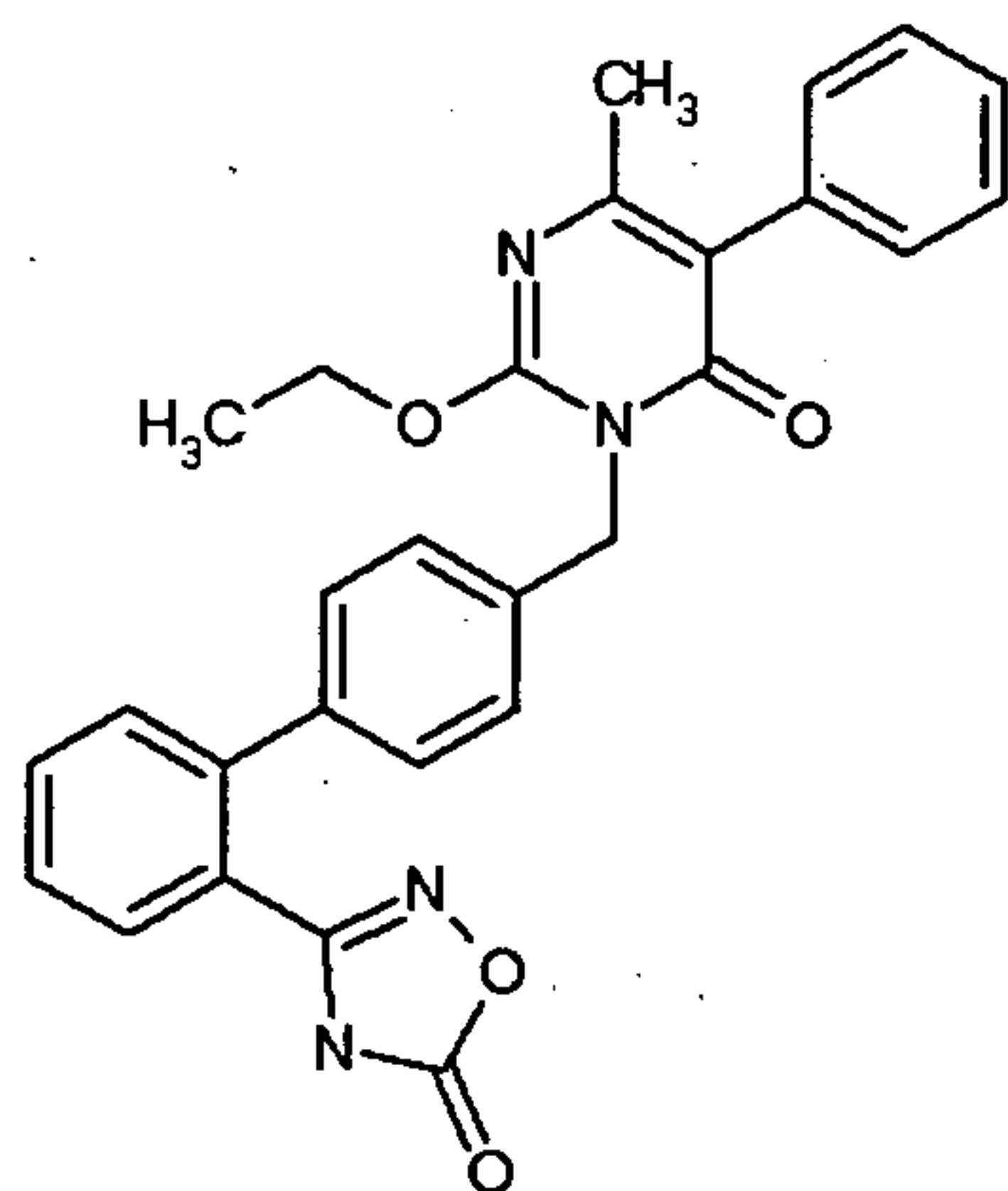


22c) 4'-[(2-ethoxy-4-methyl-6-oxo-5-phenylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-ethoxy-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1 g) and phenylboronic acid (0.43 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (2 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the

residue was purified by silica gel column chromatography to give the title compound (0.77 g, 78%) as a pale-yellow solid.

¹H NMR (300 MHz, DMSO-d₆) δ 1.32 (3H, t, J = 7.2), 2.07 (3H, s), 4.45 (2H, q, J = 7.2), 5.19 (2H, s), 7.23-7.50 (7H, m), 7.53-7.65 (4H, m), 7.74-7.84 (1H, m), 7.95 (1H, d, J = 7.8)



22d) 2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-5-phenylpyrimidin-4(3H)-one

10 A mixture of hydroxylammonium chloride (1.08 g), sodium hydrogen carbonate (1.53 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-[(2-ethoxy-4-methyl-6-oxo-5-phenylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.77 g) was added, and the mixture was stirred at 90°C for 5 hr.

15 The mixture was allowed to cool to room temperature. Water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was

20 evaporated. The residue was dissolved in tetrahydrofuran (5 mL), N,N'-carbonyldiimidazole (0.44 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.41 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1

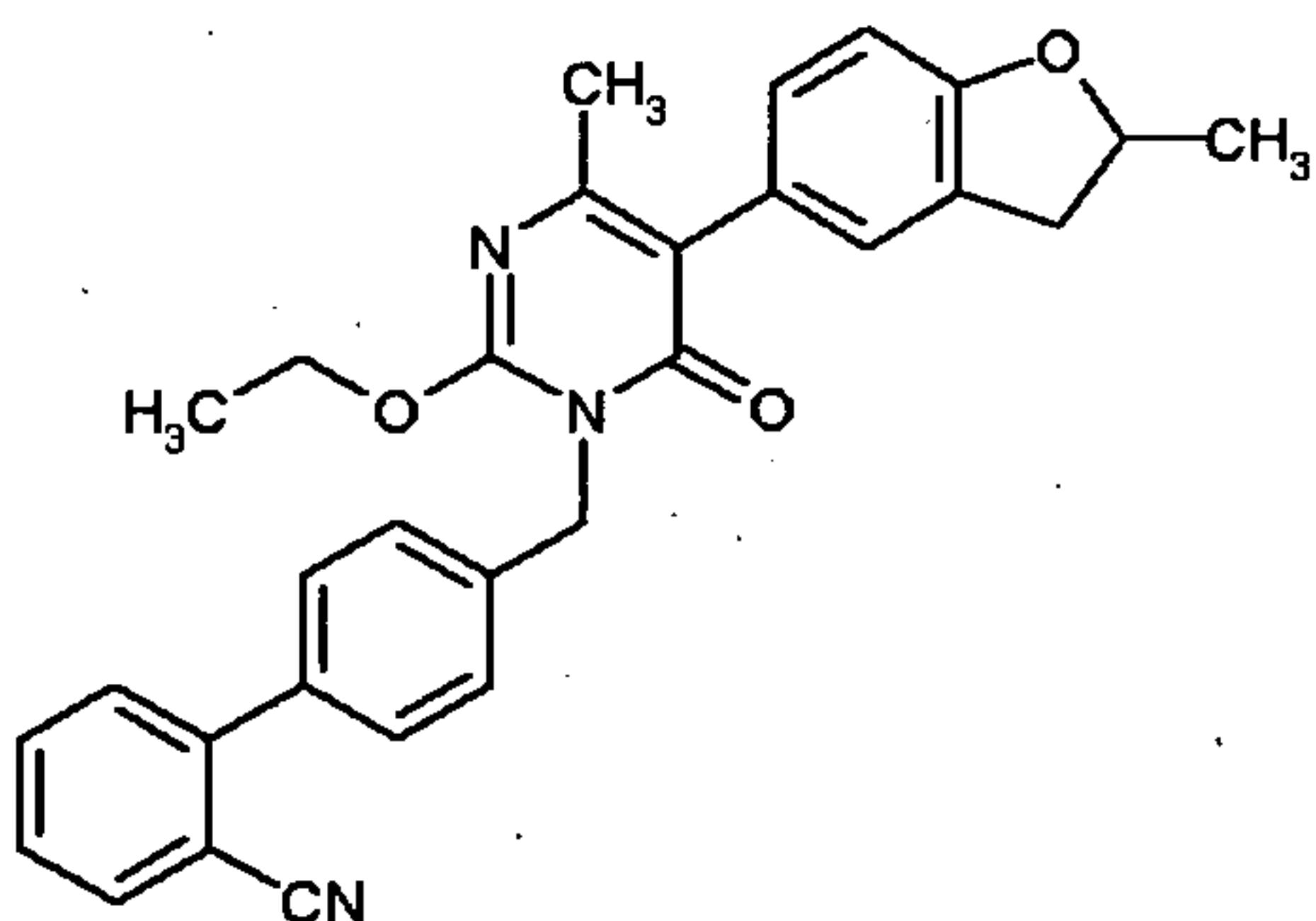
25 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless

crystals (0.21 g, 24%).

^1H NMR (300 MHz, DMSO- d_6) δ 1.29 (3H, t, J = 7.5), 2.06 (3H, s), 4.42 (2H, q, J = 7.5), 5.14 (2H, s), 7.21-7.48 (9H, m), 7.48-7.61 (2H, m), 7.62-7.75 (2H, m), 12.40 (1H, br)

5 Example 23

2-ethoxy-6-methyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

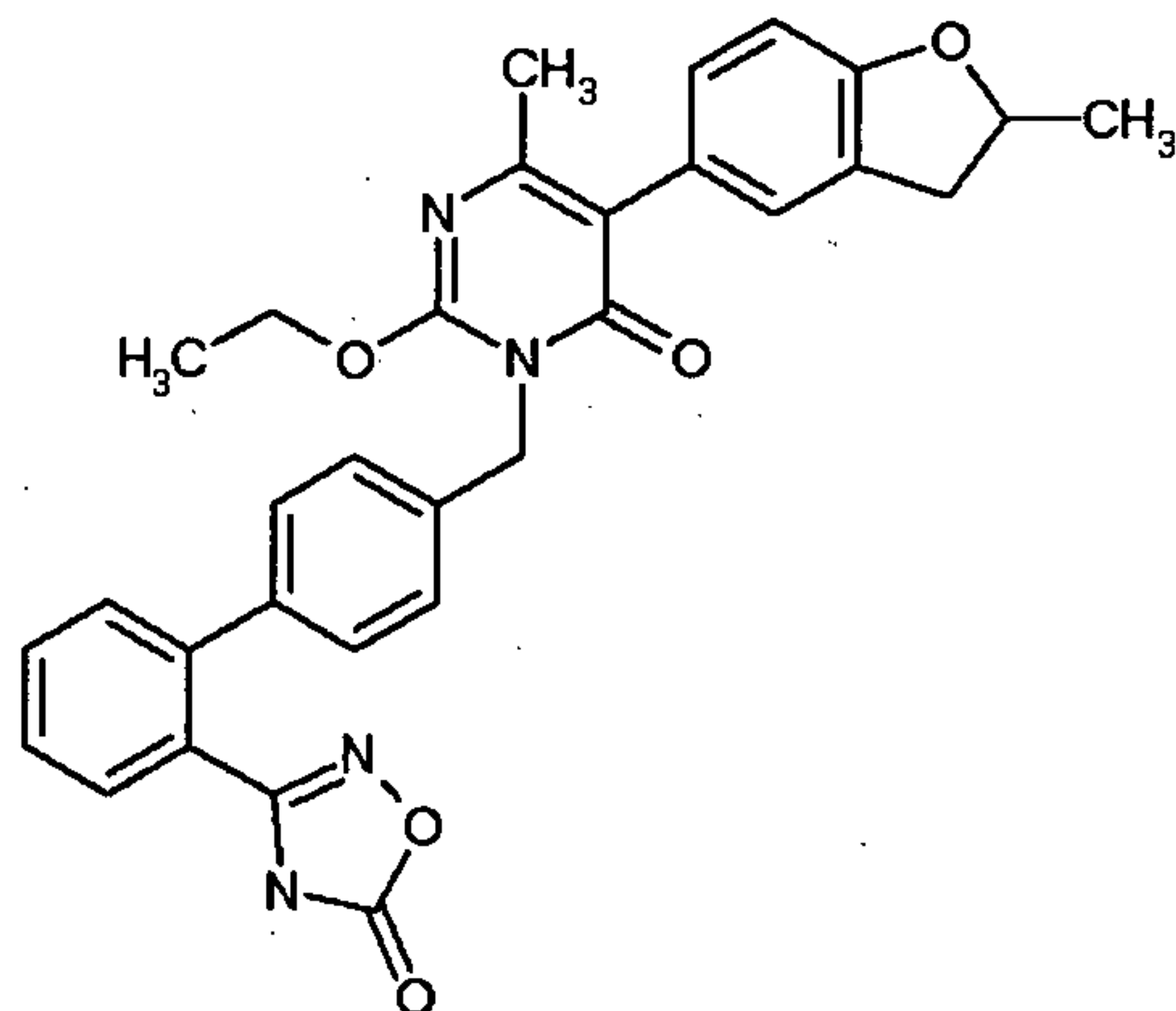


10 23a) 4'-{[2-ethoxy-4-methyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-ethoxy-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1 g) and
 15 2-methyl-2,3-dihydro-1-benzofuran-5-ylboronic acid (0.63 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (2 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon
 20 atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate.
 25 The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (0.77 g, 68%) as a pale-yellow solid.

^1H NMR (300 MHz, DMSO- d_6) δ 1.31 (3H, t, J = 7.2), 1.40 (3H, d, J = 6.6), 2.07 (3H, s), 2.79 (1H, dd, J = 15.6, 7.8), 3.32 (1H, dd, J = 15.6, 9.0), 4.43 (2H, q, J = 7.2), 4.84-4.99 (1H, m),
 30

5.17 (2H, s), 6.73 (1H, d, J = 8.1), 6.95 (1H, d, J = 8.1),
 7.08 (1H, s), 7.45 (2H, d, J = 8.4), 7.54-7.63 (4H, m), 7.74-
 7.84 (1H, m), 7.95 (1H, d, J = 7.5)



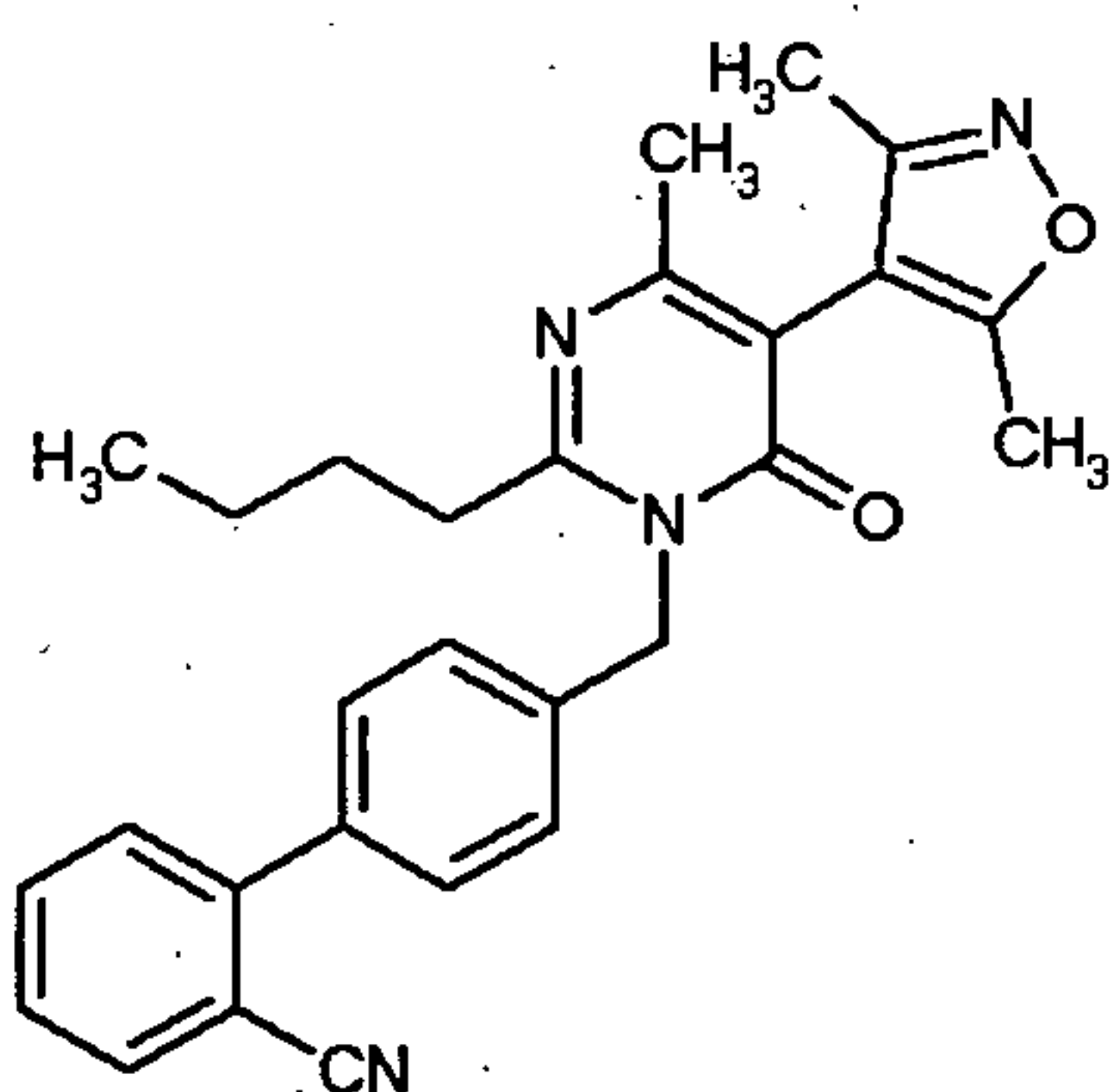
5 23b) 2-ethoxy-6-methyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.95 g), sodium hydrogen carbonate (1.35 g) and dimethyl sulfoxide (10 mL) was
 10 stirred at 40°C for 30 min, 4'-{[2-ethoxy-4-methyl-5-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.77 g) was added, and the mixture was stirred at 90°C for 5 hr. The mixture was allowed to cool to room temperature. Water was added to the reaction
 15 mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (5 mL), N,N'-
 20 carbonyldiimidazole (0.39 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.36 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried
 25 over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.58 g, 69%).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28 (3H, t, J = 7.5), 1.41 (3H, d, J = 6.6), 2.06 (3H, s), 2.80 (1H, dd, J = 15.6, 7.5), 3.33 (1H, dd, J = 15.6, 9.0), 4.40 (2H, q, J = 7.5), 4.81-5.03 (1H, m), 5.13 (2H, s), 6.73 (1H, d, J = 8.4), 6.95 (1H, d, J = 8.4), 7.07 (1H, s), 7.23-7.40 (4H, m), 7.49-7.61 (2H, m), 7.61-7.76 (2H, m), 12.40 (1H, br)

Example 24

2-butyl-5-(3,5-dimethylisoxazol-4-yl)-6-methyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

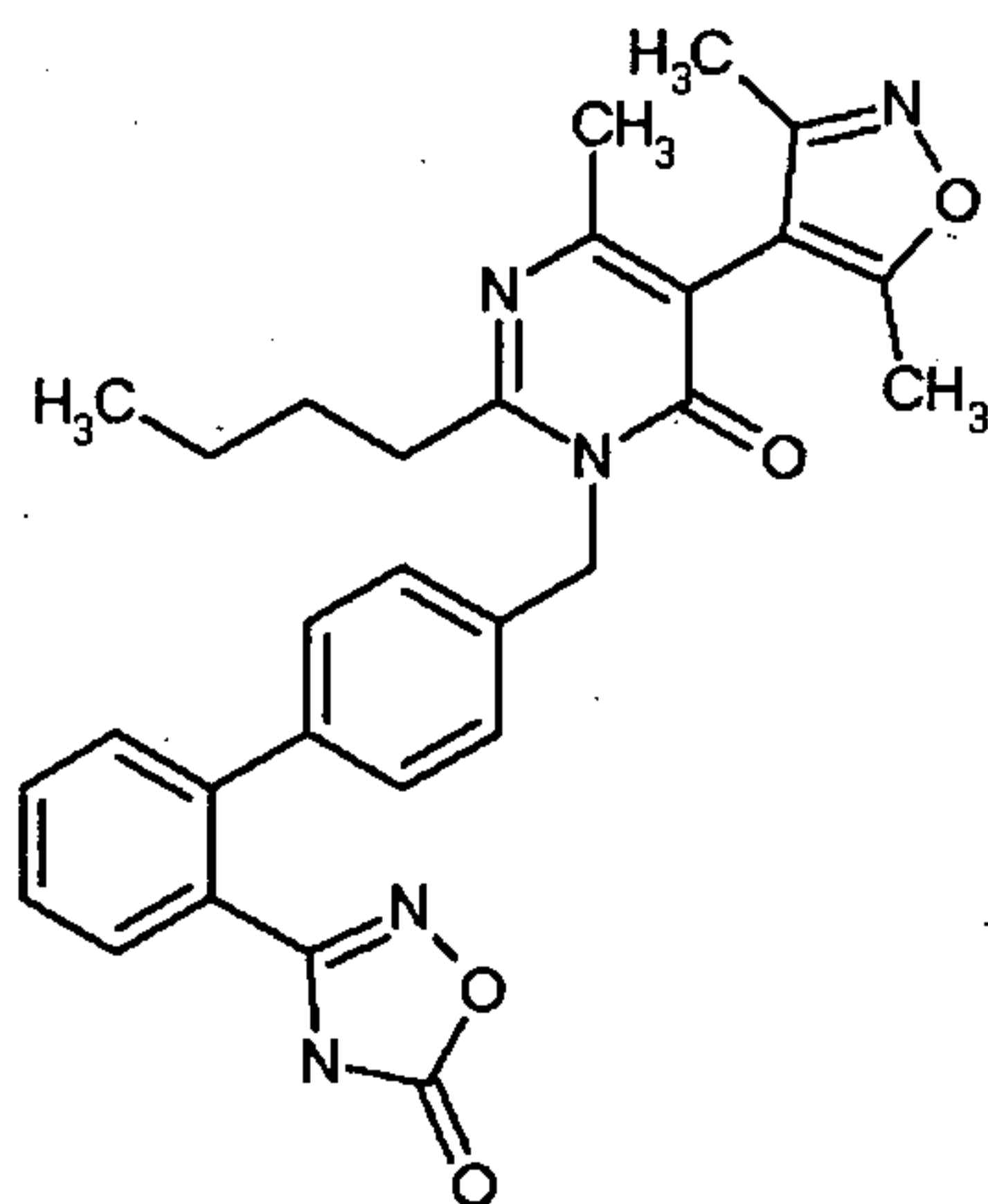


24a) 4'-([2-butyl-5-(3,5-dimethylisoxazol-4-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl)biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1 g) and 3,5-dimethylisoxazol-4-ylboronic acid (0.48 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (0.32 g, 31%) as a pale-yellow solid.

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.5), 1.33-1.50 (2H,

m), 1.64-1.81 (2H, m), 2.18 (6H, s), 2.29 (3H, s), 2.74 (2H, t, J = 7.5), 5.38 (2H, s), 7.28-7.35 (2H, m), 7.39-7.58 (4H, m), 7.60-7.70 (1H, m), 7.77 (1H, d, J = 7.5)



5 24b) 2-butyl-5-(3,5-dimethylisoxazol-4-yl)-6-methyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

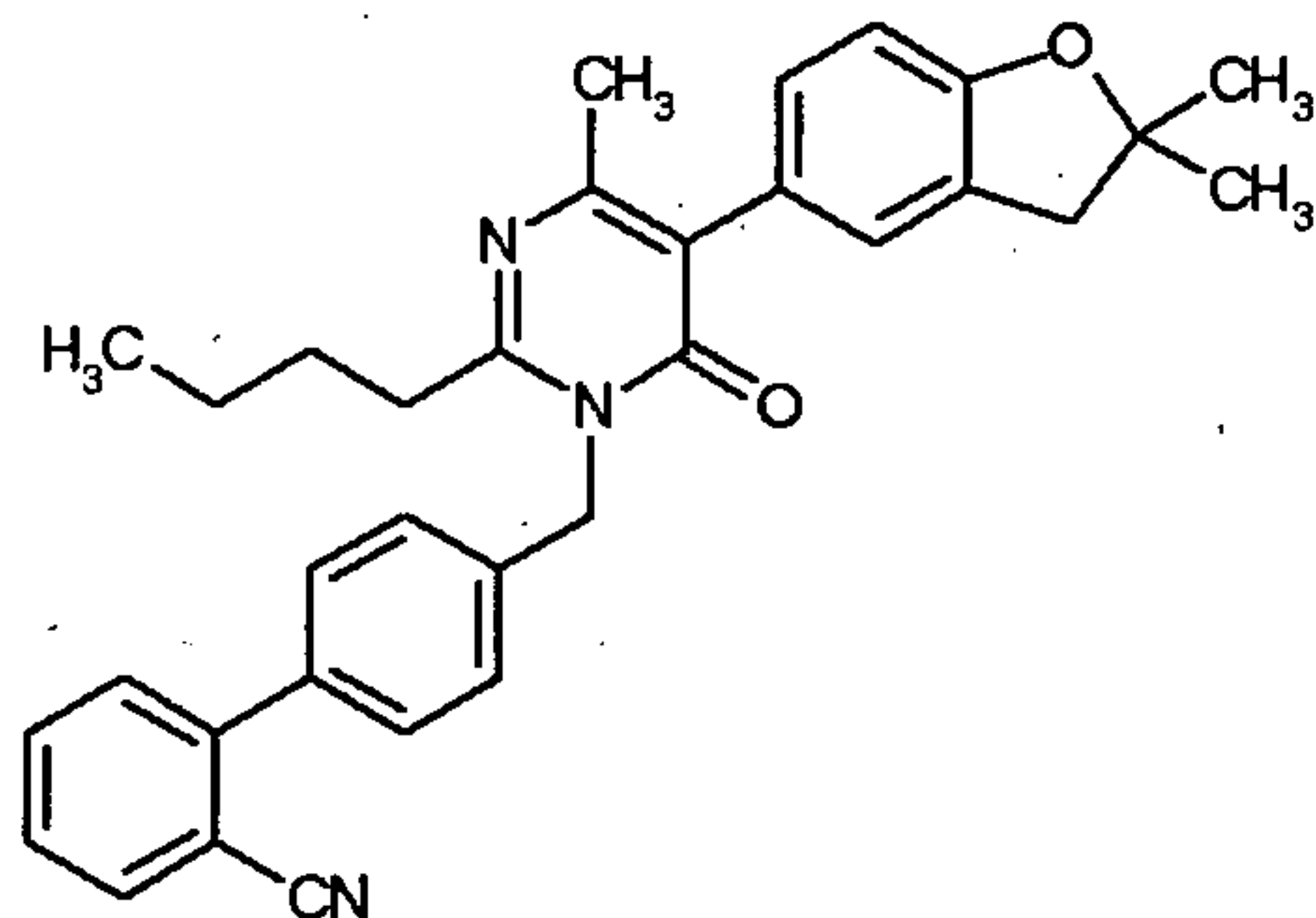
A mixture of hydroxylammonium chloride (0.42 g), sodium hydrogen carbonate (0.6 g) and dimethyl sulfoxide (5 mL) was stirred at 40°C for 30 min, 4'-{[2-butyl-5-(3,5-dimethylisoxazol-4-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.32 g) was added, and the mixture was stirred at 90°C for 5 hr. The mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (5 mL), N,N'-carbonyldiimidazole (0.12 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.11 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless

crystals (0.12 g, 19%).

^1H NMR (300 MHz, DMSO- d_6) δ 0.83 (3H, t, J = 7.8), 1.23-1.37 (2H, m), 1.53-1.65 (2H, m), 2.05 (3H, s), 2.10 (3H, s), 2.23 (3H, s), 2.70 (2H, t, J = 7.5), 5.29-5.45 (2H, m), 7.22 (2H, d, J = 8.4), 7.31 (2H, d, J = 8.4), 7.48-7.61 (2H, m), 7.64-7.74 (2H, m), 12.41 (1H, s)

Example 25

2-butyl-5-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

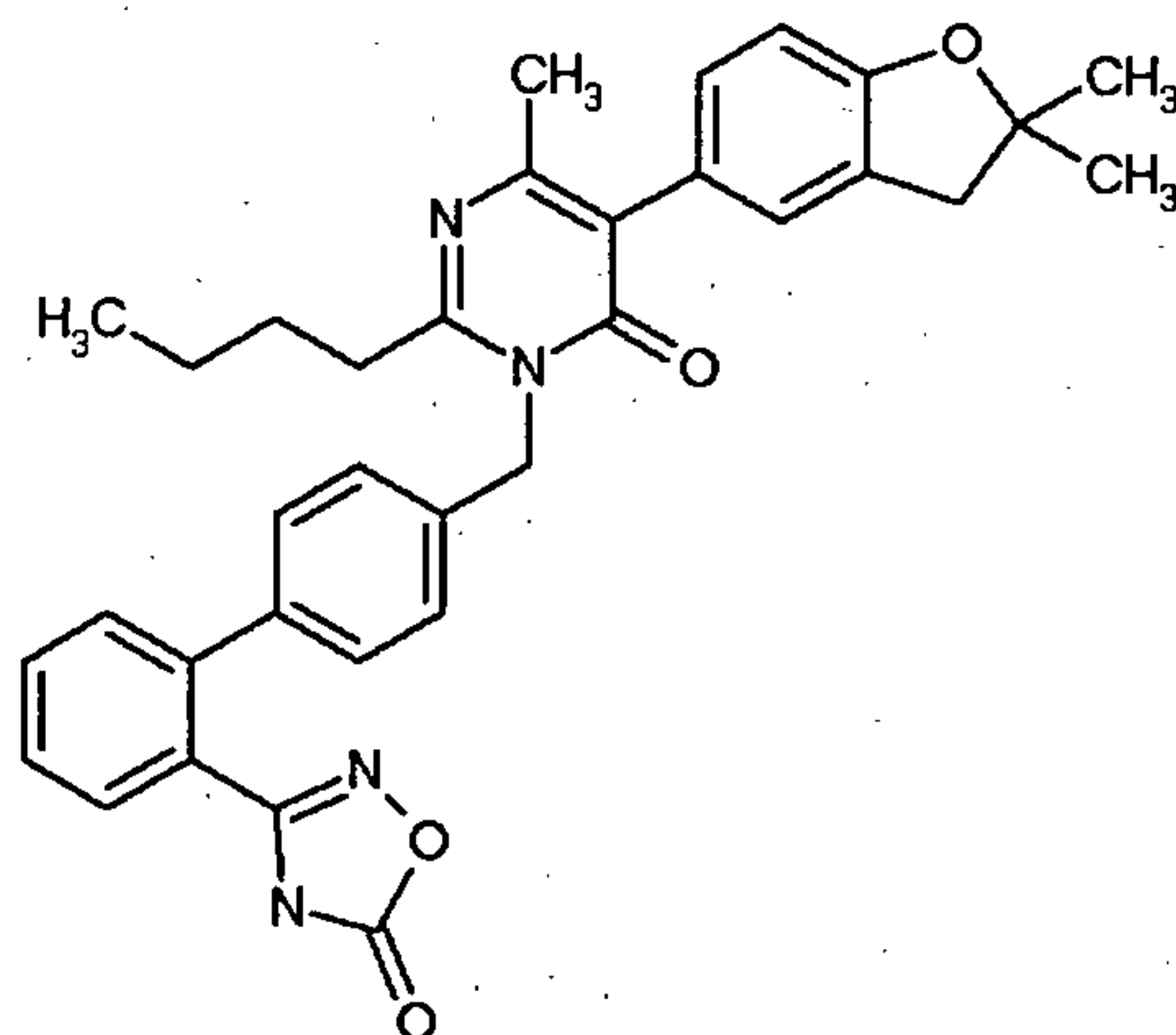


25a) 4'-{[2-butyl-5-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (0.76 g) and 2,2-dimethyl-2,3-dihydro-1-benzofuran-5-ylboronic acid (0.50 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (0.72 g, 82%) as a colorless solid.

^1H NMR (300 MHz, CDCl_3) δ 0.93 (3H, t, J = 7.5), 1.35-1.50 (2H,

m), 1.49 (6H, s), 1.65-1.79 (2H, m), 2.25 (3H, s), 2.76 (2H, t, J = 7.5), 3.04 (2H, s), 5.38 (2H, s), 6.76 (1H, d, J = 8.1), 7.04 (1H, d, J = 8.1), 7.13 (1H, s), 7.35 (2H, d, J = 8.1), 7.40-7.56 (4H, m), 7.60-7.68 (1H, m), 7.76 (1H, d, J = 7.5)



5

25b) 2-butyl-5-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-6-methyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

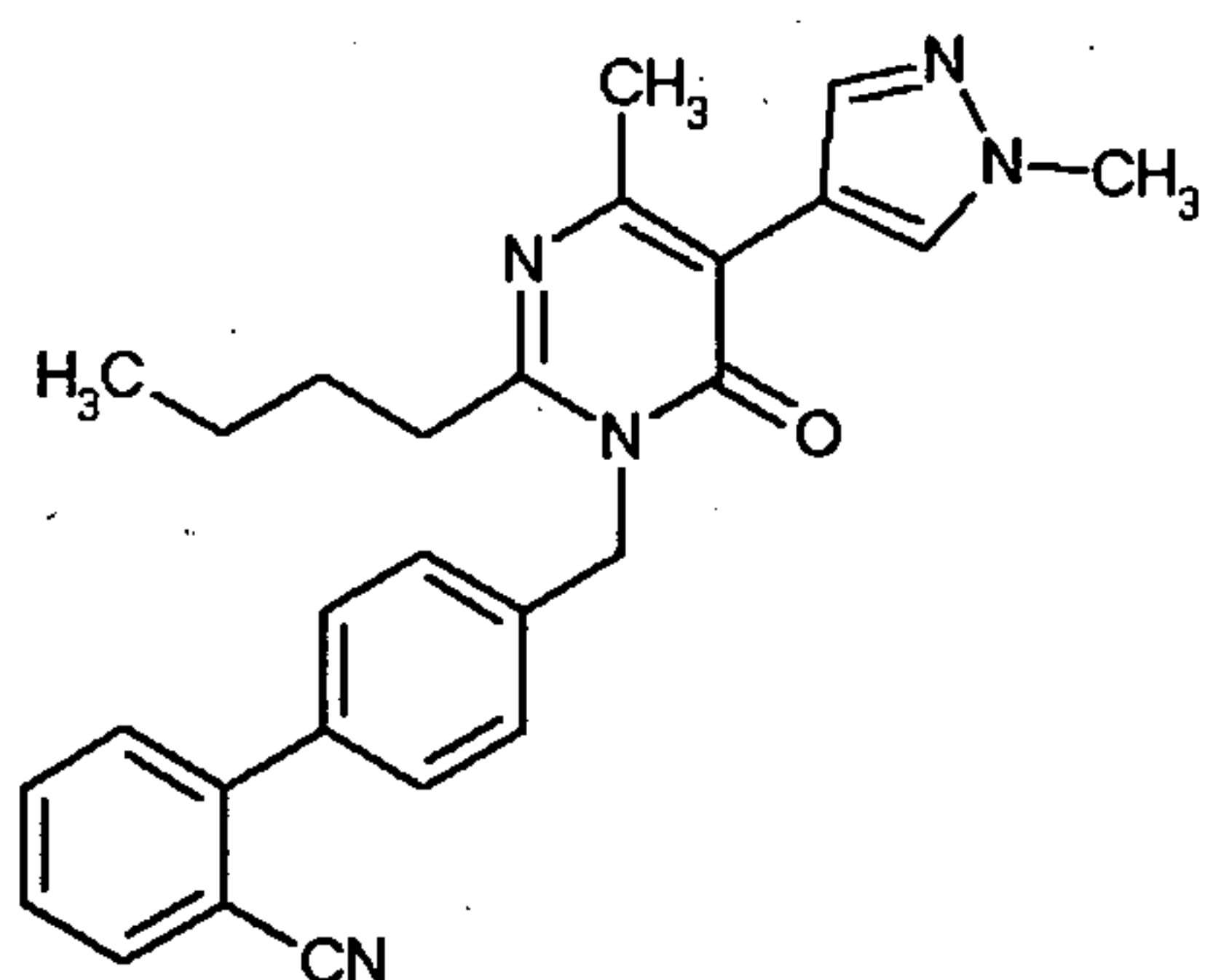
A mixture of hydroxylammonium chloride (0.84 g), sodium
 10 hydrogen carbonate (1.2 g) and dimethyl sulfoxide (15 mL) was
 stirred at 40°C for 30 min, 4'-{[2-butyl-5-(2,2-dimethyl-2,3-
 dihydro-1-benzofuran-5-yl)-4-methyl-6-oxopyrimidin-1(6H)-
 yl]methyl}biphenyl-2-carbonitrile (0.72 g) was added, and the
 mixture was stirred at 90°C for 5 hr. The mixture was allowed
 15 to cool to room temperature, water was added to the reaction
 mixture, and the precipitate was collected by filtration. The
 obtained solid was dissolved in ethyl acetate. The solution
 was washed with saturated brine and dried over anhydrous
 sodium sulfate, and the solvent was evaporated. The residue
 20 was dissolved in tetrahydrofuran (5 mL), N,N'-
 carbonyldiimidazole (0.35 g) and then 1,8-
 diazabicyclo[5.4.0]undec-7-ene (0.33 mL) were added, and the
 mixture was stirred at room temperature for 30 min. The
 reaction mixture was diluted with ethyl acetate, washed with 1
 25 M hydrochloric acid and then with saturated brine, and dried
 over anhydrous sodium sulfate. The solvent was evaporated
 under reduced pressure. The residue was purified by silica gel
 column chromatography to give the title compound as colorless

crystals (0.68 g, 85%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.5), 1.22-1.37 (2H, m), 1.43 (6H, s), 1.49-1.65 (2H, m), 2.13 (3H, s), 2.68 (2H, t, J = 7.5), 3.30 (2H, s), 5.34 (2H, s), 6.72 (1H, d, J = 8.1), 7.00 (1H, d, J = 8.1), 7.12 (1H, s), 7.25 (2H, d, J = 8.1), 7.32 (2H, d, J = 8.1), 7.49-7.61 (2H, m), 7.64-7.74 (2H, m), 12.43 (1H, s)

Example 26

2-butyl-6-methyl-5-(1-methyl-1H-pyrazol-4-yl)-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

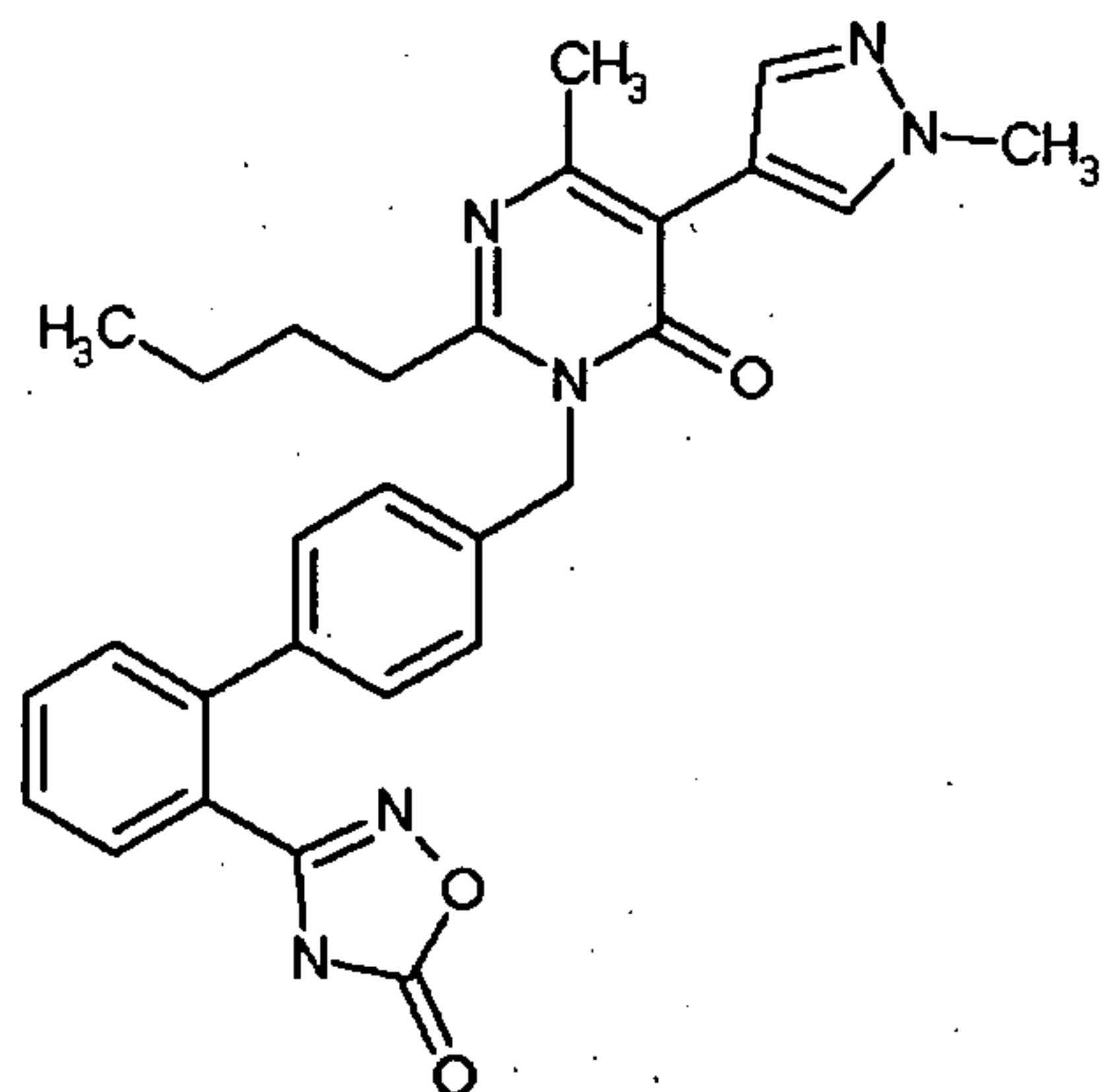


26a) 4'-([2-butyl-4-methyl-5-(1-methyl-1H-pyrazol-4-yl)-6-oxopyrimidin-1(6H)-yl]methyl)biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-2-butyl-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1 g) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.72 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (0.44 g, 43%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 0.92 (3H, t, J = 7.2), 1.34-1.48 (2H,

m), 1.64-1.78 (2H, m), 2.49 (3H, s), 2.72 (2H, t, $J = 7.2$), 3.94 (3H, s), 5.40 (2H, s), 7.30 (2H, d, $J = 8.4$), 7.40-7.50 (2H, m), 7.53 (2H, d, $J = 8.4$), 7.60-7.67 (1H, m), 7.71 (1H, s), 7.75 (1H, d, $J = 7.5$), 7.95 (1H, s)



5

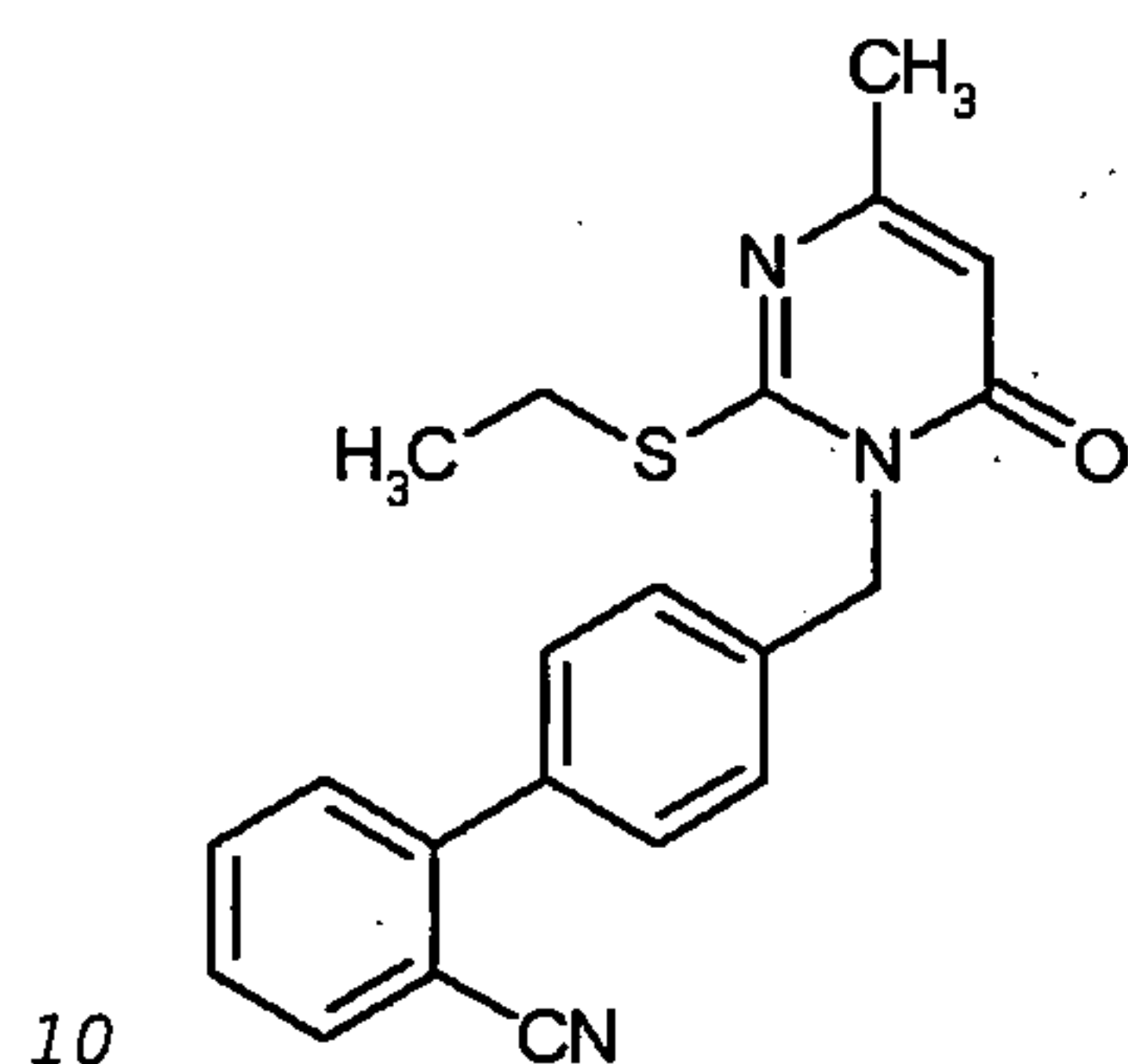
26b) 2-butyl-6-methyl-5-(1-methyl-1H-pyrazol-4-yl)-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.7 g), sodium
 10 hydrogen carbonate (1 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[2-butyl-4-methyl-5-(1-methyl-1H-pyrazol-4-yl)-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.44 g) was added, and the mixture was stirred at 90°C for 5 hr. The mixture was allowed to cool to room
 15 temperature. Water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in
 20 tetrahydrofuran (5 mL), N,N'-carbonyldiimidazole (0.24 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.22 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and
 25 dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.13 g, 27%).

^1H NMR (300 MHz, DMSO- d_6) δ 0.82 (3H, t, $J = 7.5$), 1.21-1.37 (2H, m), 1.51-1.65 (2H, m), 2.38 (3H, s), 2.67 (2H, t, $J = 7.5$), 3.87 (3H, s), 5.37 (2H, s), 7.22 (2H, d, $J = 8.4$), 7.30 (2H, d, $J = 8.4$), 7.48-7.60 (2H, m), 7.63-7.73 (3H, m), 8.05 (1H, s), 12.41 (1H, br)

Example 27

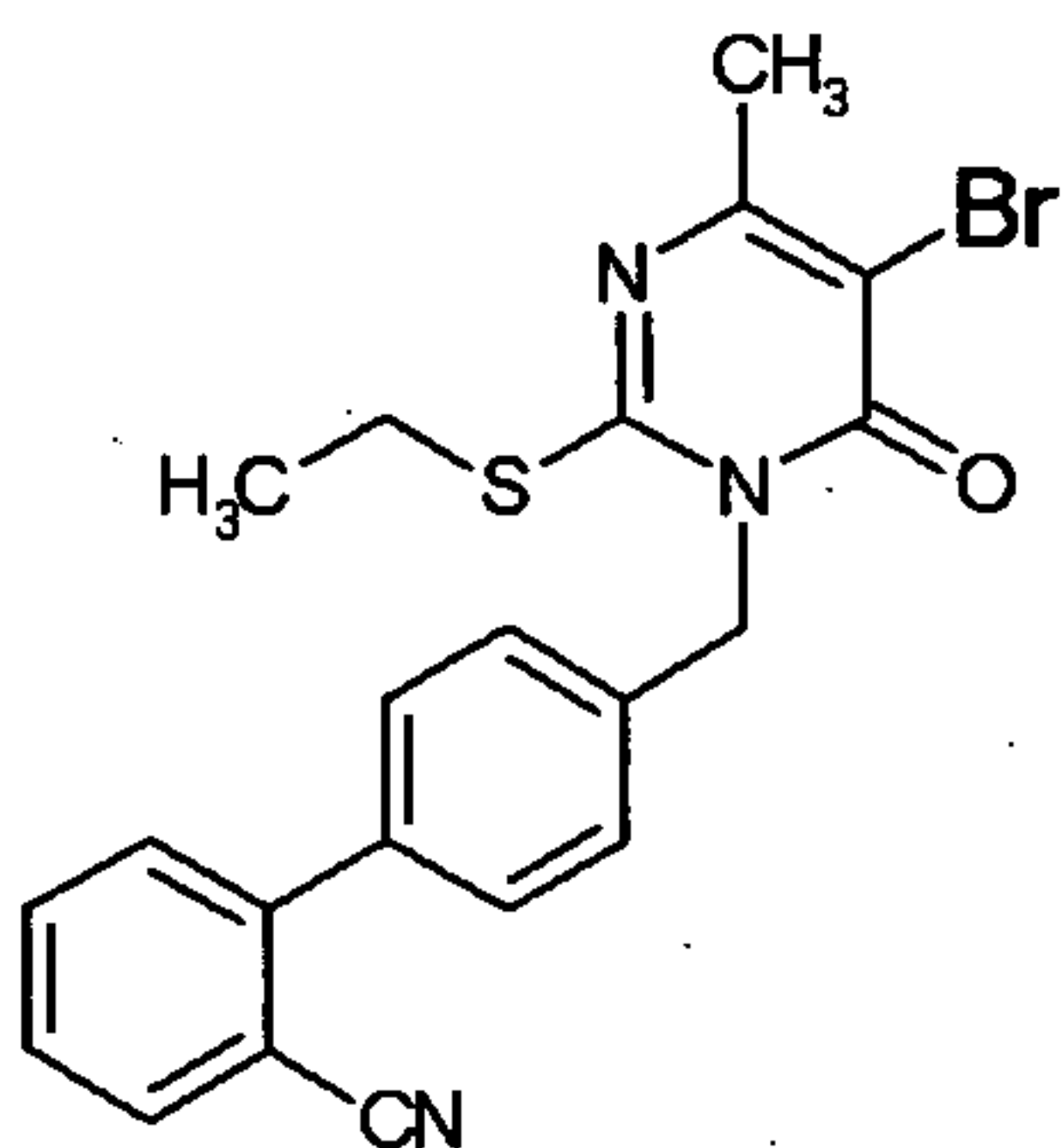
2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-5-phenylpyrimidin-4(3H)-one



27a) 4'-{[2-(ethylthio)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 2-ethylthio-6-methylpyrimidin-4(3H)-one (6.1 g) and 4'-(bromomethyl)biphenyl-2-carbonitrile (10.6 g) in acetonitrile (120 mL) was added potassium carbonate (5.9 g), and the mixture was stirred at 50°C for 12 hr. The insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the title compound (3.83 g, 30%) as a colorless solid.

20 ^1H NMR (300 MHz, CDCl_3) δ 1.36 (3H, t, $J = 7.2$), 2.24 (3H, s), 3.18 (2H, q, $J = 7.2$), 5.31 (2H, s), 6.12 (1H, s), 7.38-7.55 (6H, m), 7.59-7.67 (1H, m), 7.75 (1H, d, $J = 7.8$)

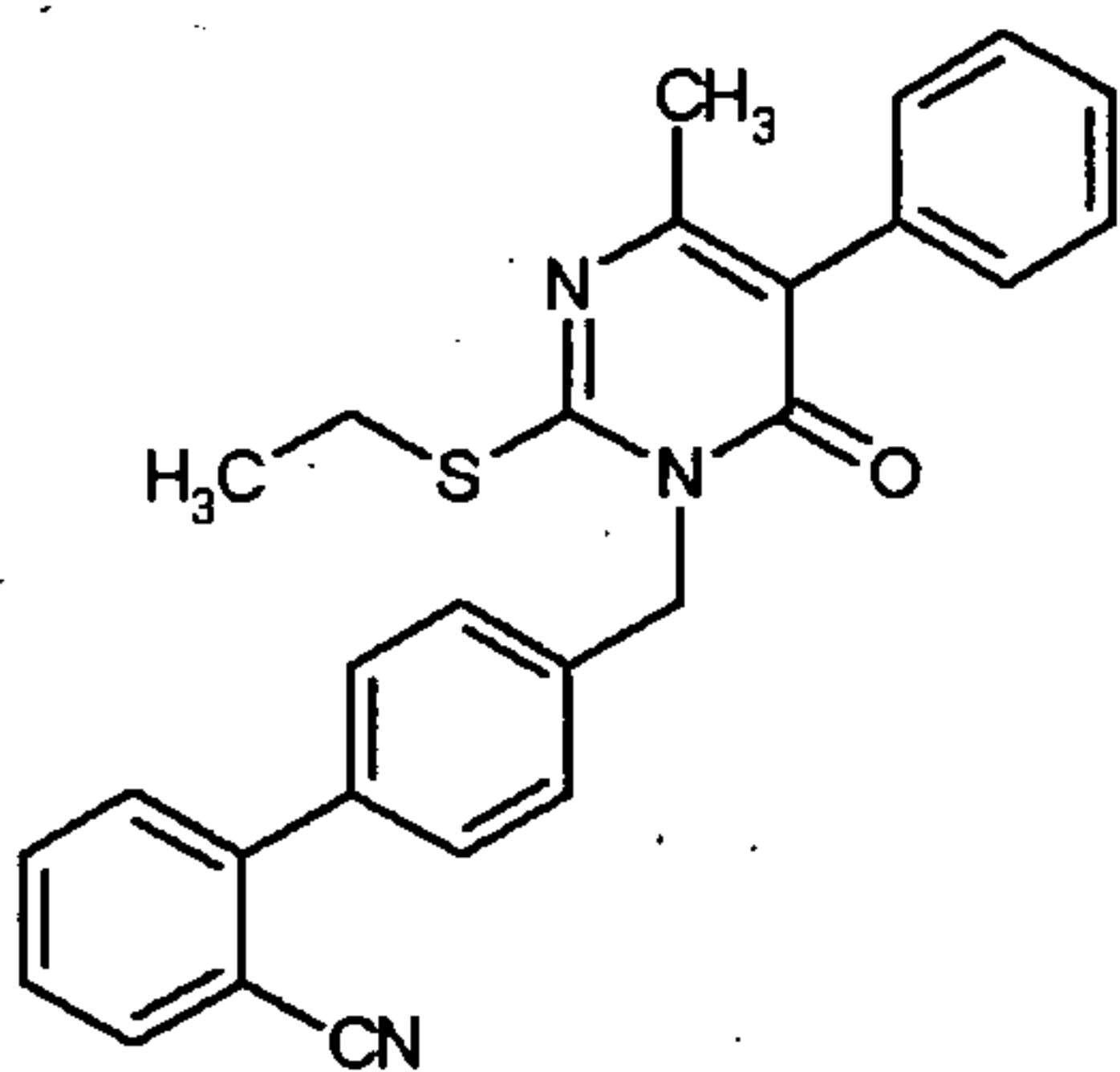


27b) 4'-{[5-bromo-2-(ethylthio)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

25

To a solution of 4'-{[2-(ethylthio)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (3.83 g) and sodium acetate (0.87 g) in acetic acid (40 mL) was added bromine (0.54 mL), and the mixture was stirred for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous sodium thiosulfate solution, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (4.66 g, 99%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 1.38 (3H, t, J = 7.2), 2.46 (3H, s), 3.20 (2H, q, J = 7.2), 5.34 (2H, s), 7.40-7.53 (6H, m), 7.60-7.68 (1H, m), 7.75 (1H, d, J = 7.8)

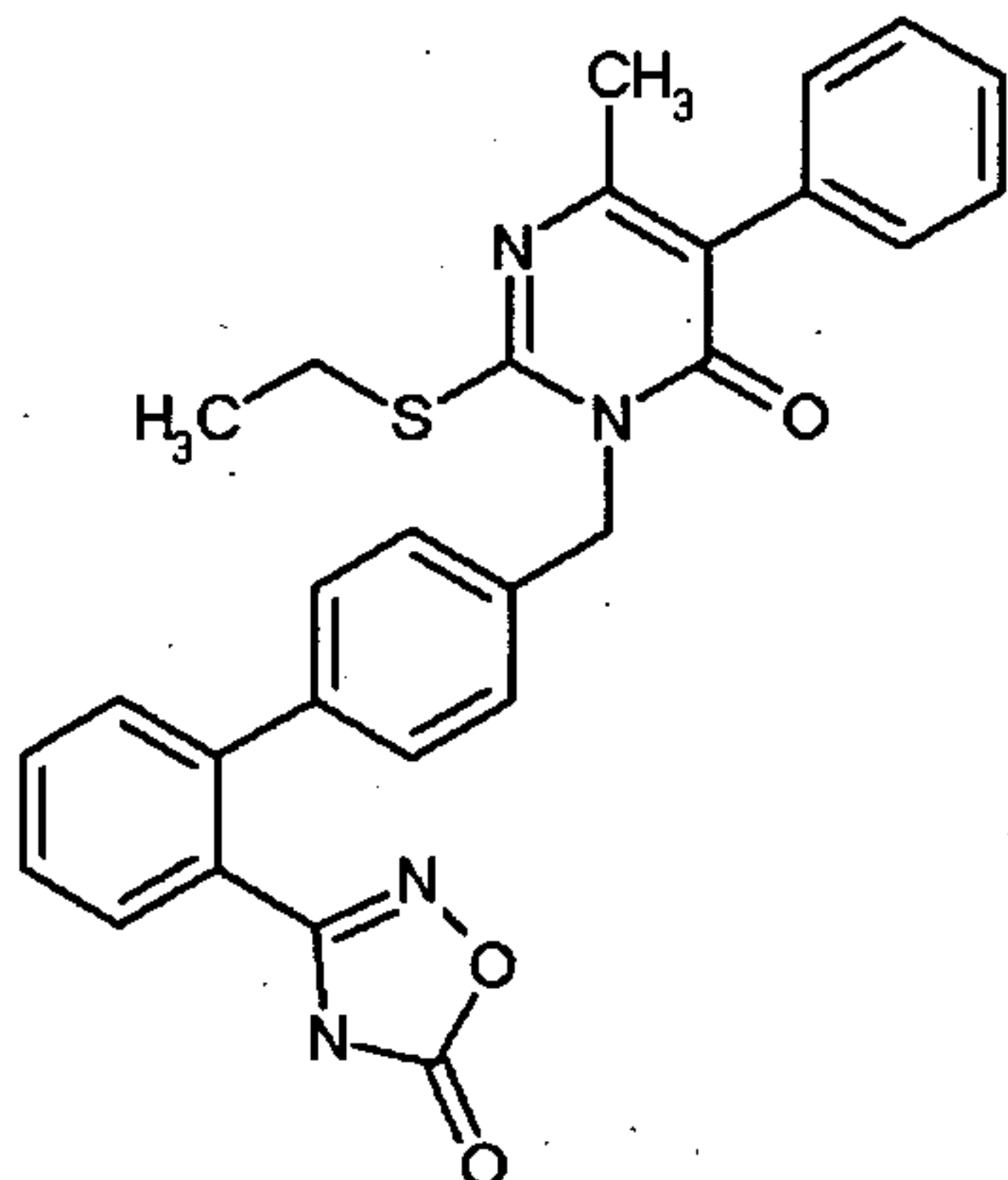


27c) 4'-{[2-(ethylthio)-4-methyl-6-oxo-5-phenylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-{[5-bromo-2-(ethylthio)-4-methyl-6-oxopyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.76 g) and phenylboronic acid (0.32 g) in 1,4-dioxane (10 mL) solution were added 2 M aqueous cesium carbonate solution (2 mL) and tetrakis(triphenylphosphine)palladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title

compound (0.2 g, 26%) as a colorless solid.

^1H NMR (300 MHz, CDCl_3) δ 1.42 (3H, t, $J = 7.5$), 2.20 (3H, s), 3.24 (2H, q, $J = 7.5$), 5.34 (2H, s), 7.28–7.36 (3H, m), 7.36–7.59 (8H, m), 7.59–7.68 (1H, m), 7.75 (1H, d, $J = 8.1$)



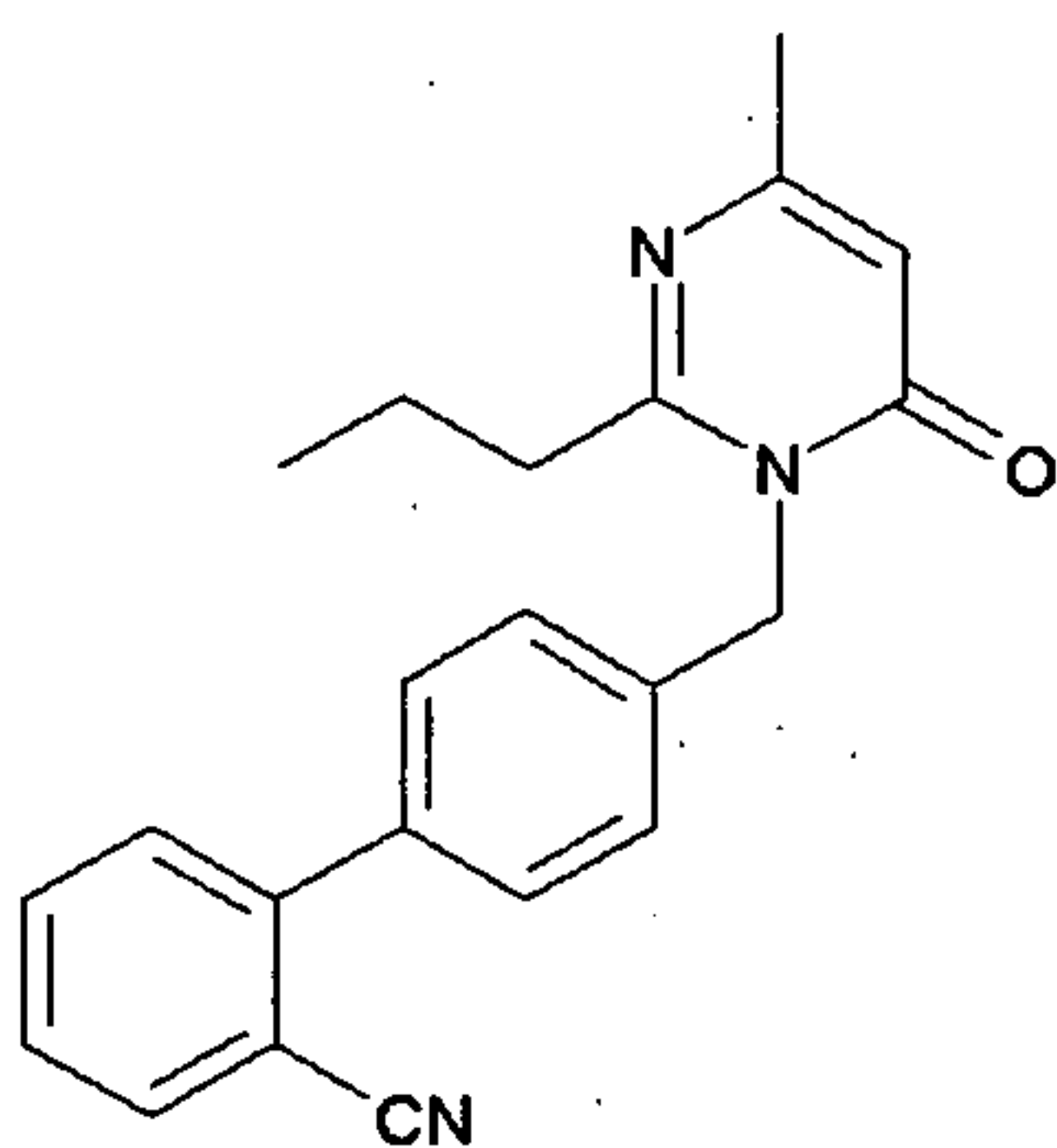
27d) 2-(ethylthio)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-5-phenylpyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.27 g), sodium
 10 hydrogen carbonate (0.38 g) and dimethyl sulfoxide (5 mL) was
 stirred at 40°C for 30 min, 4'-{[2-(ethylthio)-4-methyl-6-oxo-
 5-phenylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile
 (0.20 g) was added, and the mixture was stirred at 90°C for 5
 hr. The mixture was allowed to cool to room temperature, water
 15 was added to the reaction mixture, and the precipitate was
 collected by filtration. The obtained solid was dissolved in
 ethyl acetate. The solution was washed with saturated brine
 and dried over anhydrous sodium sulfate, and the solvent was
 evaporated. The residue was dissolved in tetrahydrofuran (5
 20 mL), N,N' -carbonyldiimidazole (0.11 g) and then 1,8-
 diazabicyclo[5.4.0]undec-7-ene (0.1 mL) were added, and the
 mixture was stirred at room temperature for 30 min. The
 reaction mixture was diluted with ethyl acetate, washed with 1
 M hydrochloric acid and then with saturated brine, and dried
 25 over anhydrous sodium sulfate. The solvent was evaporated
 under reduced pressure. The residue was purified by silica gel
 column chromatography to give the title compound as colorless
 crystals (0.11 g, 50%).

^1H NMR (300 MHz, DMSO- d_6) δ 1.32 (3H, t, J = 7.2), 2.13 (3H, s), 3.19 (2H, q, J = 7.2), 5.26 (2H, s), 7.28-7.47 (9H, m), 7.49-7.61 (2H, m), 7.63-7.75 (2H, m), 12.43 (1H, br)

Example 28

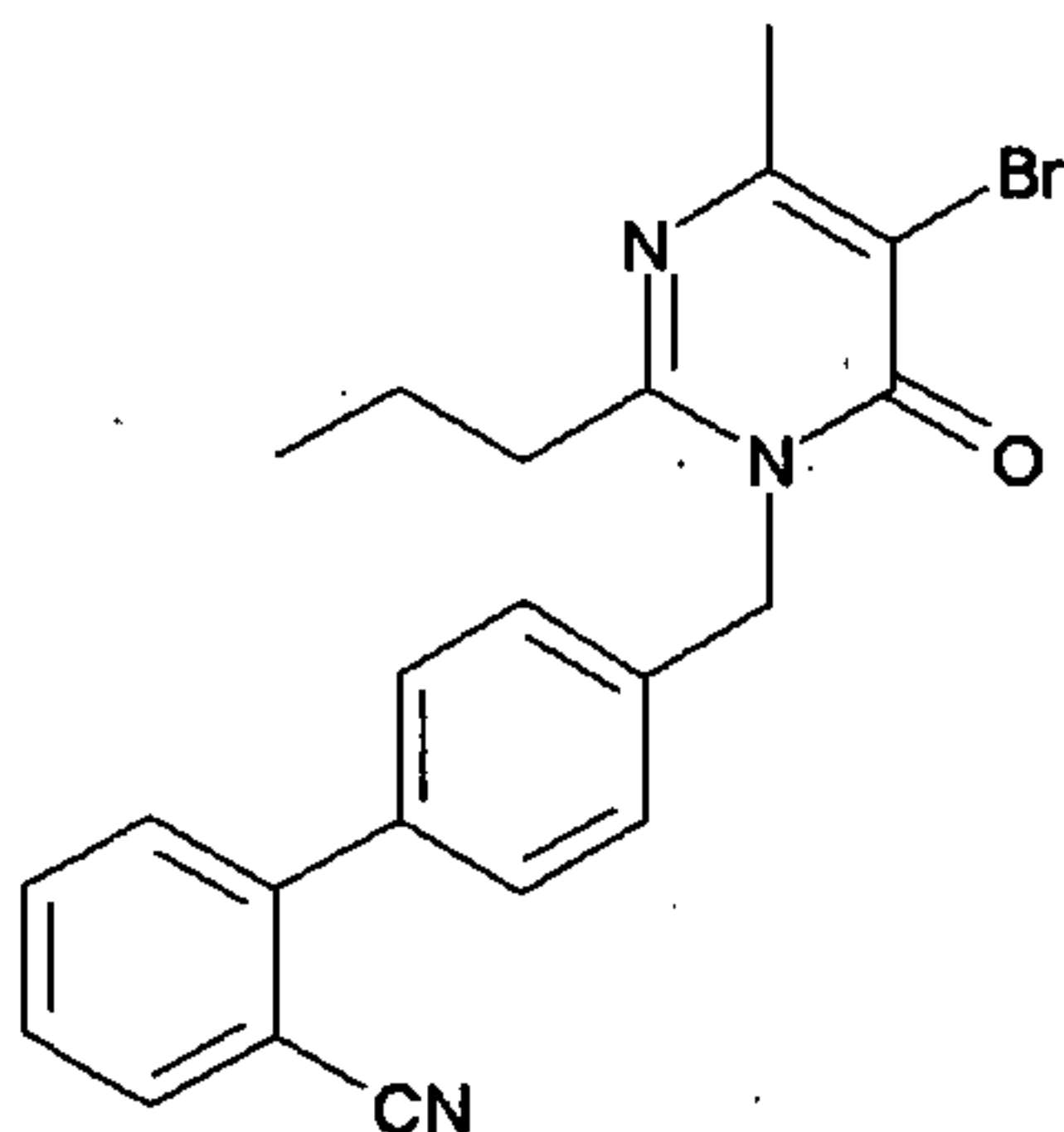
- 5 5-(4-isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one



- 28a) 4'-[(4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 6-methyl-2-propylpyrimidin-4(3H)-one (8 g) and 4'-(bromomethyl)biphenyl-2-carbonitrile (15.7 g) in acetonitrile (200 mL) was added potassium carbonate (14.5 g), and the mixture was stirred at 50°C for 12 hr. The insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the title compound (8.44 g, 47%) as a colorless solid.

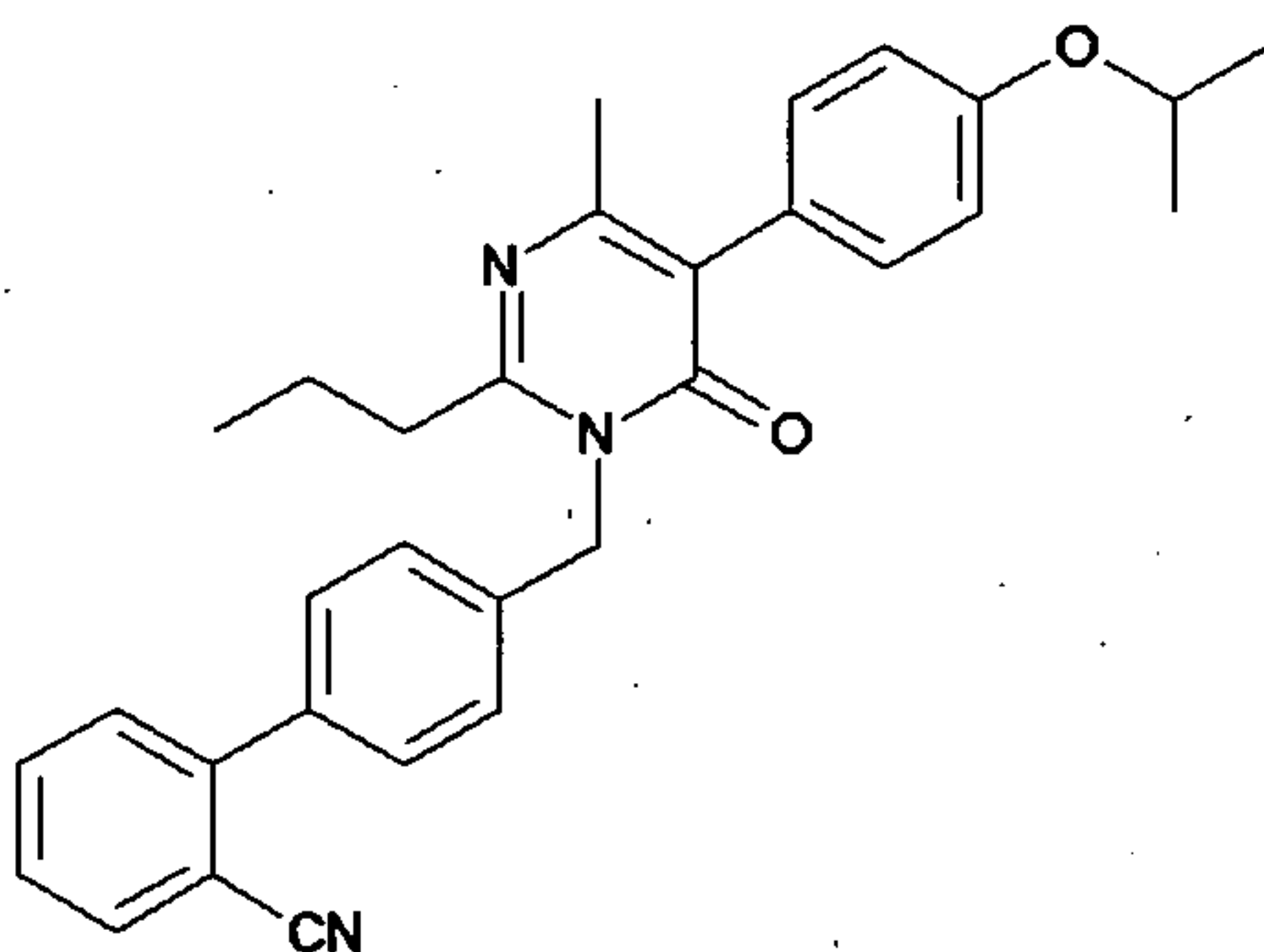
^1H NMR (300 MHz, CDCl_3) δ 0.98 (3H, t, J = 7.2), 1.66-1.81 (2H, m), 2.29 (3H, s), 2.66 (2H, t, J = 7.2), 5.36 (2H, s), 6.29 (1H, s), 7.27 (2H, d, J = 8.1), 7.40-7.56 (4H, m), 7.60-7.67 (1H, m), 7.75 (1H, d, J = 6.9)



- 28b) 4'-[(5-bromo-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile

To a solution of 4'-[(4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (8.44 g) and sodium acetate (2.22 g) in acetic acid (100 mL) was added bromine (1.39 mL), and the mixture was stirred for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous sodium thiosulfate solution, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (6.68 g, 64%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.86 (3H, t, J = 7.2), 1.55-1.70 (2H, m), 2.40 (3H, s), 2.67 (2H, t, J = 7.2), 5.39 (2H, s), 7.29 (2H, d, J = 8.1), 7.50-7.63 (4H, m), 7.72-7.82 (1H, m), 7.92 (1H, d, J = 7.5)

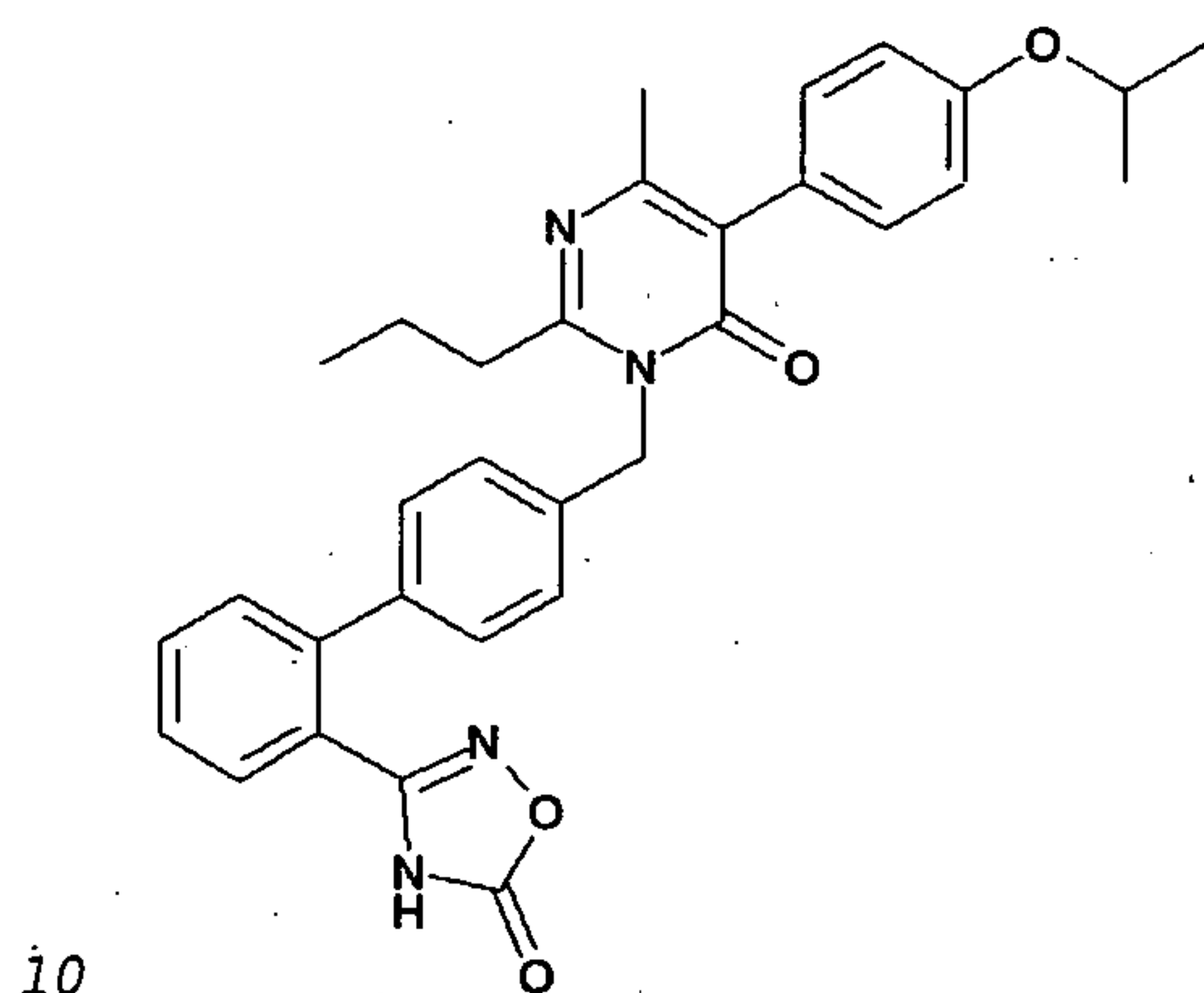


28c) 4'-{[5-(4-isopropoxyphenyl)-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

To a solution of 4'-[(5-bromo-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.0 g) and 4-isopropoxyphenylboronic acid (0.64 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate

and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (1.01 g, 89%) as a colorless solid.

- 5 ¹H NMR (300 MHz, CDCl₃) δ 1.02 (3H, t, J = 7.2), 1.34 (6H, d, J = 6.0), 1.71-1.85 (2H, m), 2.25 (3H, s), 2.72 (2H, t, J = 7.2), 4.50-4.63 (1H, m), 5.38 (2H, s), 6.93 (2H, d, J = 8.7), 7.23 (2H, d, J = 8.7), 7.30-7.38 (2H, m), 7.39-7.57 (4H, m), 7.58-7.68 (1H, m), 7.75 (1H, d, J = 7.5)



28d) 5-(4-isopropoxyphenyl)-6-methyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-2-propylpyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (2.49 g), sodium
 15 hydrogen carbonate (3.54 g) and dimethyl sulfoxide (20 mL) was stirred at 40°C for 30 min, 4'-{[5-(4-isopropoxyphenyl)-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (1.01 g) was added, and the mixture was stirred
 20 at 90°C for 5 hr. The mixture was allowed to cool to room temperature. Water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in
 25 tetrahydrofuran (10 mL), N,N'-carbonyldiimidazole (0.51 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.47 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed

with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as
 5 colorless crystals (0.75 g, 66%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.88 (3H, t, J = 7.2), 1.29 (6H, d, J = 6.3), 1.52-1.71 (2H, m), 2.13 (3H, s), 2.66 (2H, t, J = 7.2), 4.55-4.73 (1H, m), 5.35 (2H, s), 6.93 (2H, d, J = 8.1), 7.16-7.37 (6H, m), 7.47-7.62 (2H, m), 7.63-7.75 (2H, m), 12.40
 10 (1H, br)

5-(4-Isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following
 15 salts.

5-(4-isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one sodium salt

5-(4-isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one potassium salt
 20

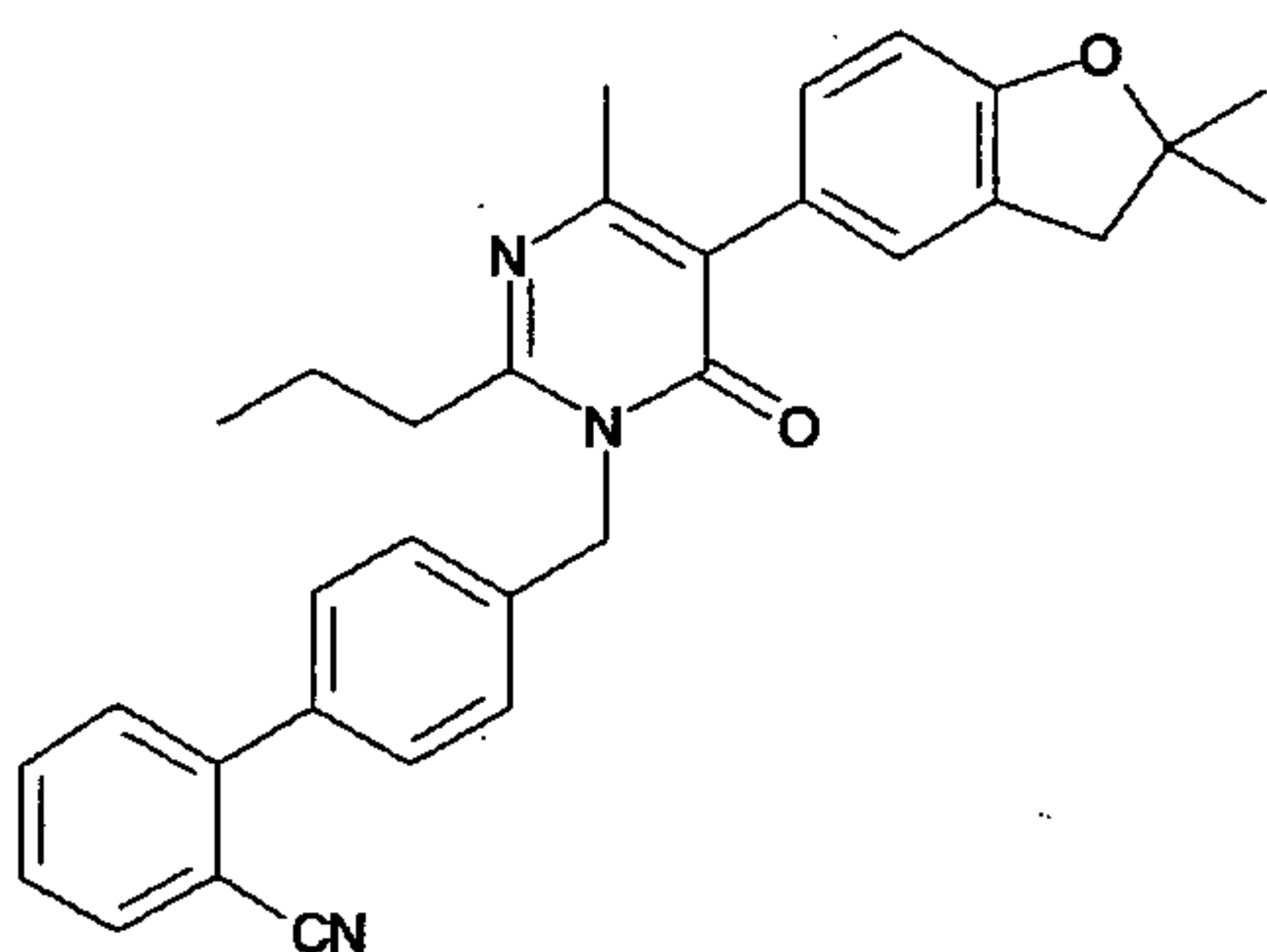
5-(4-isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one 0.5 calcium salt

5-(4-isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one hydrochloride
 25

5-(4-isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one hydrobromide
 30

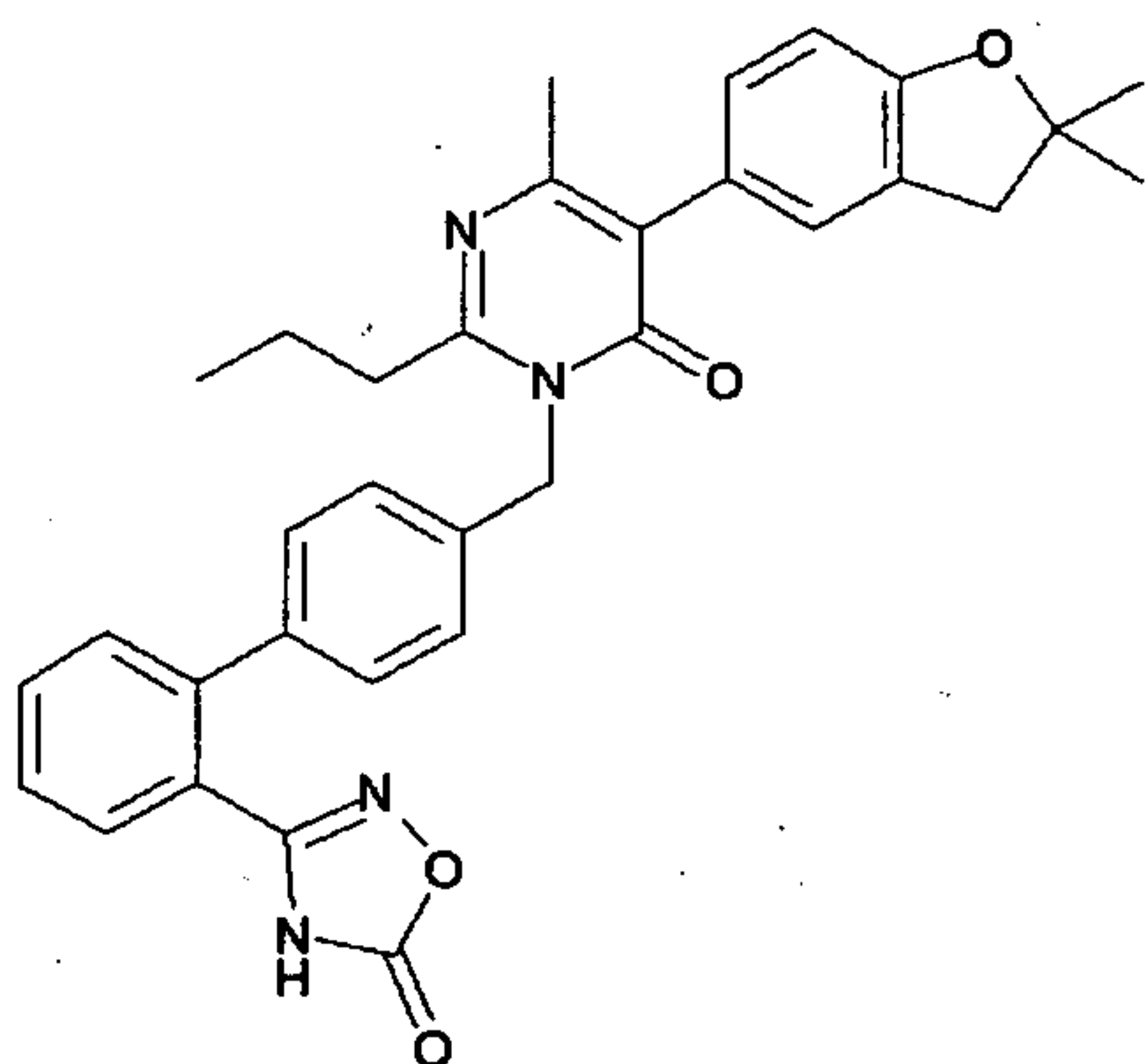
Example 29

5-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one



29a) 4'-{[5-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile

- 5 To a solution of 4'-[(5-bromo-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.0 g) and 2,2-dimethyl-2,3-dihydro-1-benzofuran-5-ylboronic acid (0.68 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium carbonate solution (4 mL) and [1,1'-
- 10 bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through celite. The filtrate was washed successively with 1 M
- 15 hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (1.03 g, 89%) as a colorless solid.
- 20 ¹H NMR (300 MHz, CDCl₃) δ 1.02 (3H, t, J = 7.2), 1.49 (6H, s), 1.69-1.85 (2H, m), 2.25 (3H, s), 2.71 (2H, t, J = 7.2), 3.04 (2H, s), 5.37 (2H, s), 6.76 (1H, d, J = 8.4), 7.03 (1H, d, J = 8.4), 7.13 (1H, s), 7.28-7.38 (2H, m), 7.39-7.57 (4H, m), 7.59-7.68 (1H, m), 7.76 (1H, d, J = 7.5)



29b) 5-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-6-methyl-3-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-2-propylpyrimidin-4(3H)-one

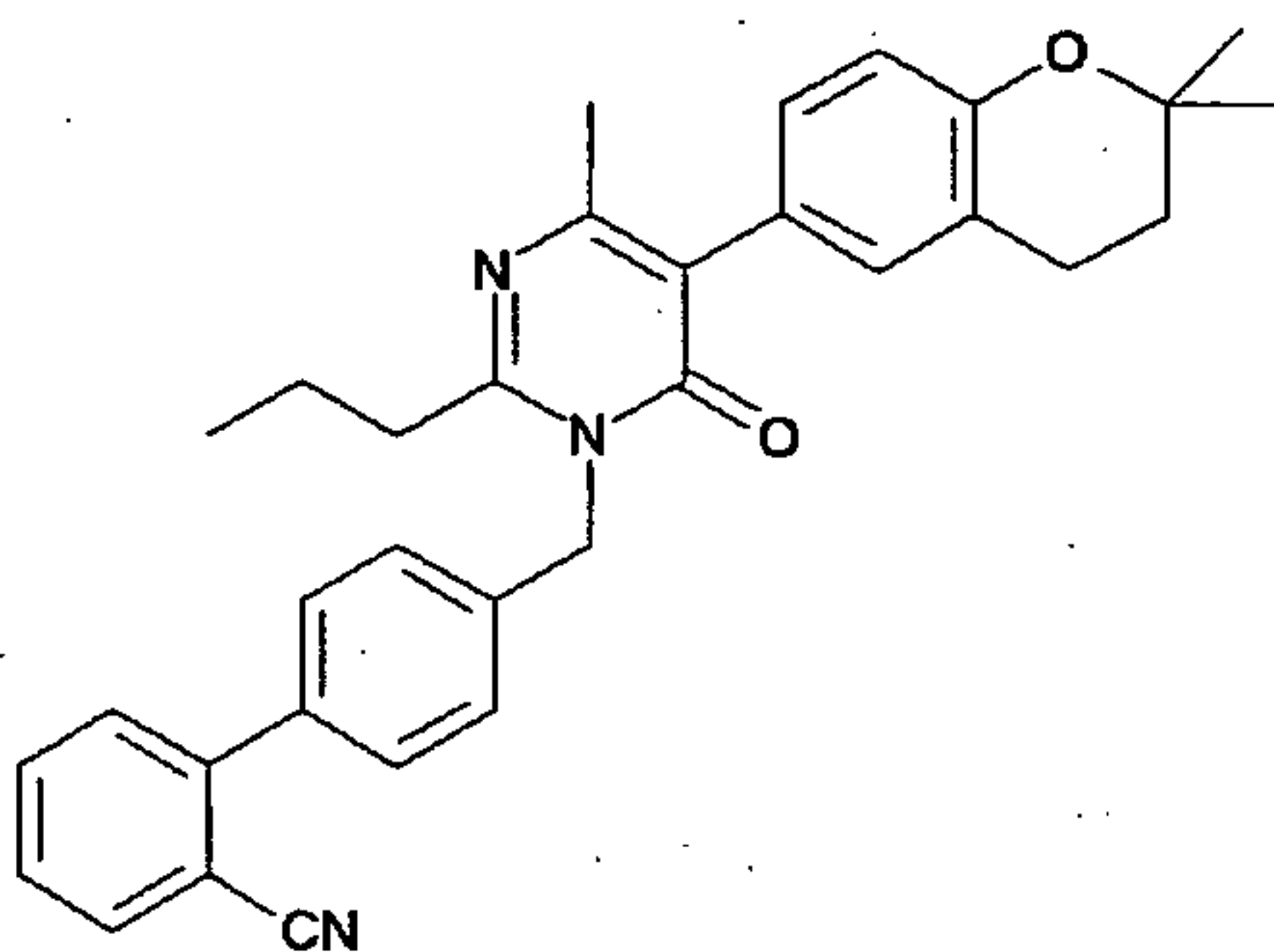
5 A mixture of hydroxylammonium chloride (2.49 g), sodium hydrogen carbonate (3.54 g) and dimethyl sulfoxide (20 mL) was stirred at 40°C for 30 min, 4'-{[5-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (1.03 g) was added, and the
10 mixture was stirred at 90°C for 5 hr. The mixture was allowed to cool to room temperature. Water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous
15 sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (10 mL), N,N'-carbonyldiimidazole (0.51 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.47 mL) were added, and the mixture was stirred at room temperature for 30 min. The
20 reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless
25 crystals (0.18 g, 16%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.88 (3H, t, J = 7.2), 1.43 (6H, s), 1.55-1.70 (2H, m), 2.13 (3H, s), 2.66 (2H, t, J = 7.2), 3.02 (2H, s), 5.34 (2H, s), 6.72 (1H, d, J = 7.8), 7.11 (1H, d, J =

7.8), 7.12 (1H, s), 7.24 (2H, d, J = 8.4), 7.31 (2H, d, J = 8.4), 7.49-7.60 (2H, m), 7.63-7.73 (2H, m), 12.39 (1H, s)

Example 30

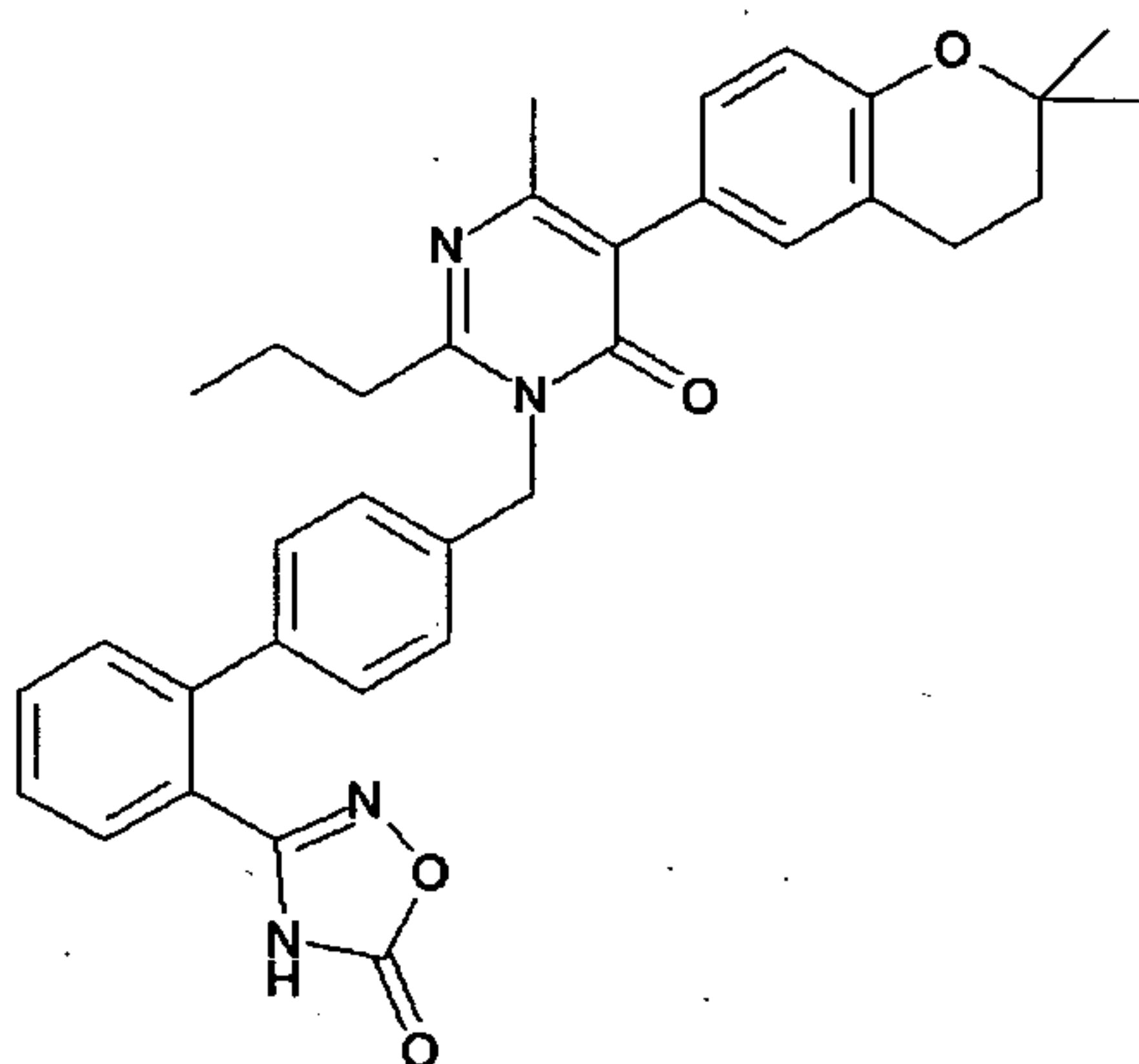
5 5-(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one



30a) 4'-{[5-(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-
 10 carbonitrile

To a solution of 4'-[(5-bromo-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl)methyl]biphenyl-2-carbonitrile (1.0 g) and (2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)boronic acid (0.73 g) in 1,4-dioxane (20 mL) were added 2 M aqueous cesium
 15 carbonate solution (4 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 g), and the mixture was stirred at 90°C for 12 hr under an argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the insoluble material was filtered off through
 20 celite. The filtrate was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to
 25 give the title compound (0.58 g, 49%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 1.03 (3H, t, J = 7.2), 1.35 (6H, s), 1.72-1.86 (4H, m), 2.25 (3H, s), 2.67-2.74 (2H, m), 2.80 (2H, t, J = 6.6), 5.38 (2H, s), 6.81 (1H, d, J = 8.1), 7.00-7.08 (2H, m), 7.34 (2H, d, J = 8.1), 7.40-7.56 (4H, m), 7.60-7.68
 30 (1H, m), 7.76 (1H, d, J = 7.8)



30b) 5-(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-6-methyl-3-
{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
yl]methyl}-2-propylpyrimidin-4(3H)-one

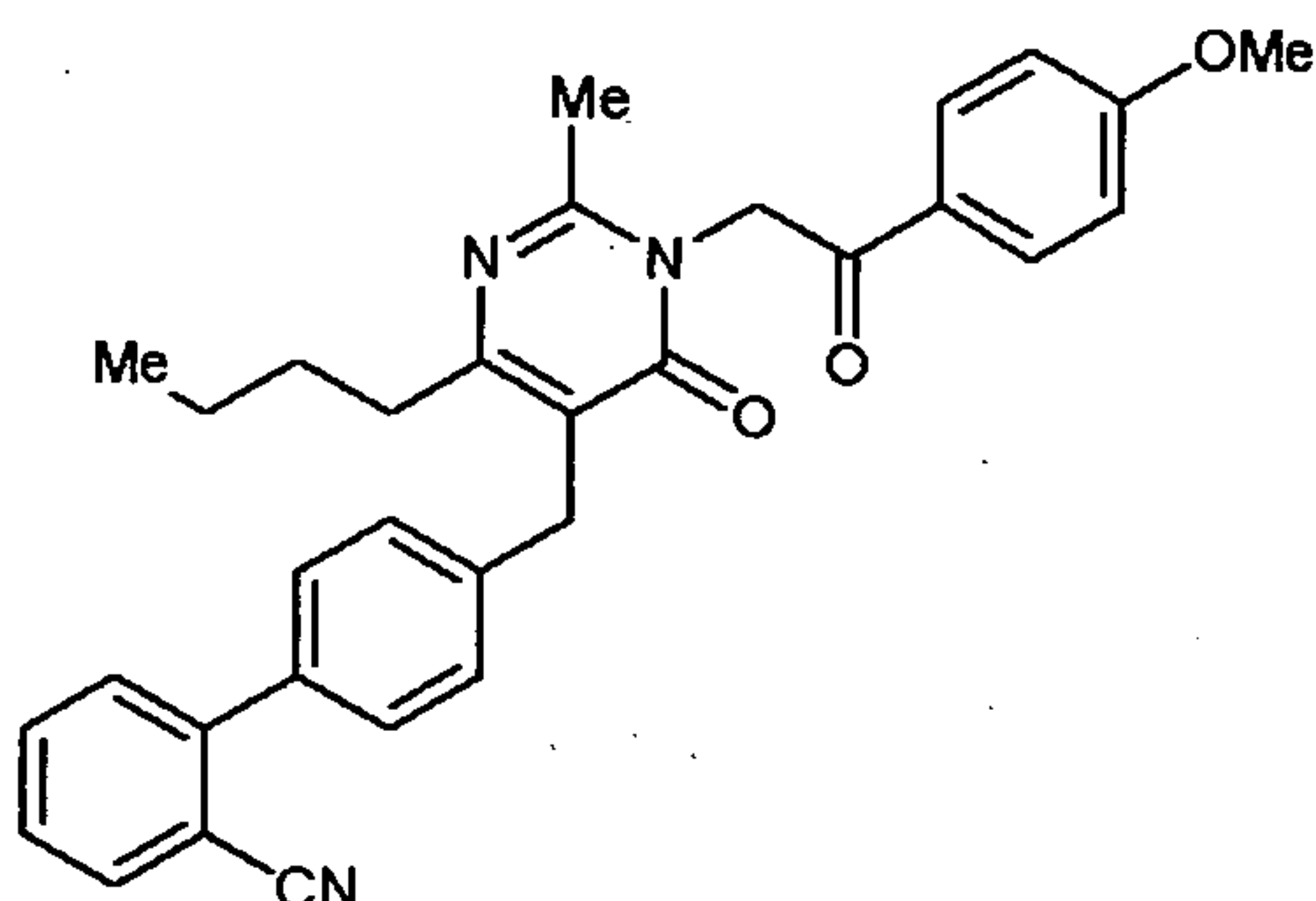
5 A mixture of hydroxylammonium chloride (1.37 g), sodium hydrogen carbonate (1.95 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-{[5-(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-4-methyl-6-oxo-2-propylpyrimidin-1(6H)-yl]methyl}biphenyl-2-carbonitrile (0.58 g) was added, and the
10 mixture was stirred at 90°C for 5 hr. The mixture was allowed to cool to room temperature. Water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine and dried over anhydrous
15 sodium sulfate, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (10 mL), N,N'-carbonyldiimidazole (0.28 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.26 mL) were added, and the mixture was stirred at room temperature for 30 min. The
20 reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as colorless
25 crystals (0.46 g, 70%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.88 (3H, t, J = 7.2), 1.30 (6H, s), 1.55-1.70 (2H, m), 1.78 (2H, t, J = 6.6), 2.13 (3H, s), 2.60-2.70 (2H, m), 2.74 (2H, t, J = 6.6), 5.34 (2H, s), 6.72 (1H, d,

J = 8.1), 6.95-7.05 (2H, m), 7.21-7.35 (4H, m), 7.49-7.61 (2H, m), 7.63-7.74 (2H, m), 12.40 (1H, br)

Example 31

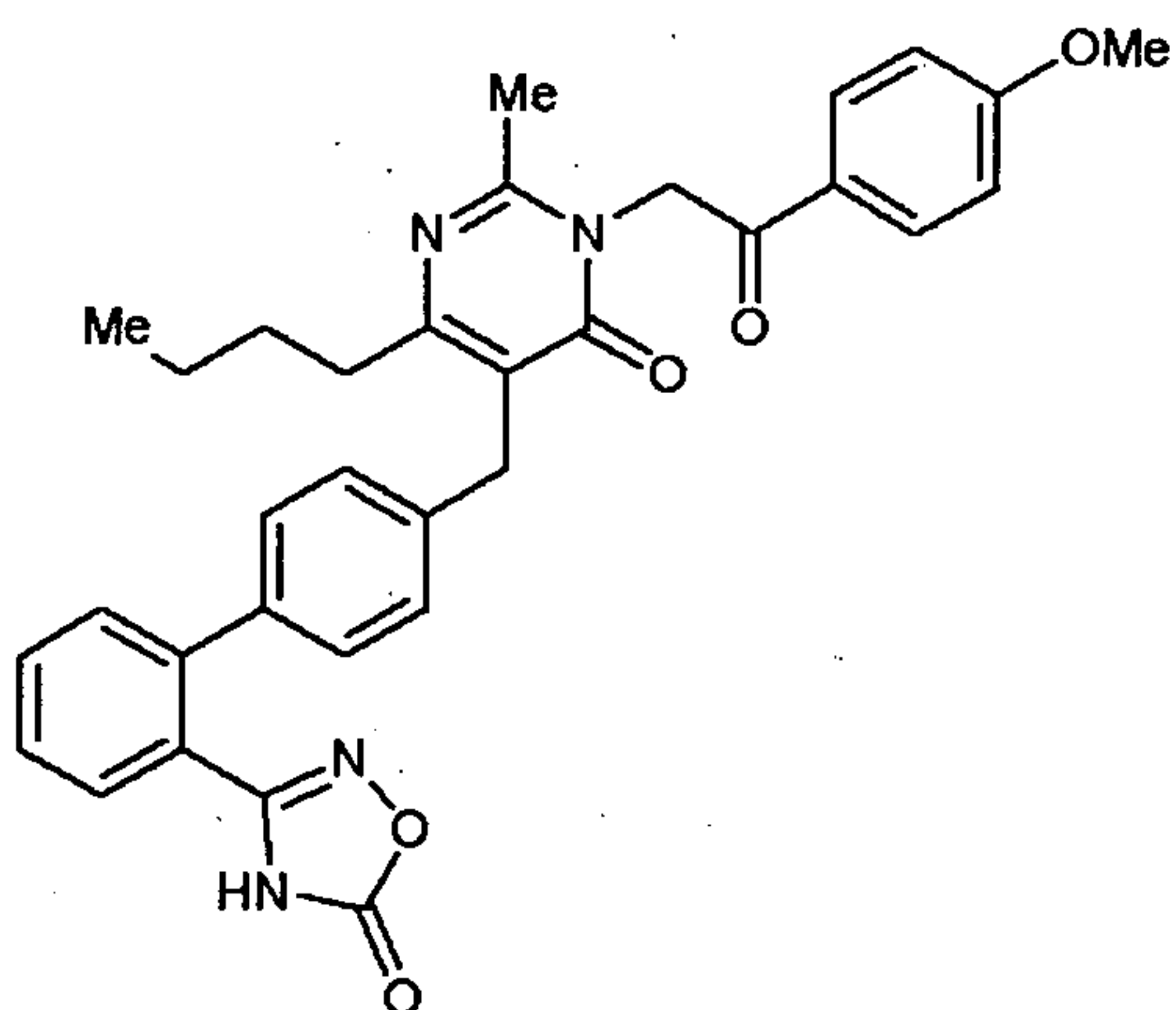
6-butyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



31a) 4'-({4-butyl-1-[2-(4-methoxyphenyl)-2-oxoethyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}methyl)biphenyl-2-carbonitrile

10 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 2-bromo-1-(4-methoxyphenyl)ethanone (0.77 g) was added, and the mixture was
15 stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was
20 purified by silica gel column chromatography to give the title compound as a colorless solid (0.68 g, 48%).

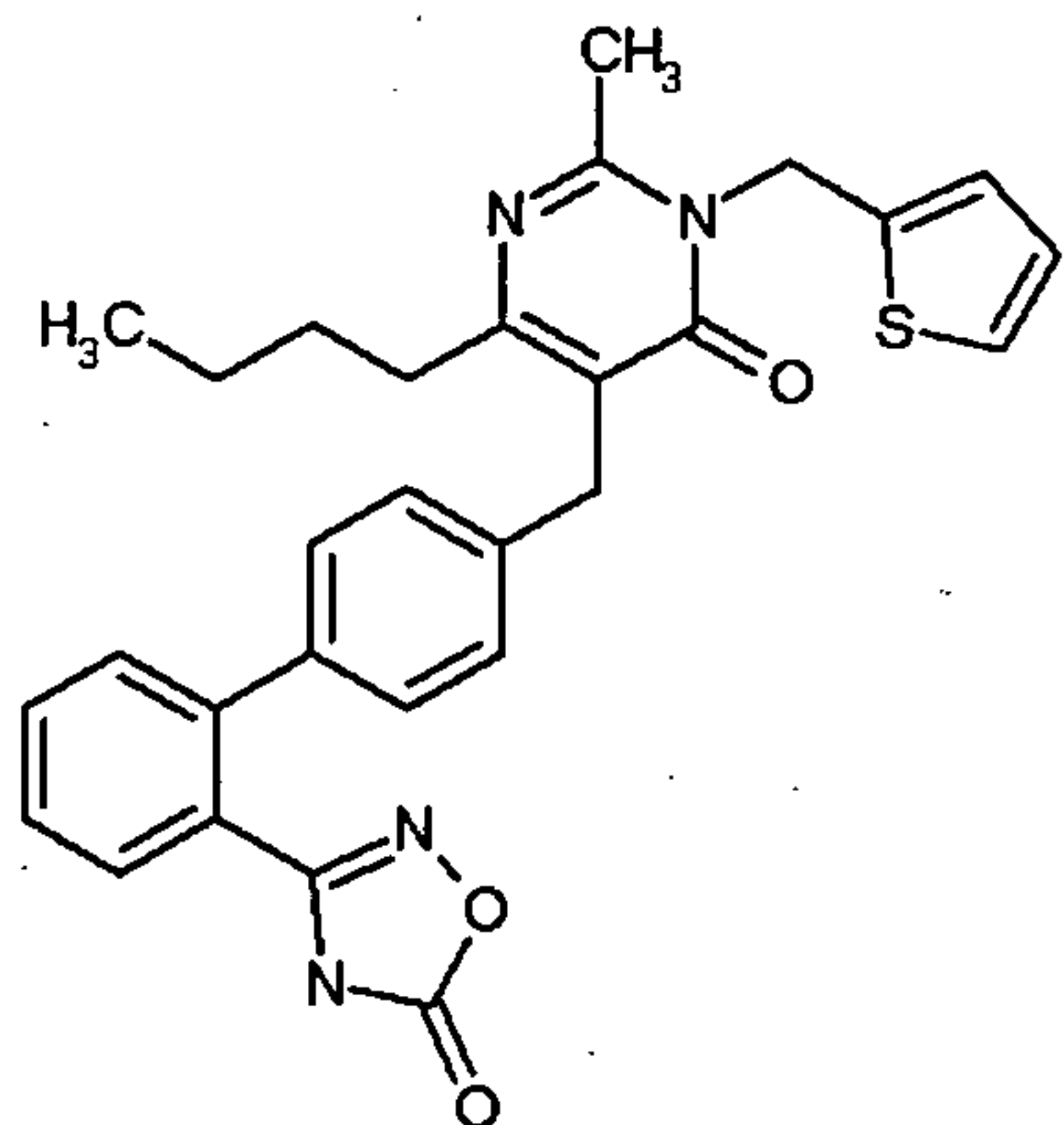
¹H NMR (300 MHz, CDCl₃) δ 0.88 (3H, t, J = 7.3), 1.29-1.43 (2H, m), 1.45-1.61 (2H, m), 2.45 (3H, s), 2.65-2.73 (2H, m), 3.87 (3H, s), 4.13 (2H, s), 5.62 (2H, s), 6.93-6.99 (2H, m), 7.32-
25 7.52 (6H, m), 7.58-7.66 (1H, m), 7.75 (1H, dd, J = 7.7, 0.9), 7.92-8.00 (2H, m).



31b) 6-butyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]-2-methyl-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (1.12 g), sodium hydrogen carbonate (1.69 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-1-[2-(4-methoxyphenyl)-2-oxoethyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}methyl)biphenyl-2-carbonitrile (0.68 g)
 10 was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL),
 15 N,N'-carbonyldiimidazole (0.19 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.17 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
 20 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.051 g, 7%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.4), 1.20-1.38 (2H, m), 1.40-1.59 (2H, m), 2.35 (3H, s), 2.51-2.57 (2H, m), 3.76-3.93 (5H, m), 5.60 (2H, s), 7.13 (2H, d, J = 9.0), 7.17-7.34 (4H, m), 7.44-7.58 (2H, m), 7.59-7.72 (2H, m), 8.08 (2H, d, J = 8.9), 12.41 (1H, br)

Example 32



6-butyl-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-3-(2-thienylmethyl)pyrimidin-4(3H)-

5 one

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 2-(bromomethyl)thiophene (5 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (1.1 g), sodium hydrogen carbonate (1.66 g) and dimethyl sulfoxide (10 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr. The mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.26 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.22 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated

aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.41 g, 61%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.81 (3H, t, J = 7.3), 1.21-1.32 (2H, m), 1.35-1.47 (2H, m), 2.43-2.49 (2H, m), 2.54 (3H, s), 3.89 (2H, s), 5.38 (2H, s), 6.99 (1H, dd, J = 5.1, 3.4), 7.16-7.28 (5H, m), 7.44-7.58 (3H, m), 7.62-7.72 (2H, m), 12.39 (1H, s)

6-Butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one sodium salt

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one potassium salt

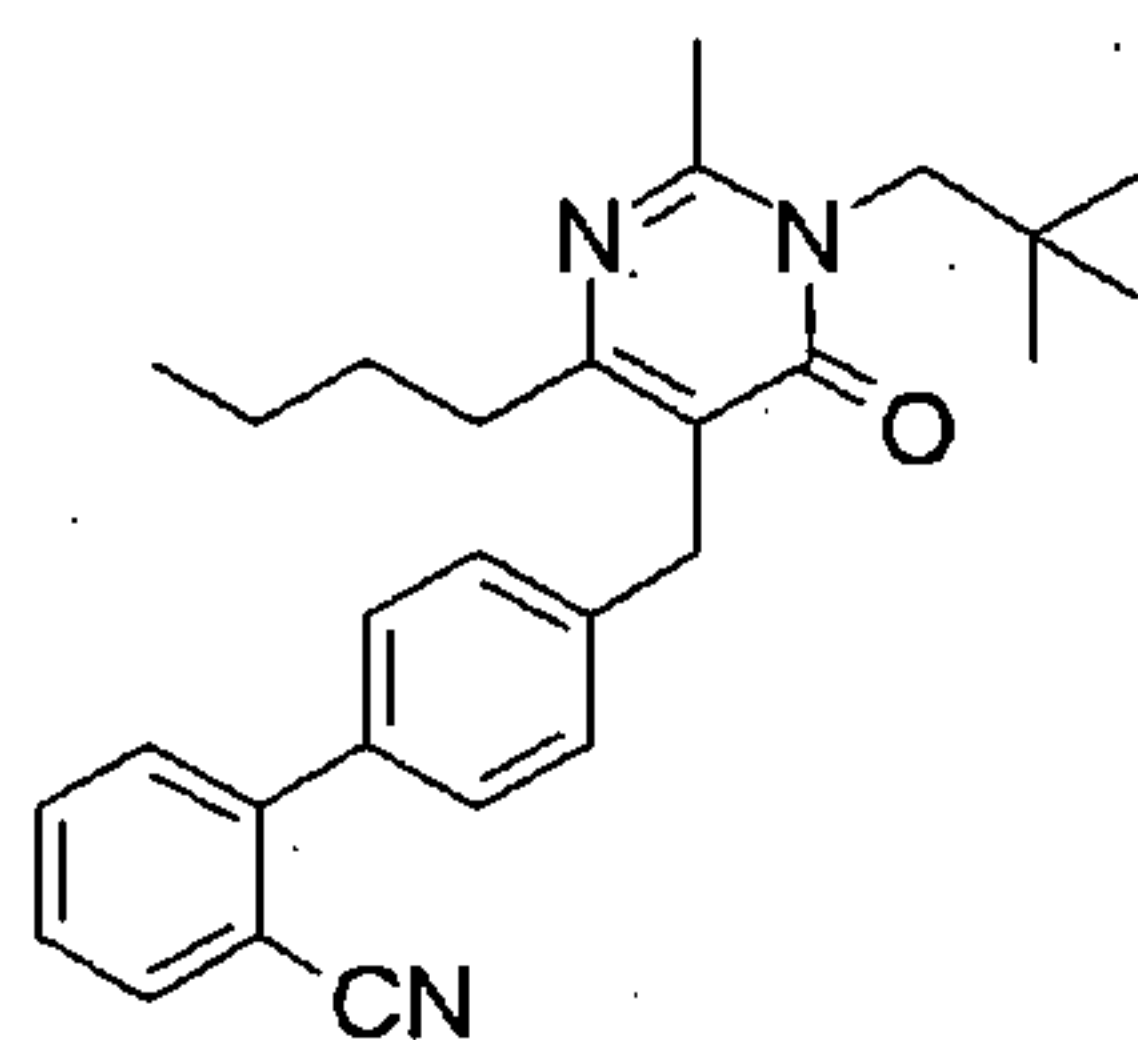
6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one 0.5 calcium salt

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one hydrochloride

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one hydrobromide

Example 33

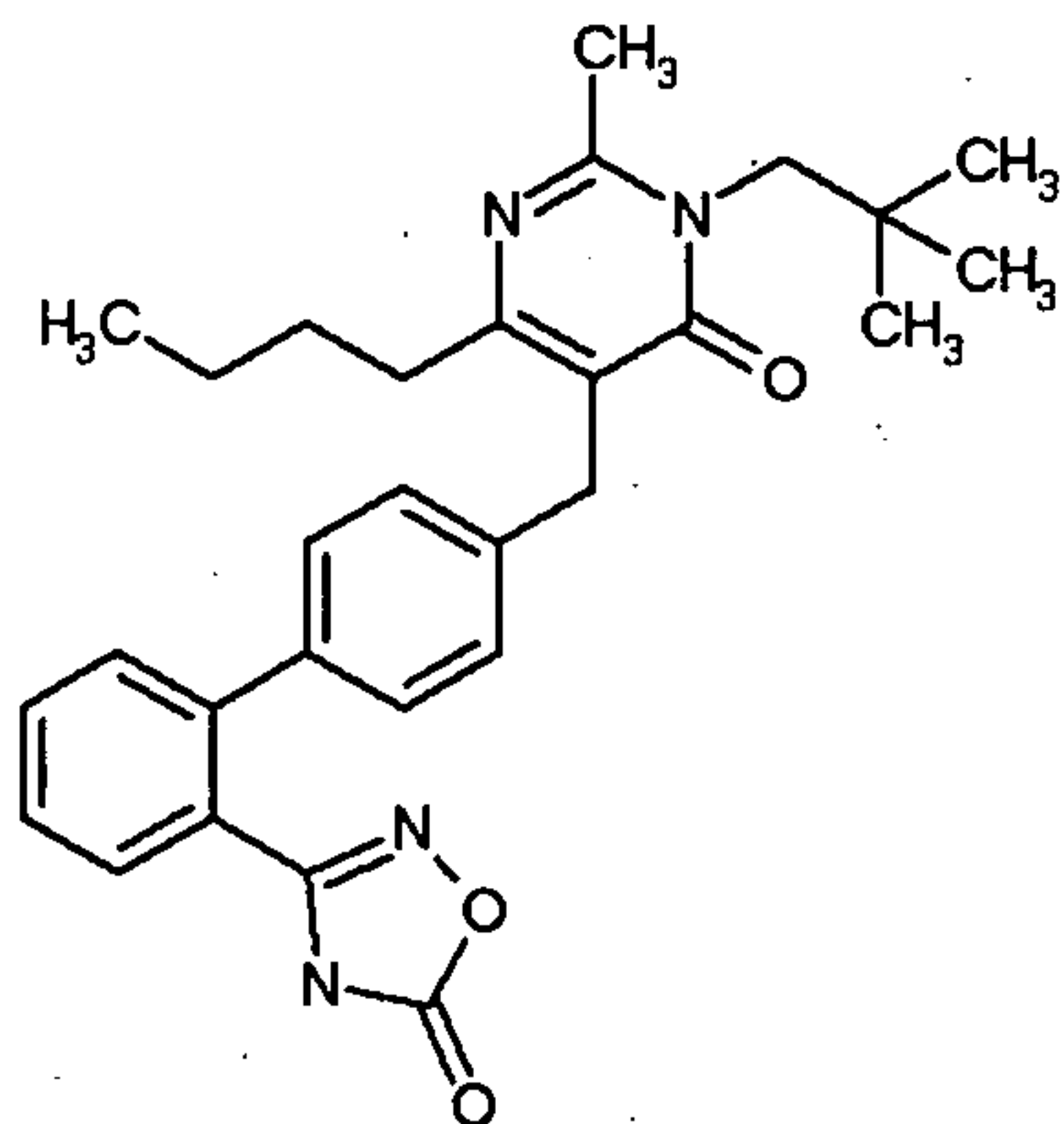
6-butyl-3-(2,2-dimethylpropyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



33a) 4'-{[4-butyl-1-(2,2-dimethylpropyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), cesium carbonate (1.82 g), 1-iodo-2,2-dimethylpropane (0.74 mL) and N,N-dimethylacetamide (10 mL) was stirred at 130°C for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.36 g, 30%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.00 (9H, s), 1.32-1.44 (2H, m), 1.51-1.63 (2H, m), 2.51-2.62 (5H, m), 3.80-4.10 (4H, m), 7.31-7.51 (6H, m), 7.57-7.66 (1H, m), 7.74 (1H, dd, J = 7.7, 0.9)



33b) 6-butyl-3-(2,2-dimethylpropyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

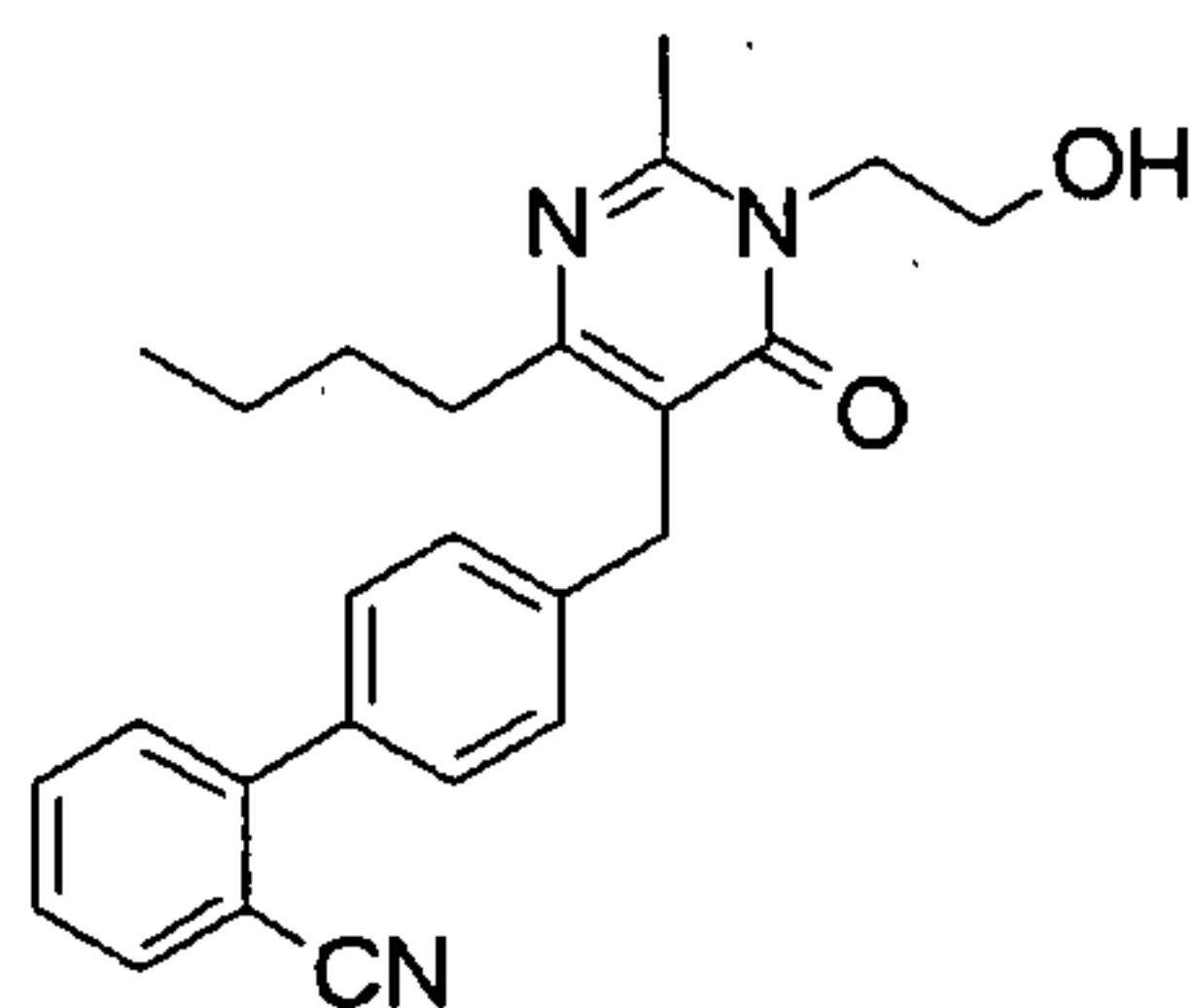
A mixture of hydroxylammonium chloride (0.7 g), sodium hydrogen carbonate (1.06 g) and dimethyl sulfoxide (15 mL) was

stirred at 40°C for 30 min, 4'-{[4-butyl-1-(2,2-dimethylpropyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.36 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.16 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.14 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.13 g, 31%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 0.91 (9H, s), 1.20-1.34 (2H, m), 1.38-1.52 (2H, m), 2.41-2.48 (2H, m), 3.32 (3H, s), 3.84 (2H, s), 3.95 (2H, br), 7.16-7.26 (4H, m), 7.45-7.58 (2H, m), 7.62-7.71 (2H, m), 12.37 (1H, s)

Example 34

6-butyl-3-(2-hydroxyethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

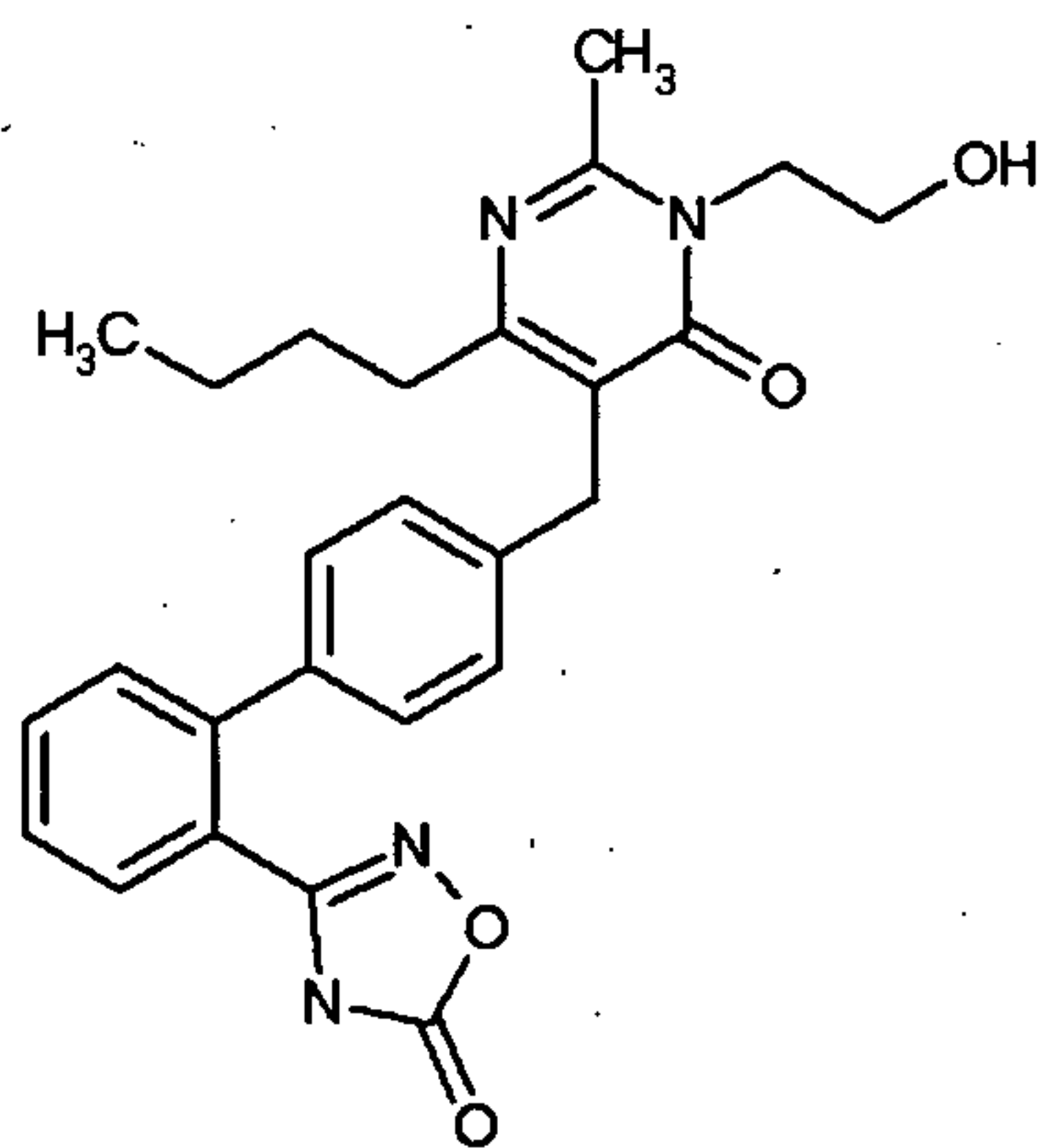


34a) 4'-{[4-butyl-1-(2-hydroxyethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-{[4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 2-bromoethanol (0.40

mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.26 g, 23%).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.3), 1.31-1.45 (2H, m), 1.53-1.62 (2H, m), 2.58 (3H, s), 2.69-2.79 (2H, m), 3.17 (1H, t, J = 5.2), 3.84 (2H, d, J = 3.6), 4.03 (2H, s), 4.45-4.53 (2H, m), 7.21-7.28 (2H, m), 7.39-7.51 (4H, m), 7.59-7.67 (1H, m), 7.75 (1H, dd, J = 7.4, 1.0)



34b) 6-butyl-3-(2-hydroxyethyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

A mixture of 4'-{[4-butyl-1-(2-hydroxyethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.26 g), tert-butyl(dimethyl)silyl trifluoromethanesulfonate (0.45 mL), 2,6-lutidine (0.25 mL) and tetrahydrofuran (10 mL) was stirred at 0°C for 3 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (10 mL), and added to a mixture of hydroxylammonium chloride (0.4 g), sodium hydrogen carbonate (0.61 g) and

dimethyl sulfoxide (10 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr. The mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (10 mL), N,N'-carbonyldiimidazole (0.094 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.08 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL).

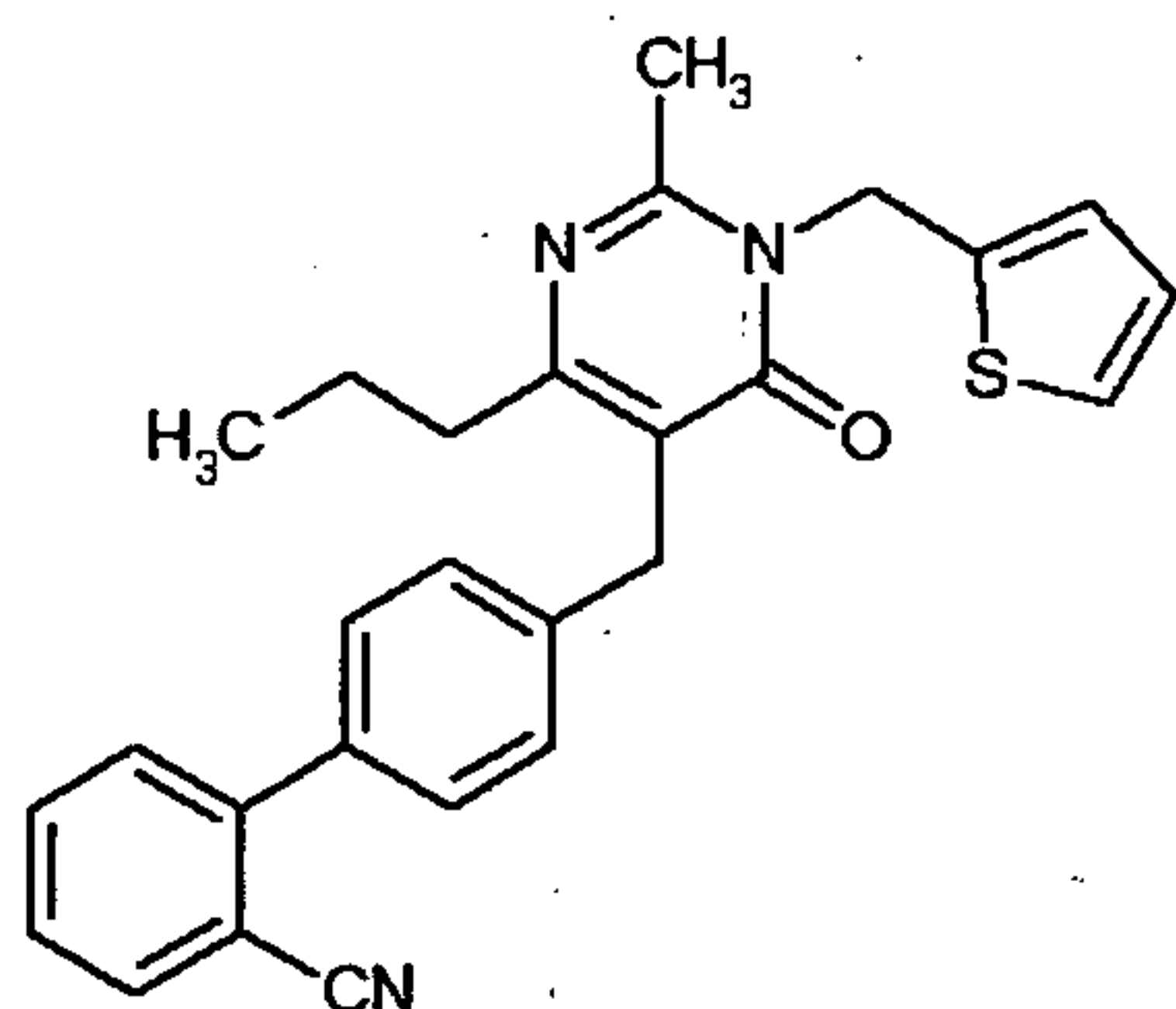
15 Tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution, 2.08 mL) was added thereto, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was extracted with 1 M hydrochloric acid and ethyl acetate, and the ethyl acetate layer was washed with saturated brine and concentrated.

20 The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.055 g, 19%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.3), 1.21-1.33 (2H, m), 1.39-1.50 (2H, m), 2.45 (3H, s), 2.57-2.66 (2H, m), 3.66-3.73 (2H, m), 3.98 (2H, s), 4.30-4.37 (2H, m), 4.79-4.89 (1H, m), 7.18-7.26 (4H, m), 7.46-7.58 (2H, m), 7.62-7.71 (2H, m), 12.36 (1H, s)

Example 35

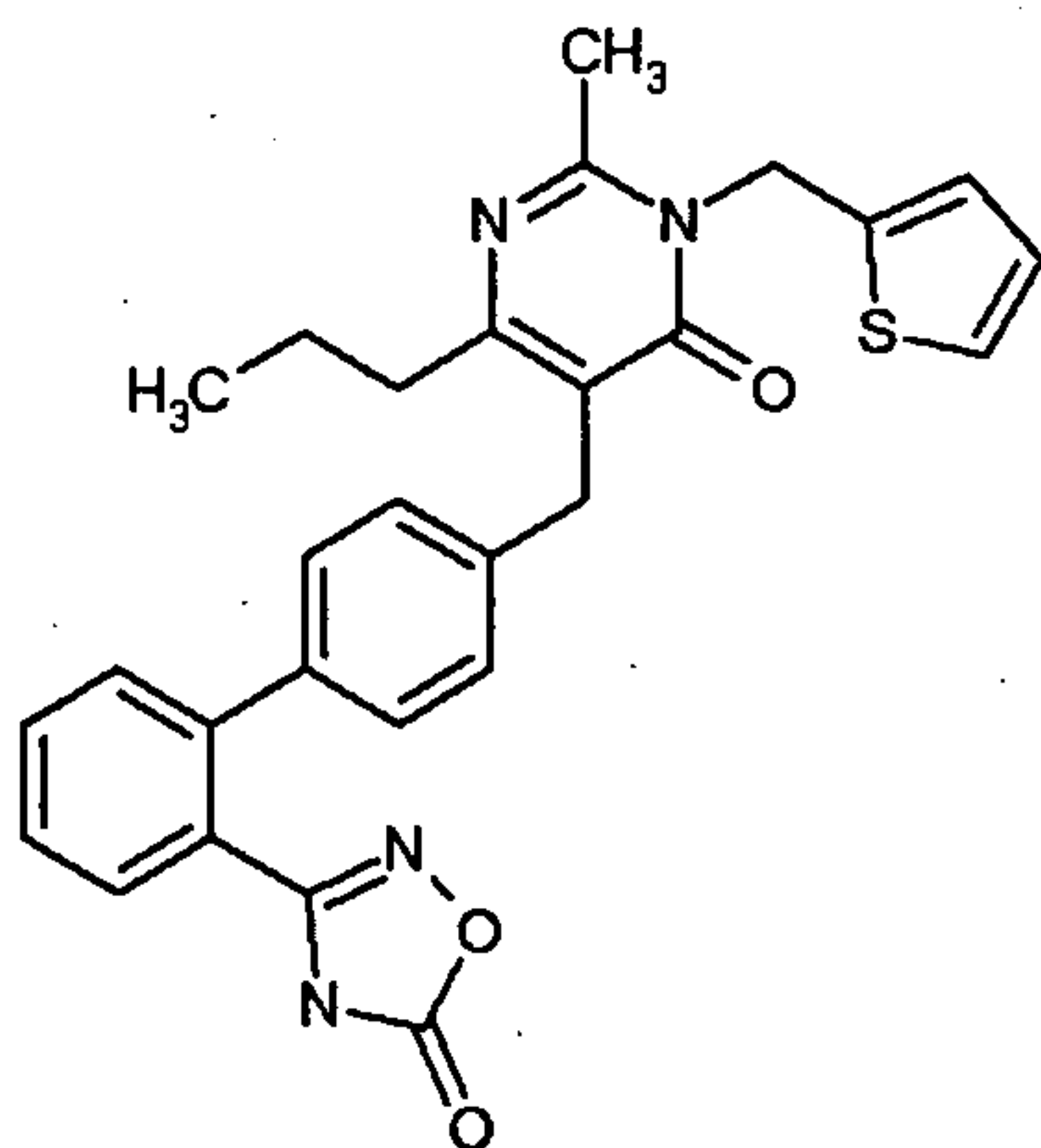
2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(2-thienylmethyl)pyrimidin-4(3H)-one



35a) 4'-{[2-methyl-6-oxo-4-propyl-1-(2-thienylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 2-(bromomethyl)thiophene (4.5 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.74 g, 58%).

¹H NMR (300 MHz, CDCl₃) δ 0.94 (3H, t, J = 7.3), 1.53-1.65 (2H, m), 2.51-2.59 (2H, m), 2.61 (3H, s), 4.00 (2H, s), 5.38 (2H, s), 6.96 (1H, dd, J = 5.1, 3.6), 7.07 (1H, dd, J = 3.4, 0.9), 7.23-7.28 (1H, m), 7.34-7.52 (6H, m), 7.58-7.66 (1H, m), 7.74 (1H, dd, J = 7.7, 0.9)



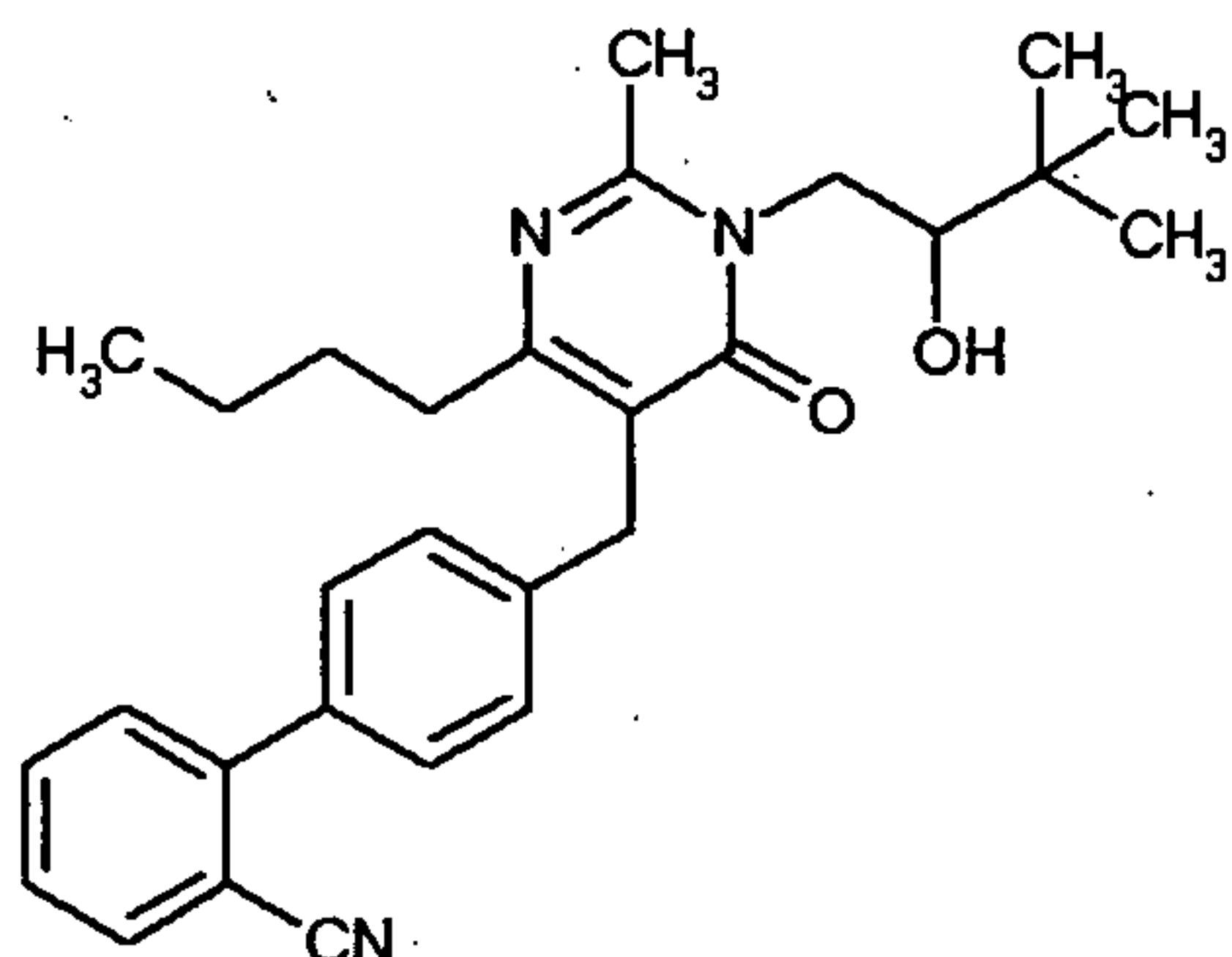
35b) 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(2-

thienylmethyl)pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.41 g), sodium hydrogen carbonate (2.13 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[2-methyl-6-oxo-4-propyl-1-(2-thienylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.74 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.33 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.28 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.39 g, 46%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.3), 1.40-1.53 (2H, m), 2.45 (2H, dd, J = 8.6, 6.7), 2.54 (3H, s), 3.90 (2H, s), 5.38 (2H, s), 6.99 (1H, dd, J = 5.1, 3.4), 7.16-7.28 (5H, m), 7.44-7.58 (3H, m), 7.63-7.72 (2H, m), 12.38 (1H, s)

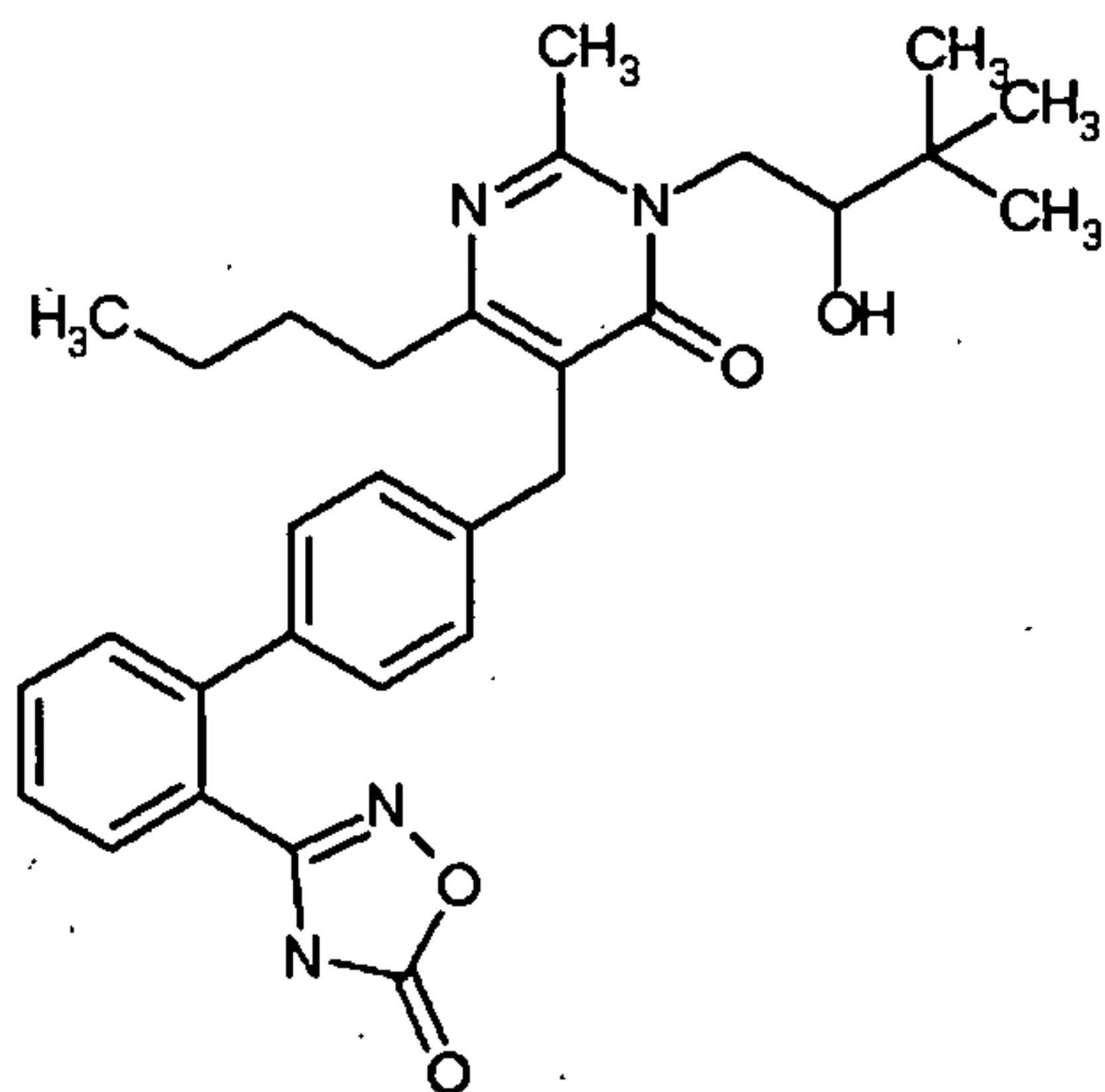
Example 36

6-butyl-3-(2-hydroxy-3,3-dimethylbutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

36a) 4'-{[4-butyl-1-(2-hydroxy-3,3-dimethylbutyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-bromo-3,3-dimethylbutan-2-one (0.75 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in methanol (10 mL), sodium borohydride (0.092 g) was added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, and the residue was extracted with ethyl acetate and saturated aqueous ammonium chloride solution. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.21 g, 16%).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.2), 1.03 (9H, s), 1.31-1.44 (2H, m), 1.49-1.65 (2H, m), 2.53-2.63 (5H, m), 3.64 (1H, dd, J = 10.3, 1.8), 3.96 (2H, s), 4.01-4.11 (1H, m), 4.17-4.28 (1H, m), 7.29-7.36 (2H, m), 7.37-7.50 (4H, m), 7.58-7.66 (1H, m), 7.74 (1H, dd, J = 7.7, 1.1)



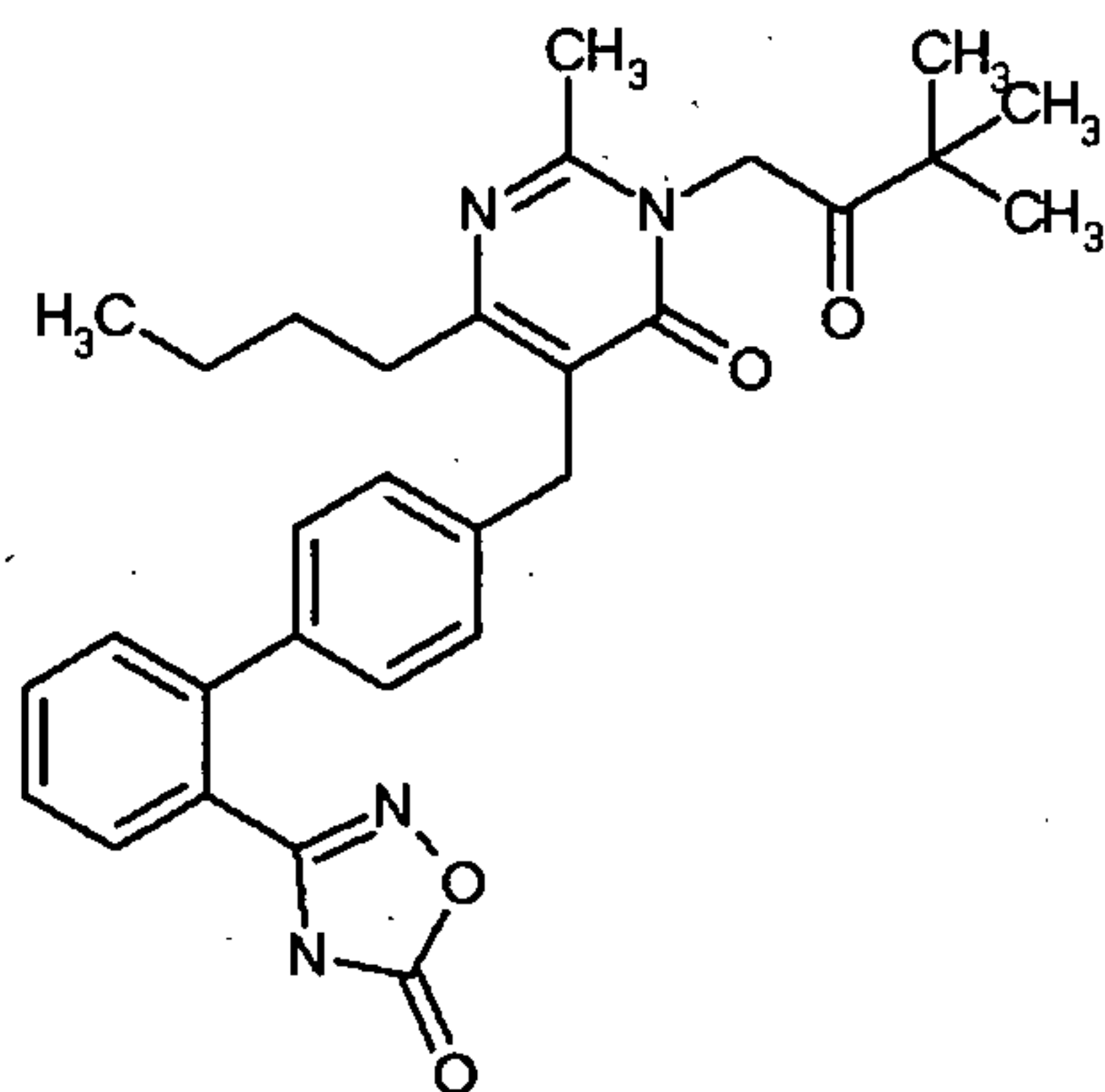
36b) 6-butyl-3-(2-hydroxy-3,3-dimethylbutyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

A mixture of 4'-{[4-butyl-1-(2-hydroxy-3,3-dimethylbutyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.21 g), tert-butyl(dimethyl)silyl trifluoromethanesulfonate (0.36 mL), 2,6-lutidine (0.16 mL) and tetrahydrofuran (10 mL) was stirred at 0°C for 3 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.97 g), sodium hydrogen carbonate (1.47 g) and dimethyl sulfoxide (10 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr. The mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.14 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.12 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution, 3.5 mL) was added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was extracted with 1 M hydrochloric acid and ethyl acetate, and the ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the

residue was purified by silica gel column chromatography to give the title compound as colorless amorphous crystals (0.2 g, 55%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.2), 0.93 (9H, s),
 5 1.22-1.33 (2H, m), 1.38-1.50 (2H, m), 2.41-2.48 (2H, m), 2.55
 (3H, s), 3.42-3.51 (1H, m), 3.63 (1H, dd, J = 13.2, 10.5),
 3.84 (2H, q, J = 15.1), 4.24 (1H, d, J = 11.9), 5.03 (1H, d, J
 = 5.7), 7.18-7.27 (4H, m), 7.47-7.58 (2H, m), 7.61-7.72 (2H,
 m), 12.39 (1H, br)

10 Example 37



6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

15 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (0.19 g),
 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one
 (0.18 g) and methylene chloride (10 mL) was stirred at room
 temperature for 2 hr. A saturated aqueous sodium hydrogen
 20 carbonate solution and sodium thiosulfate were added to the
 reaction mixture, and the mixture was stirred at room
 temperature for 2 hr and extracted with chloroform. The
 chloroform layer was washed with saturated brine, and dried
 over anhydrous magnesium sulfate. The solvent was evaporated
 25 under reduced pressure. The obtained residue was purified by
 silica gel column chromatography to give the title compound as
 colorless crystals (0.13 g, 69%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.22 (9H, s),

1.25-1.34 (2H, m), 1.38-1.51 (2H, m), 2.28 (3H, s), 2.45-2.49 (2H, m), 3.83 (2H, s), 5.16 (2H, s), 7.21 (4H, s), 7.52 (2H, dd, J = 16.3, 7.6), 7.62-7.72 (2H, m), 12.38 (1H, s)

6-Butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one sodium salt

6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one potassium salt

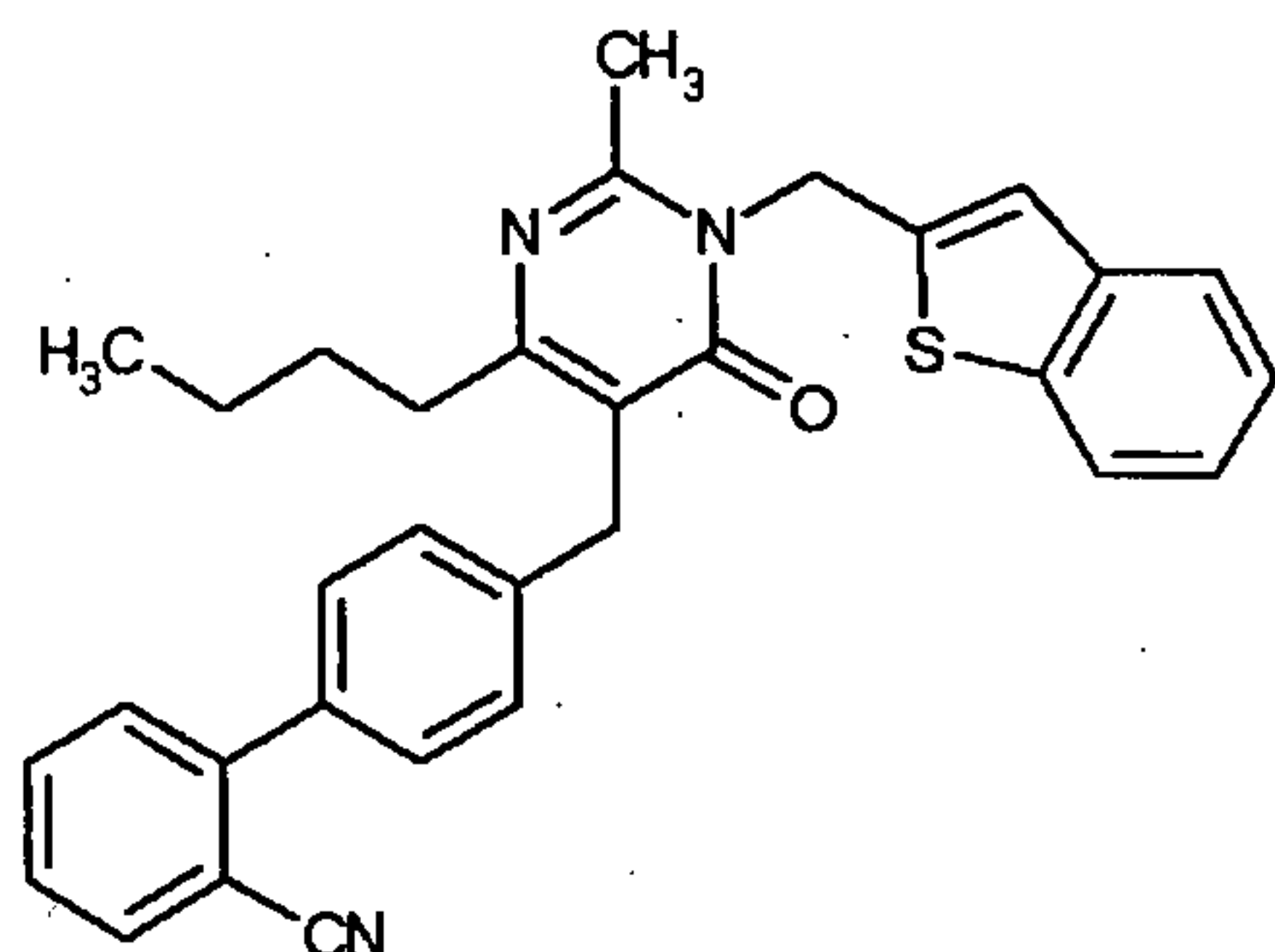
6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one 0.5 calcium salt

6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrochloride

6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrobromide

Example 38

3-(1-benzothien-2-ylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

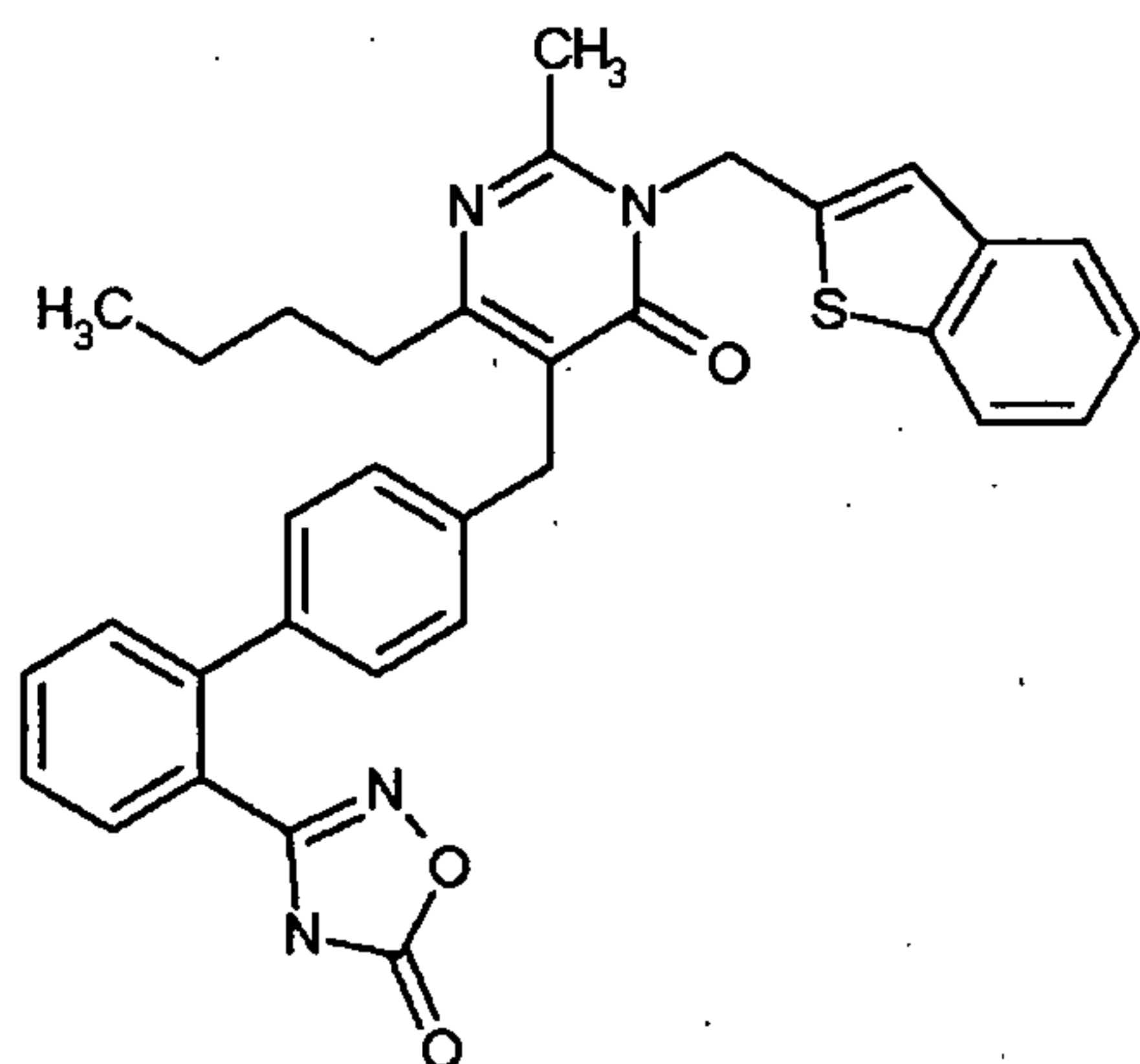


38a) 4'-{[1-(1-benzothien-2-ylmethyl)-4-butyl-2-methyl-6-oxo-

1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.23 g), tributylphosphine (1.52 mL), 1-benzothien-2-ylmethanol (0.56 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.55 g, 45%).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.3), 1.31-1.43 (2H, m), 1.49-1.57 (2H, m), 2.55-2.62 (2H, m), 2.64 (3H, s), 4.02 (2H, s), 5.48 (2H, s), 7.24-7.28 (2H, m), 7.30-7.34 (2H, m), 7.37-7.51 (5H, m), 7.57-7.68 (1H, m), 7.68-7.81 (3H, m)



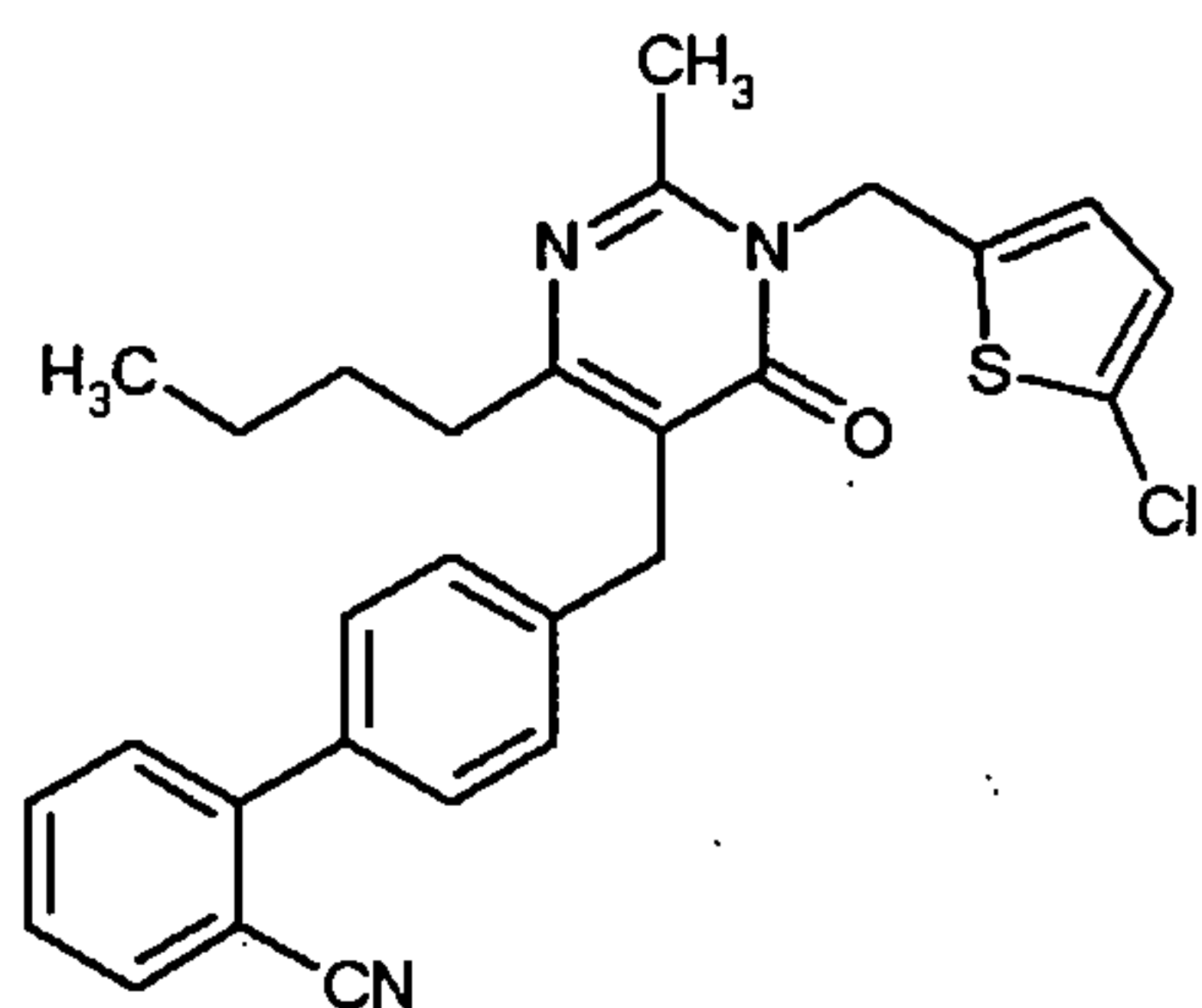
38b) 3-(1-benzothien-2-ylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.91 g), sodium hydrogen carbonate (1.38 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[1-(1-benzothien-2-ylmethyl)-4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile (0.55 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium

sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.21 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.18 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.31 g, 51%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.3), 1.20-1.33 (2H, m), 1.36-1.48 (2H, m), 2.43-2.49 (2H, m), 2.57 (3H, s), 3.92 (2H, s), 5.51 (2H, s), 7.21-7.30 (4H, m), 7.30-7.39 (2H, m), 7.45-7.58 (3H, m), 7.64-7.71 (2H, m), 7.79-7.86 (1H, m), 7.89-7.96 (1H, m), 12.39 (1H, s)

Example 39

6-butyl-3-[(5-chloro-2-thienyl)methyl]-2-methyl-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

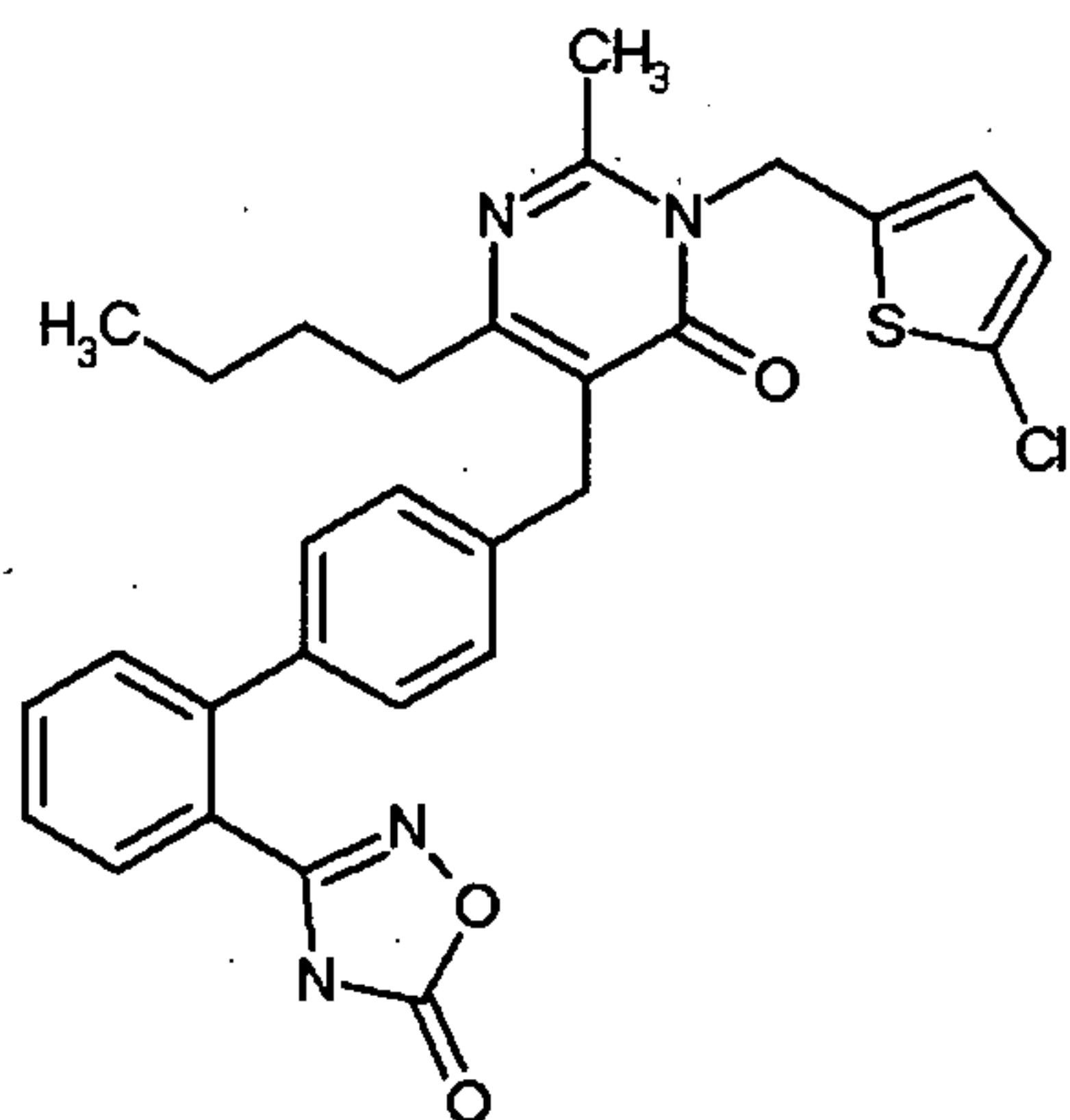


39a) 4'-({4-butyl-1-[(5-chloro-2-thienyl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 2-chloro-5-(chloromethyl)thiophene (2.39 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction

mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was
 5 purified by silica gel column chromatography to give the title compound as a colorless solid (0.63 g, 45%).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.3), 1.37 (2H, dq, J = 7.3, 7.1), 1.48-1.59 (2H, m), 2.53-2.66 (5H, m), 3.99 (2H, s), 5.24 (2H, s), 6.76 (1H, d, J = 3.8), 6.85 (1H, d, J = 3.8),
 10 7.34-7.51 (6H, m), 7.55-7.67 (1H, m), 7.74 (1H, d, J = 7.3)



39b) 6-butyl-3-[(5-chloro-2-thienyl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

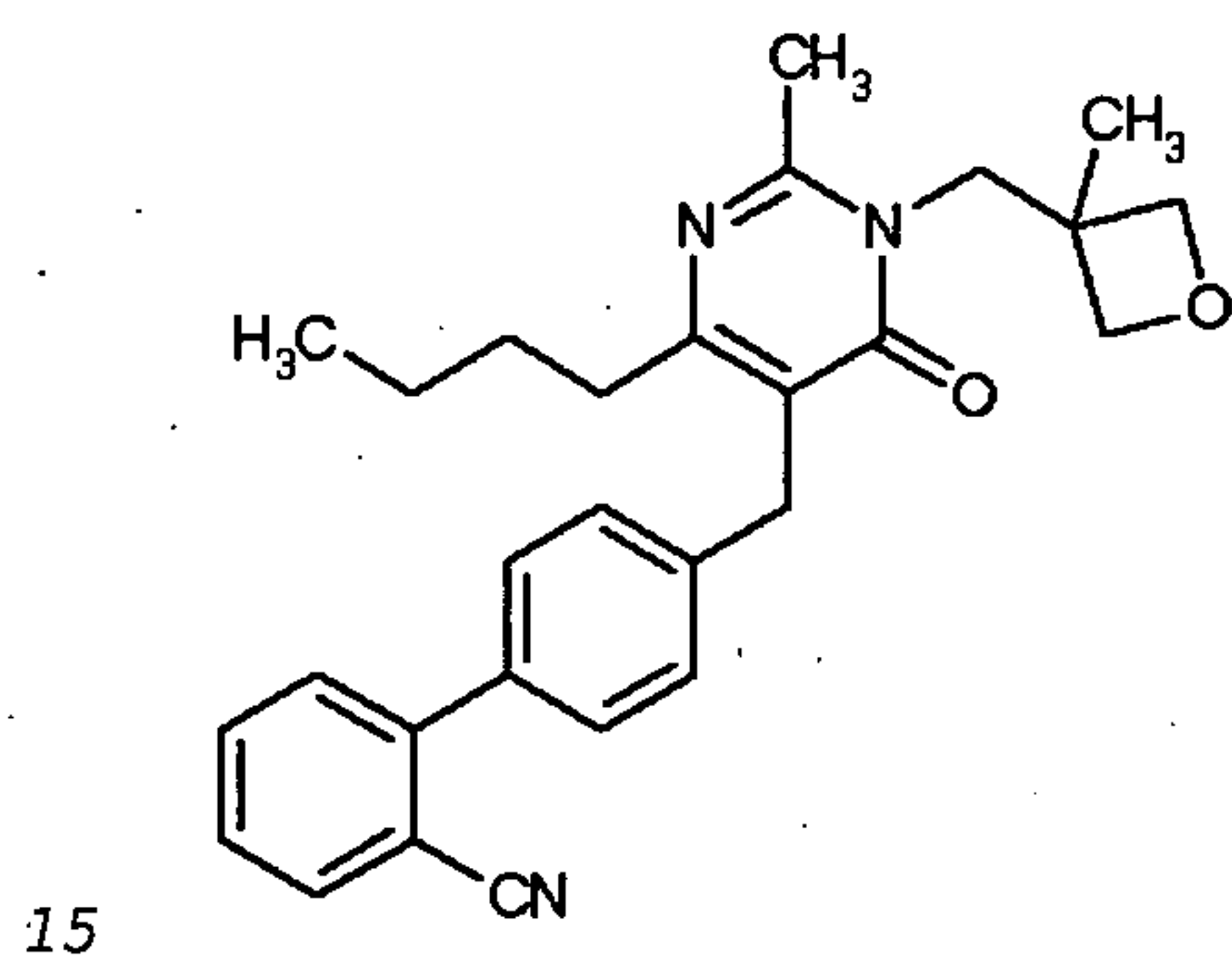
15 A mixture of hydroxylammonium chloride (1.1 g), sodium hydrogen carbonate (1.64 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-1-[(5-chloro-2-thienyl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile (0.64 g) was added, and the
 20 mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-
 25 carbonyldiimidazole (0.25 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.21 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated

aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.32 g, 45%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.81 (3H, t, J = 7.3), 1.20-1.32 (2H, m), 1.35-1.46 (2H, m), 2.43-2.50 (2H, m), 2.55 (3H, s), 3.89 (2H, s), 5.28 (2H, s), 7.00 (1H, d, J = 3.8), 7.11 (1H, d, J = 3.8), 7.19-7.28 (4H, m), 7.47-7.58 (2H, m), 7.63-7.72 (2H, m), 12.38 (1H, br)

Example 40

6-butyl-2-methyl-3-[(3-methyloxetan-3-yl)methyl]-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one

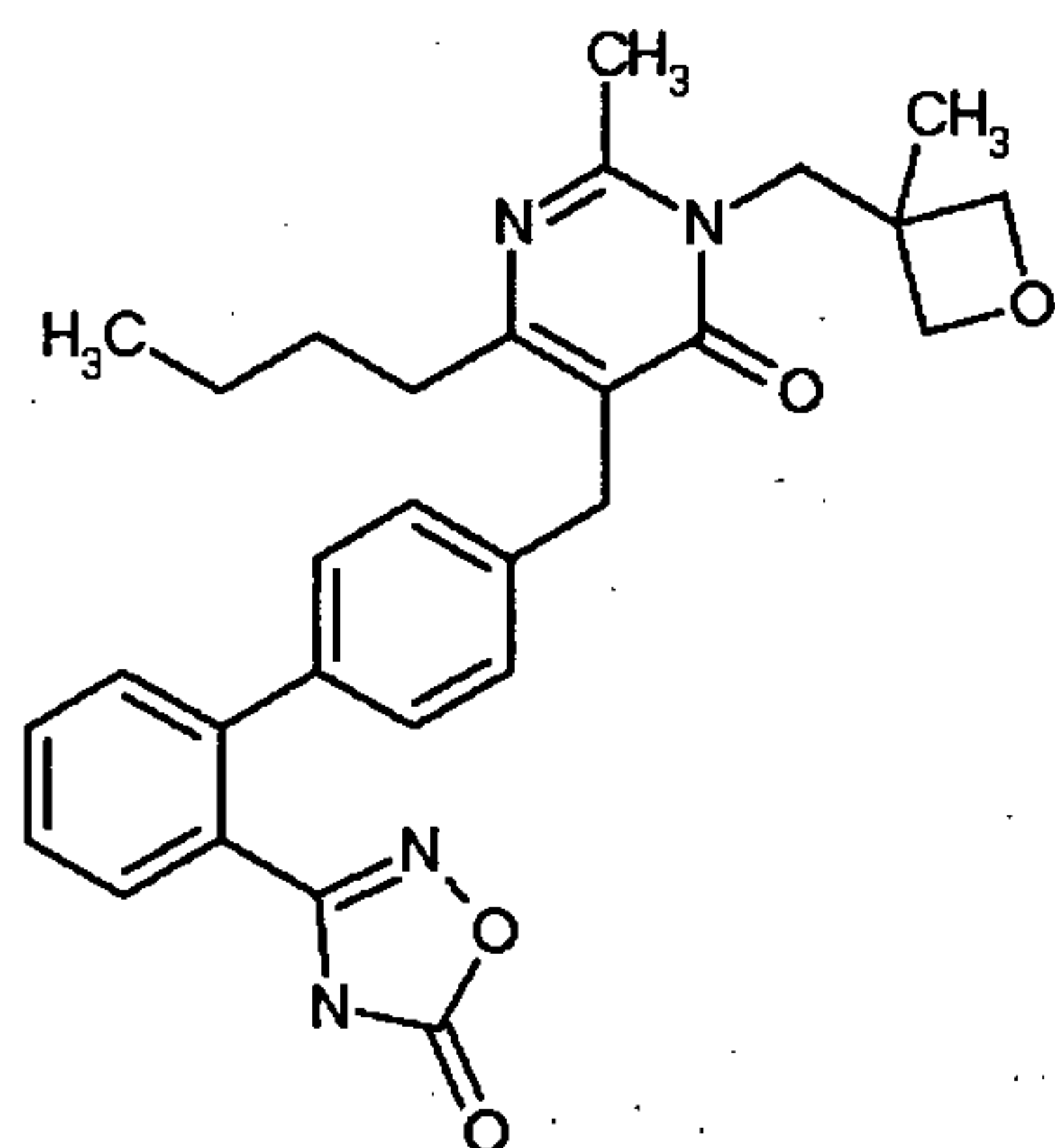


40a) 4'-({4-butyl-2-methyl-1-[(3-methyloxetan-3-yl)methyl]-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.44 g), tributylphosphine (1.78 mL), (3-methyloxetan-3-yl)methanol (0.44 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.78 g, 62%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.2), 1.34-1.46 (2H,

m), 1.55-1.69 (2H, m), 2.17 (3H, s), 2.59 (3H, s), 2.71-2.82 (2H, m), 4.02 (2H, s), 4.26-4.48 (6H, m), 7.20 (2H, d, J = 8.1), 7.38-7.52 (4H, m), 7.57-7.67 (1H, m), 7.75 (1H, d, J = 7.7)



5

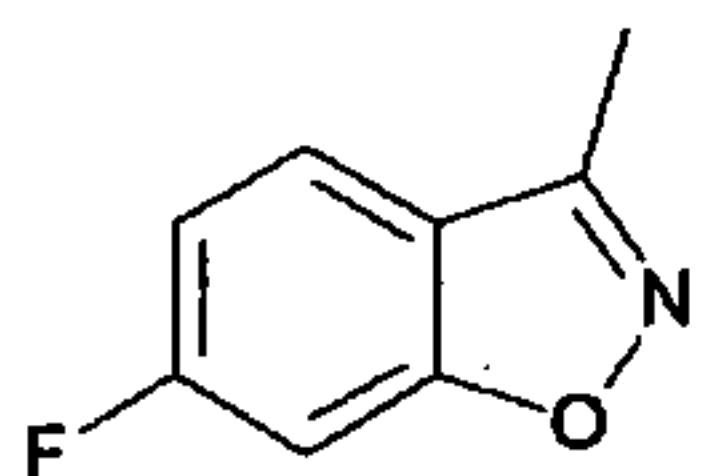
40b) 6-butyl-2-methyl-3-[(3-methyloxetan-3-yl)methyl]-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.47 g), sodium
 10 hydrogen carbonate (2.23 g) and dimethyl sulfoxide (15 mL) was
 stirred at 40°C for 30 min, 4'-({4-butyl-2-methyl-1-[(3-
 methyloxetan-3-yl)methyl]-6-oxo-1,6-dihydropyrimidin-5-
 yl)methyl)biphenyl-2-carbonitrile (0.78 g) was added, and the
 mixture was stirred at 90°C for 16 hr. The reaction mixture
 15 was diluted with ethyl acetate, washed with water and then
 with saturated brine, and dried over anhydrous magnesium
 sulfate. The solvent was evaporated under reduced pressure.
 The residue was dissolved in tetrahydrofuran (20 mL), N,N'-
 carbonyldiimidazole (0.34 g) and then 1,8-
 20 diazabicyclo[5.4.0]undec-7-ene (0.29 mL) were added, and the
 mixture was stirred at room temperature for 2 hr. The reaction
 mixture was diluted with ethyl acetate, washed with saturated
 aqueous potassium hydrogen sulfate solution and then with
 saturated brine, and dried over anhydrous magnesium sulfate.
 25 The solvent was evaporated under reduced pressure, and the
 residue was purified by silica gel column chromatography to
 give the title compound as a colorless powder (0.048 g, 5%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.4), 1.20 (3H, s),

1.25-1.37 (2H, m), 1.44-1.57 (2H, m), 2.47 (3H, s), 2.65-2.75 (2H, m), 3.96 (2H, s), 4.20 (2H, d, $J = 6.0$), 4.31-4.39 (4H, m), 7.13-7.24 (4H, m), 7.46 (1H, d, $J = 7.7$), 7.54 (1H, dt, $J = 7.5, 1.3$), 7.62-7.72 (2H, m), 12.38 (1H, br)

5 Example 41

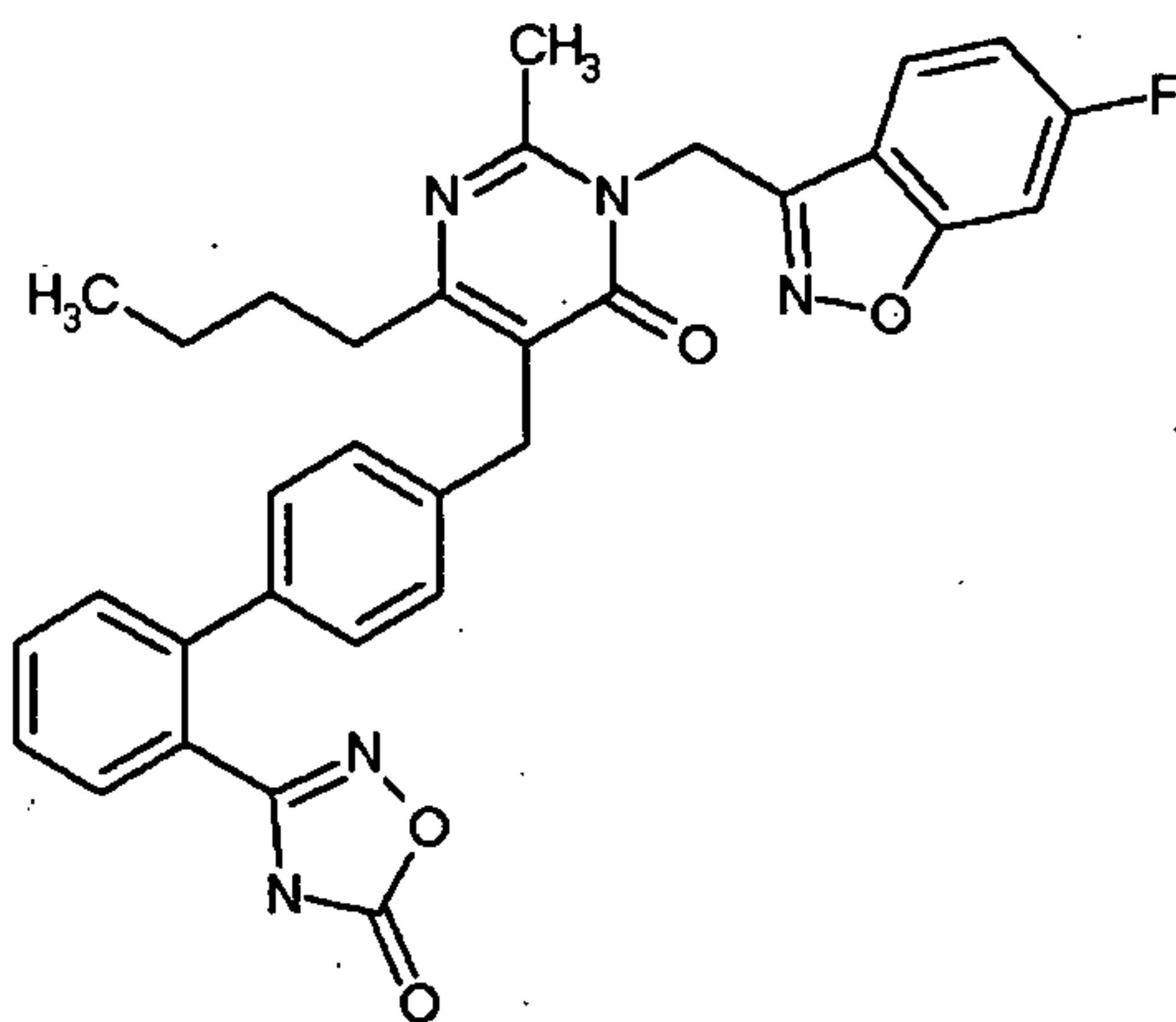
6-butyl-3-[(6-fluoro-1,2-benzisoxazol-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one



10 41a) 6-fluoro-3-methyl-1,2-benzisoxazole

A mixture of 1-(4-fluoro-2-hydroxyphenyl)ethanone (20 g), hydroxyammonium chloride (18.1 g), sodium acetate (16 g) and methanol (500 mL) was stirred at 60°C for 1 hr. The reaction mixture was added to ice water, and the obtained crystallized
 15 product was collected by filtration and dissolved in tetrahydrofuran (400 mL). *N,N'*-carbonyldiimidazole (22.5 g) and then a solution of triethylamine (22.3 mL) in tetrahydrofuran (100 mL) were added, and the mixture was stirred at 70°C for 1 hr. The reaction mixture was diluted
 20 with diethyl ether, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound as colorless crystals (13.7 g, 70%).

¹H NMR (300 MHz, CDCl₃) δ 2.34 (3H, s), 6.52-6.74 (2H, m), 7.39
 25 (1H, dd, $J = 8.8, 6.3$)



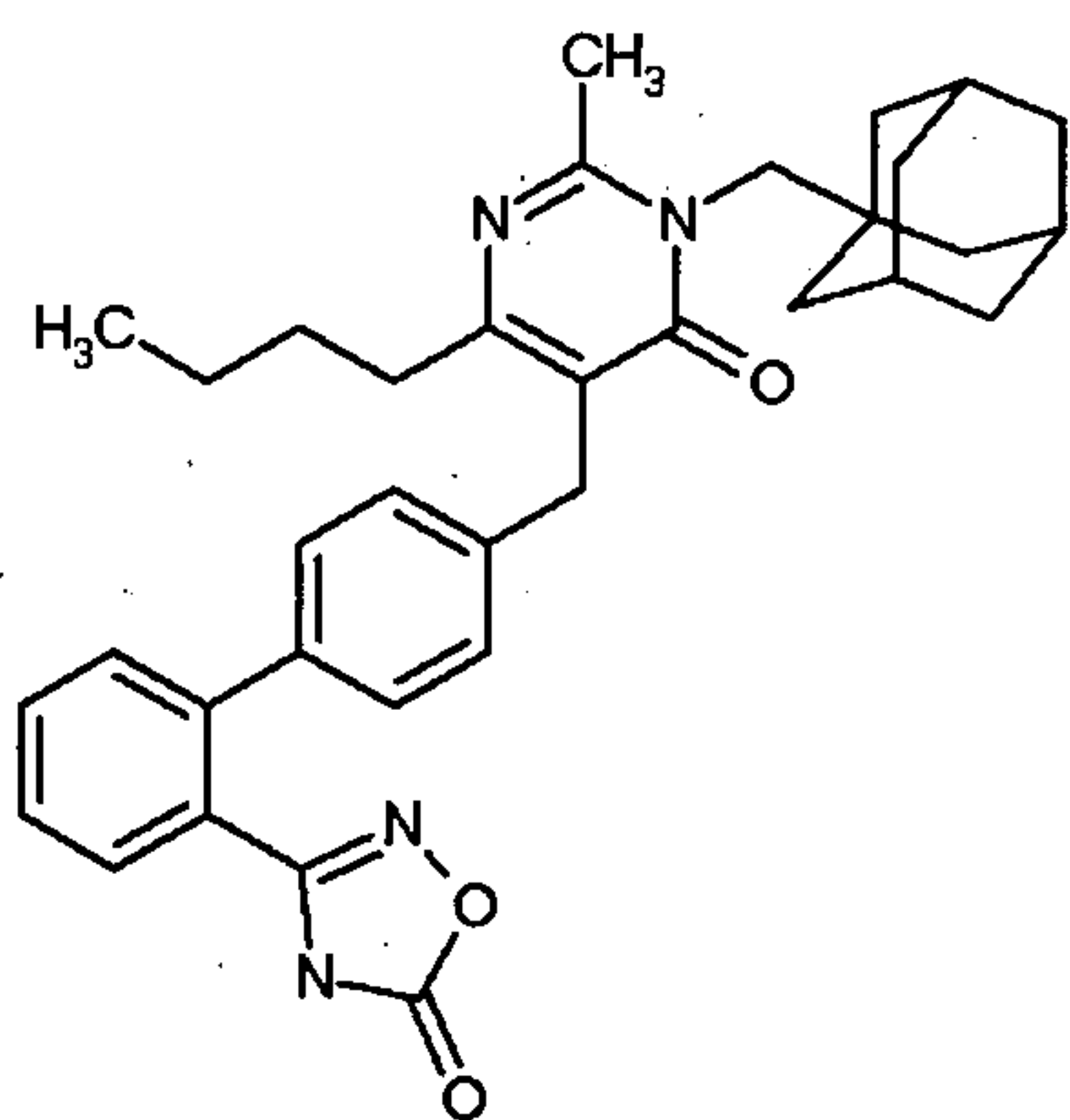
41b) 6-butyl-3-[(6-fluoro-1,2-benzisoxazol-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

To a mixture of 6-fluoro-3-methyl-1,2-benzisoxazole (2.0 g) and carbon tetrachloride (100 mL) was added a mixture of N-bromosuccinimide (2.58 g) and benzoyl peroxide (0.43 g) at 80°C, and the mixture was stirred at the same temperature for 4 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was extracted with water and ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the obtained oil was added to a mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) previously stirred at room temperature for 10 min. The reaction mixture was stirred at room temperature for 16 hr, and diluted with ethyl acetate. The mixture was washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (1.03 g), sodium hydrogen carbonate (1.65 g) and dimethyl sulfoxide (10 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.19 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.16 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with

saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.14 g, 25%).

5 ¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (3H, t, J = 7.4), 1.22-1.38 (2H, m), 1.39-1.54 (2H, m), 2.50-2.55 (2H, m), 2.57 (3H, s), 3.88 (2H, s), 5.69 (2H, s), 7.17-7.27 (4H, m), 7.33 (1H, dt, J = 9.1, 2.3), 7.46-7.59 (2H, m), 7.62-7.71 (2H, m), 7.76 (1H, dd, J = 9.0, 2.3), 7.97 (1H, dd, J = 8.9, 5.3), 12.39 (1H, br)

10 Example 42



3-(1-adamantylmethyl)-6-butyl-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

15 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)adamantane (1.9 g) was added, and the mixture was
20 stirred at 150°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column
25 chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (1.1 g), sodium hydrogen carbonate (1.78 g) and dimethyl sulfoxide (10 mL) previously stirred at 40°C for 30 min. The reaction

mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue
 5 was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.21 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.17 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated
 10 aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.11 g, 19%).
 15 ¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.22-1.34 (2H, m), 1.39-1.48 (2H, m), 1.49-1.67 (12H, m), 1.91 (3H, s), 2.44 (2H, m), 2.50 (3H, s), 3.57-4.13 (4H, m), 7.16-7.26 (4H, m), 7.44-7.57 (2H, m), 7.61-7.71 (2H, m), 12.37 (1H, br)

3-(1-Adamantylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

3-(1-adamantylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
 25 4(3H)-one sodium salt

3-(1-adamantylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
4(3H)-one potassium salt

3-(1-adamantylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
 30 4(3H)-one 0.5 calcium salt

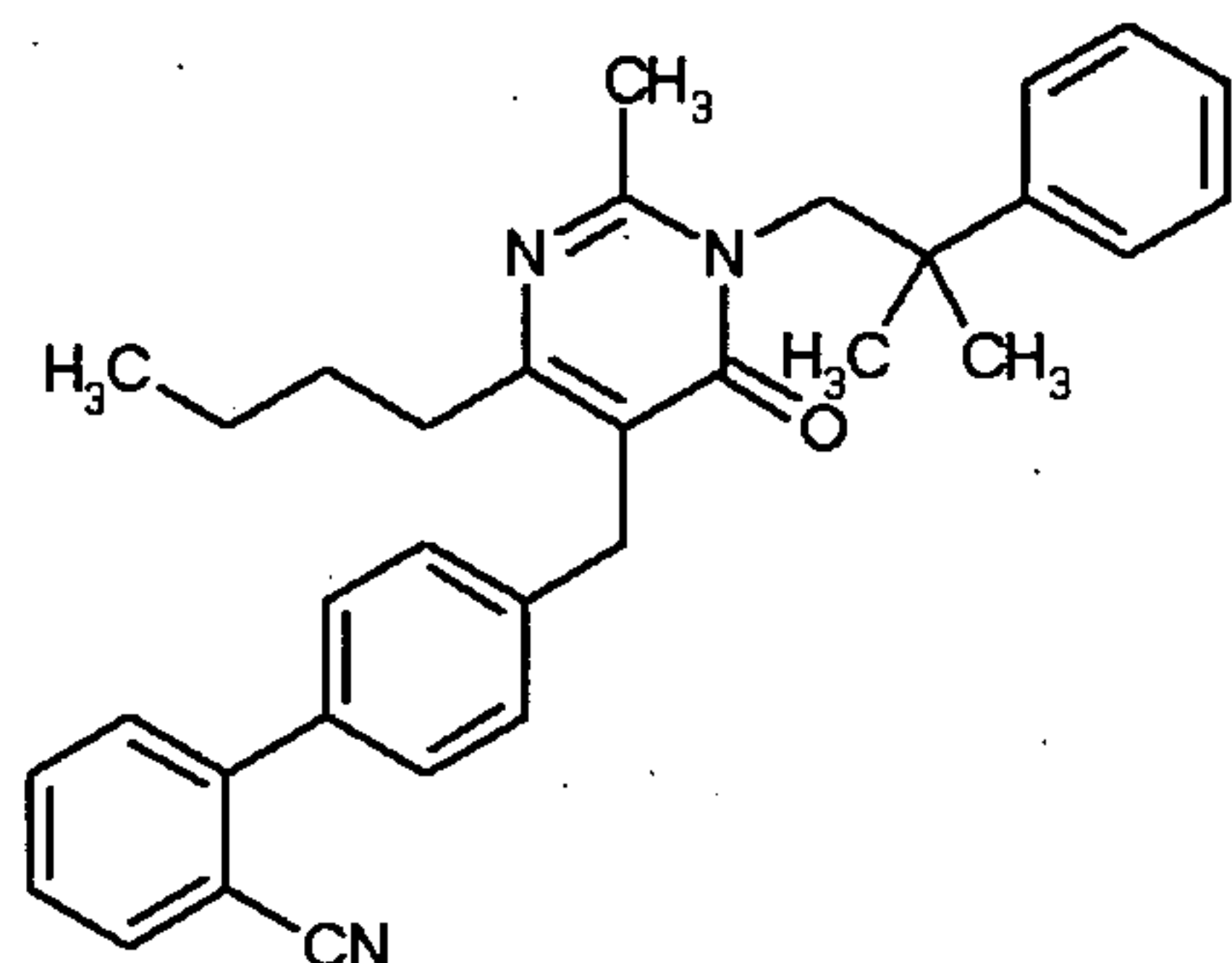
3-(1-adamantylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
4(3H)-one hydrochloride

35 3-(1-adamantylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-

dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one hydrobromide

Example 43

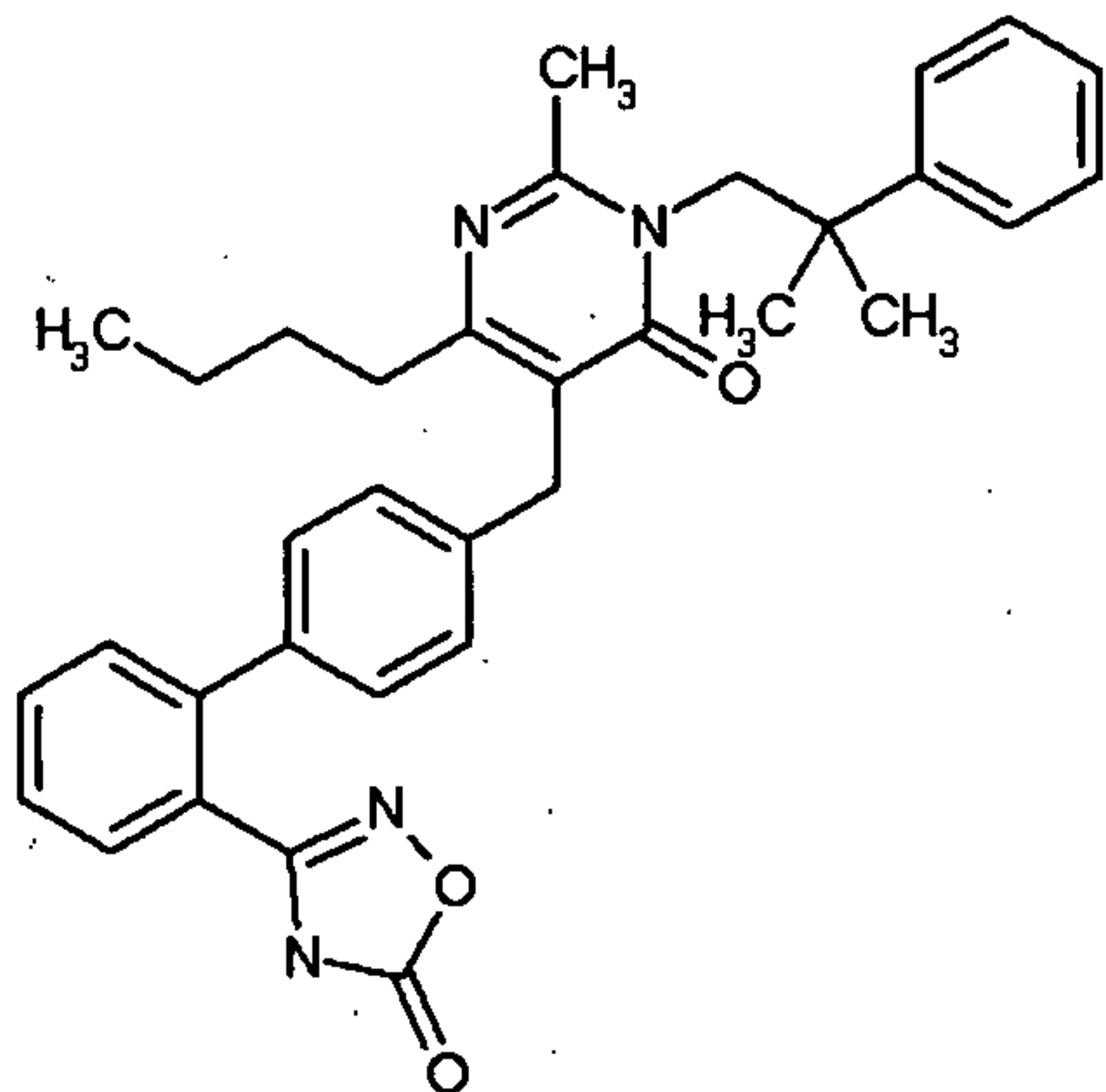
6-butyl-2-methyl-3-(2-methyl-2-phenylpropyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one



43a) 4'-{[4-butyl-2-methyl-1-(2-methyl-2-phenylpropyl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile

A mixture of 4'-{[4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile (1 g), cyanomethylene tri-n-butylphosphorane (1 g), 2-methyl-2-phenylpropan-1-ol (0.63 g) and toluene (30 mL) was stirred at 100°C for 16 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.13 g, 10%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.2), 1.30-1.48 (8H, m), 1.49-1.63 (2H, m), 1.70 (3H, s), 2.51-2.61 (2H, m), 3.94-4.00 (4H, m), 7.19-7.51 (11H, m), 7.56-7.66 (1H, m), 7.73 (1H, dd, J = 7.7, 1.3)

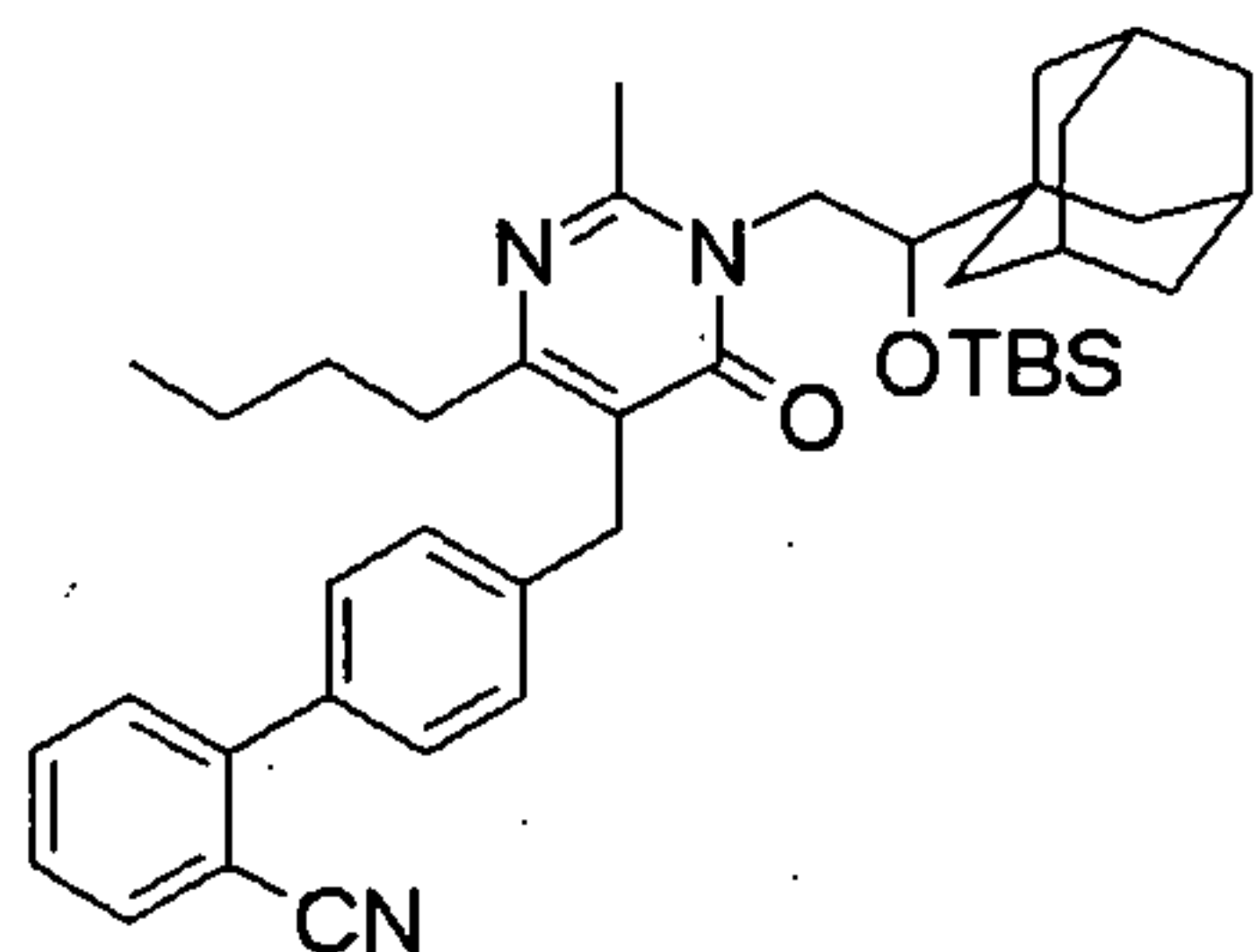


43b) 6-butyl-2-methyl-3-(2-methyl-2-phenylpropyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.27 g), sodium
 5 hydrogen carbonate (0.45 g) and dimethyl sulfoxide (10 mL) was
 stirred at 40°C for 30 min, 4'-{[4-butyl-2-methyl-1-(2-methyl-
 2-phenylpropyl)-6-oxo-1,6-dihydropyrimidin-5-
 yl]methyl}biphenyl-2-carbonitrile (0.13 g) was added, and the
 mixture was stirred at 90°C for 16 hr. The reaction mixture
 10 was diluted with ethyl acetate, washed with water and then
 with saturated brine, and dried over anhydrous magnesium
 sulfate. The solvent was evaporated under reduced pressure.
 The residue was dissolved in tetrahydrofuran (10 mL), N,N'-
 carbonyldiimidazole (0.052 g) and then 1,8-
 15 diazabicyclo[5.4.0]undec-7-ene (0.044 mL) were added, and the
 mixture was stirred at room temperature for 2 hr. The reaction
 mixture was diluted with ethyl acetate, washed with saturated
 aqueous potassium hydrogen sulfate solution and then with
 saturated brine, and dried over anhydrous magnesium sulfate.
 20 The solvent was evaporated under reduced pressure, and the
 residue was purified by silica gel column chromatography to
 give the title compound as colorless crystals (0.036 g, 24%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.20-1.48
 (10H, m), 1.72 (3H, s), 2.38-2.48 (2H, m), 3.87 (2H, s), 4.18
 25 (2H, s), 7.19-7.34 (8H, m), 7.46-7.57 (2H, m), 7.62-7.73 (2H,
 m), 12.38 (1H, br)

Example 44

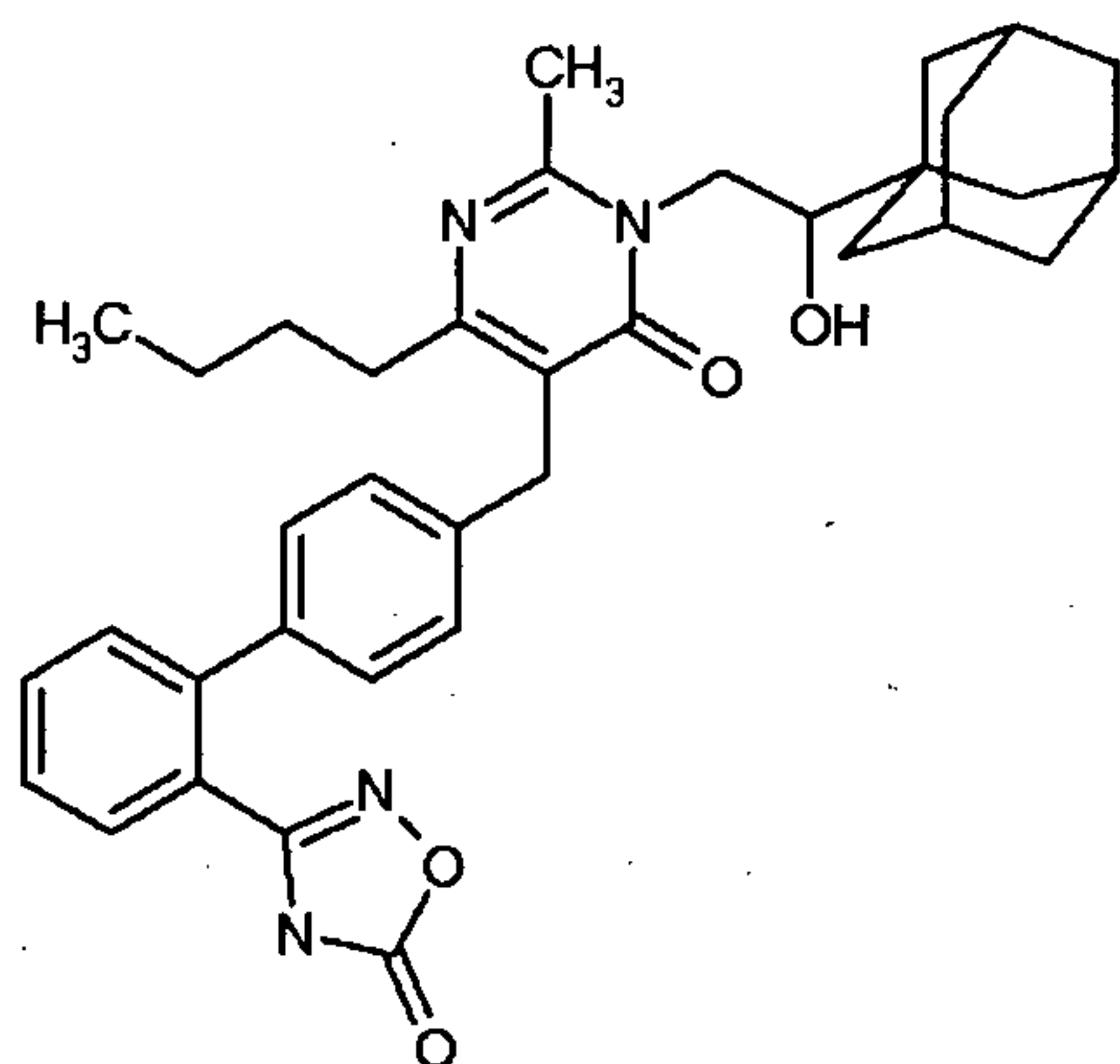
3-[2-(1-adamantyl)-2-hydroxyethyl]-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



44a) 4'-{[1-(2-(1-adamantyl)-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(1-adamantyl)-2-bromoethanone (1.08 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in methanol (20 mL), sodium borohydride (0.12 g) was added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, and the residue was extracted with ethyl acetate and saturated aqueous ammonium chloride solution. The ethyl acetate layer was washed with saturated brine, and concentrated. The obtained residue was dissolved in tetrahydrofuran (20 mL), and tert-butyl(dimethyl)silyl trifluoromethanesulfonate (0.47 mL) and 2,6-lutidine (0.24 mL) were added at 0°C. The reaction mixture was stirred at 0°C for 3 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.56 g, 31%).

¹H NMR (300 MHz, CDCl₃) δ 0.87-0.93 (18H, m), 1.31-1.44 (2H, m), 1.47-1.82 (14H, m), 2.01 (3H, br), 2.56-2.70 (5H, m), 3.64-3.78 (1H, m), 3.81-3.91 (1H, m), 4.43 (1H, d, J = 13.0), 7.33-7.50 (6H, m), 7.57-7.65 (1H, m), 7.74 (1H, d, J = 7.7)



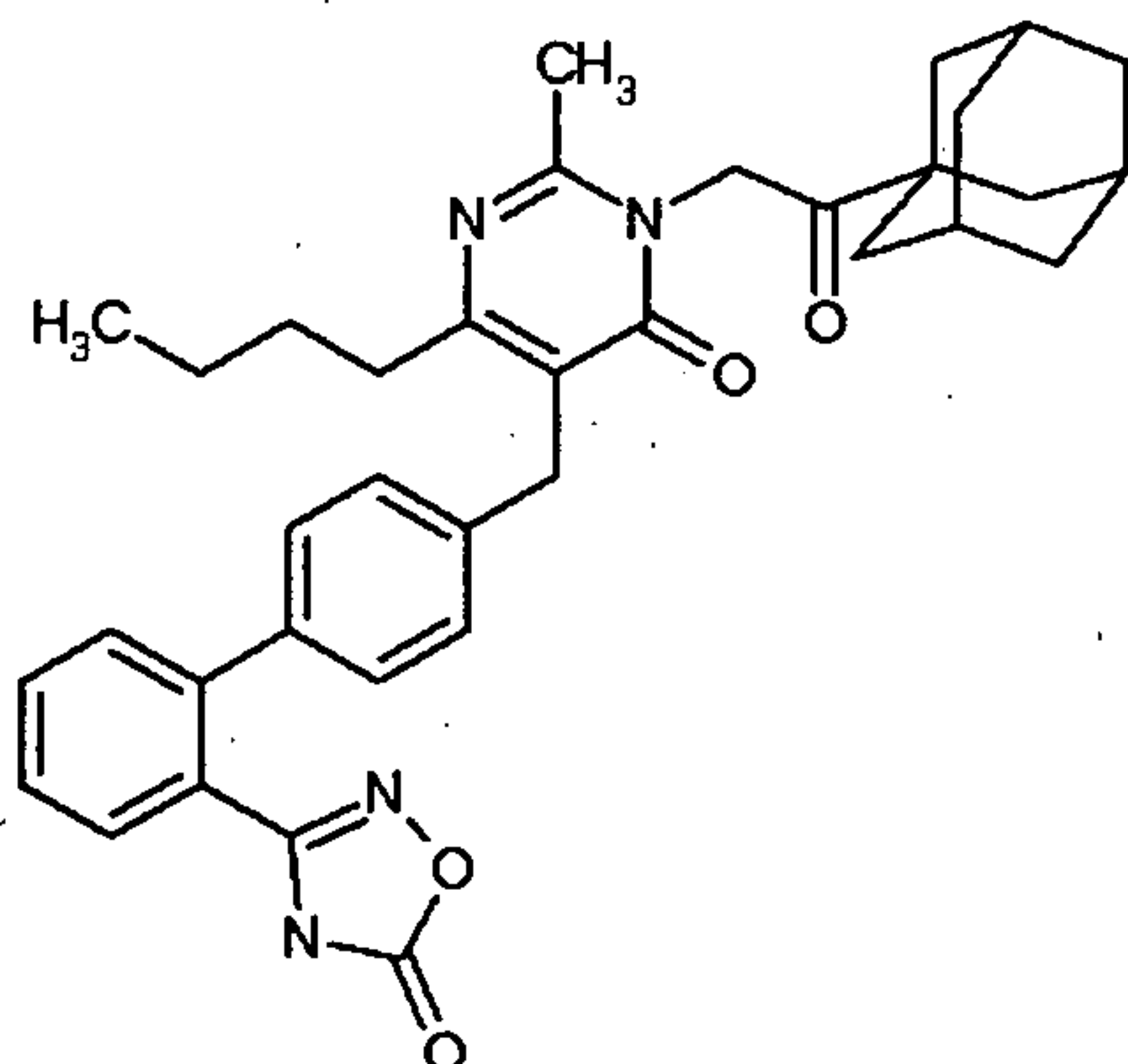
44b) 3-[2-(1-adamantyl)-2-hydroxyethyl]-6-butyl-2-methyl-5-
{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
yl]methyl}pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (0.90 g), sodium hydrogen carbonate (1.44 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[1-(2-(1-adamantyl)-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.56 g)
10 was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL),
15 N,N'-carbonyldiimidazole (0.17 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.14 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
20 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution, 3.9 mL) was added, and the mixture was stirred at room temperature for 3 hr. The
25 reaction mixture was extracted with 1 M hydrochloric acid and ethyl acetate, and the ethyl acetate layer was washed with saturated brine and concentrated. The residue was purified by silica gel column chromatography to give the title compound as

colorless crystals (0.11 g, 24%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.4), 1.20-1.33 (2H, m), 1.36-1.48 (2H, m), 1.51-1.74 (12H, m), 1.96 (3H, s), 2.39-2.48 (2H, m), 2.52 (3H, s), 3.25-3.31 (1H, m), 3.62-3.72 (1H, m), 3.74-3.93 (2H, m), 4.24 (1H, d, J = 12.1), 4.88 (1H, d, J = 5.8), 7.17-7.28 (4H, m), 7.45-7.59 (2H, m), 7.61-7.73 (2H, m), 12.38 (1H, s)

Example 45



10 3-[2-(1-adamantyl)-2-oxoethyl]-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

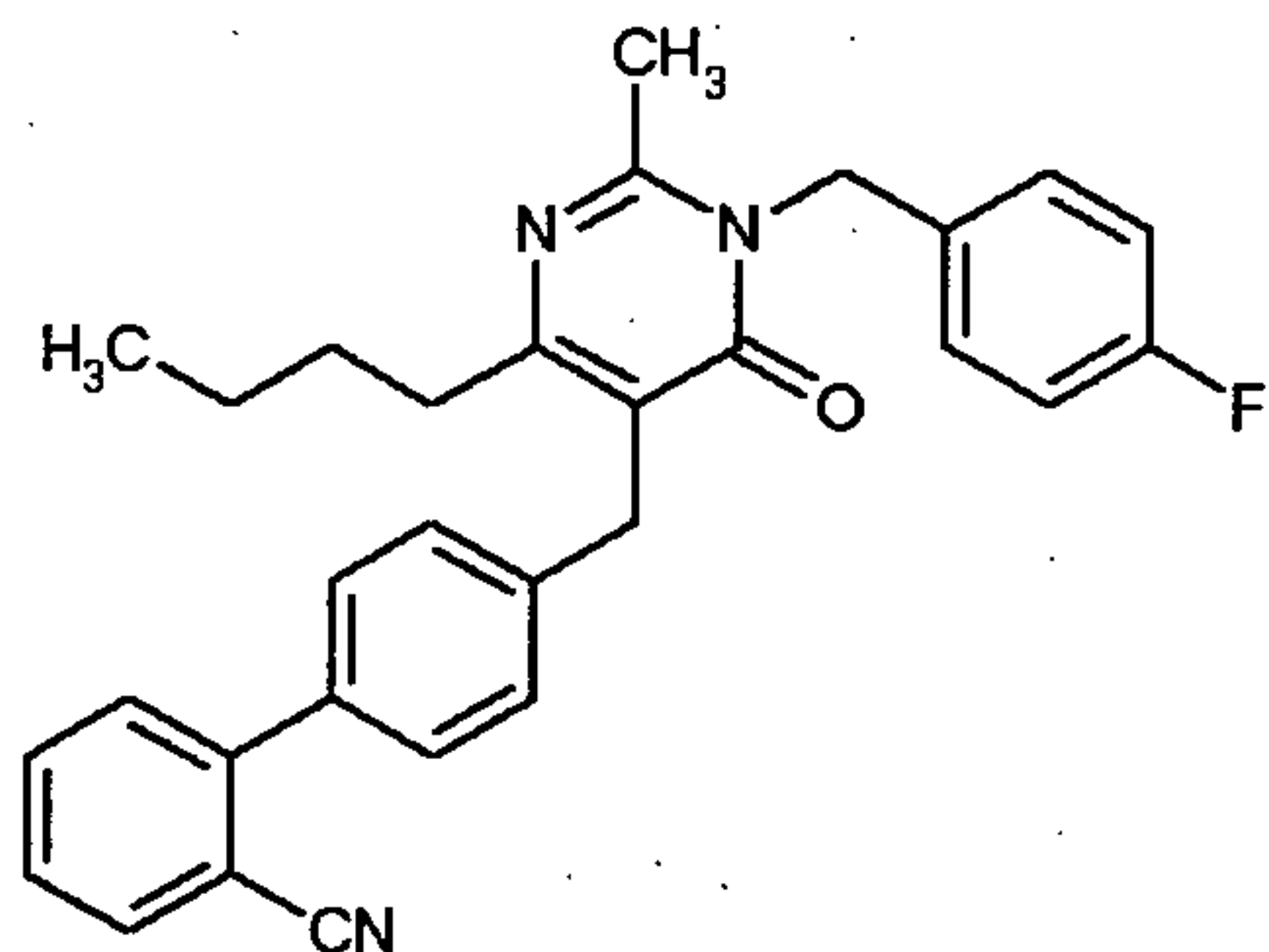
A mixture of 3-[2-(1-adamantyl)-2-hydroxyethyl]-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (0.078 g), 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (0.067 g) and methylene chloride (10 mL) was stirred at room temperature for 2 hr. A saturated aqueous sodium hydrogen carbonate solution and sodium thiosulfate were added to the reaction mixture. The mixture was stirred at room temperature for 2 hr and extracted with chloroform. The chloroform layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.057 g, 73%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.4), 1.19-1.35 (2H, m), 1.39-1.55 (2H, m), 1.63-1.79 (6H, m), 1.82-1.96 (6H,

m), 2.03 (3H, s), 2.26 (3H, s), 2.43-2.48 (2H, m), 3.83 (2H, s), 5.13 (2H, s), 7.20 (4H, s), 7.45-7.58 (2H, m), 7.60-7.73 (2H, m), 12.38 (1H, s)

Example 46

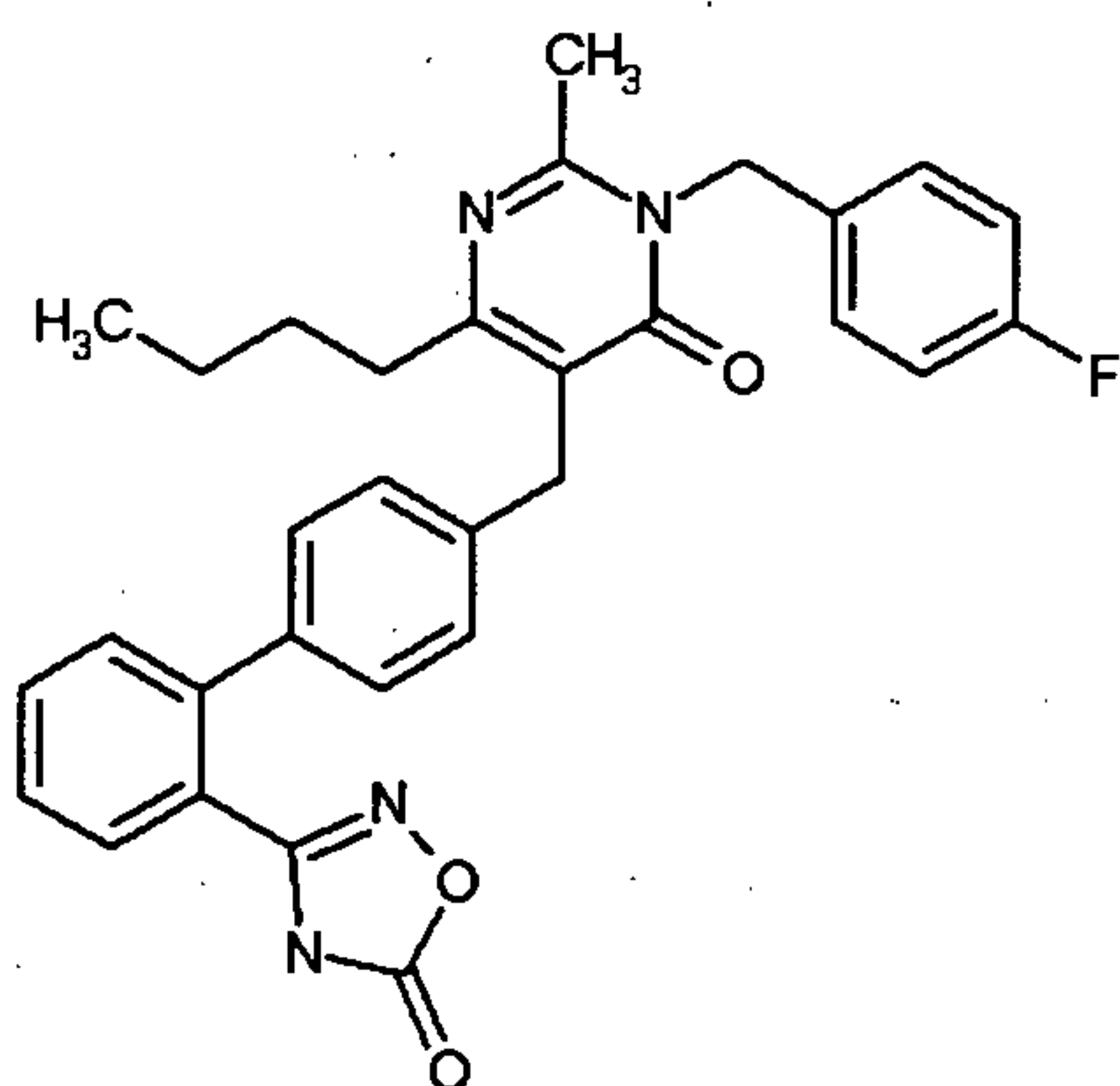
5 6-butyl-3-(4-fluorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



46a) 4'-{[4-butyl-1-(4-fluorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

10 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)-4-fluorobenzene (0.52 mL) was added, and the mixture was stirred
15 at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified
20 by silica gel column chromatography to give the title compound as a colorless solid (0.76 g, 58%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.31-1.46 (2H, m), 1.51-1.61 (2H, m), 2.46 (3H, s), 2.56-2.66 (2H, m), 4.00 (2H, s), 5.26 (2H, s), 6.98-7.10 (2H, m), 7.15-7.22 (2H, m),
25 7.33-7.52 (6H, m), 7.58-7.66 (1H, m), 7.75 (1H, d, J = 8.5)



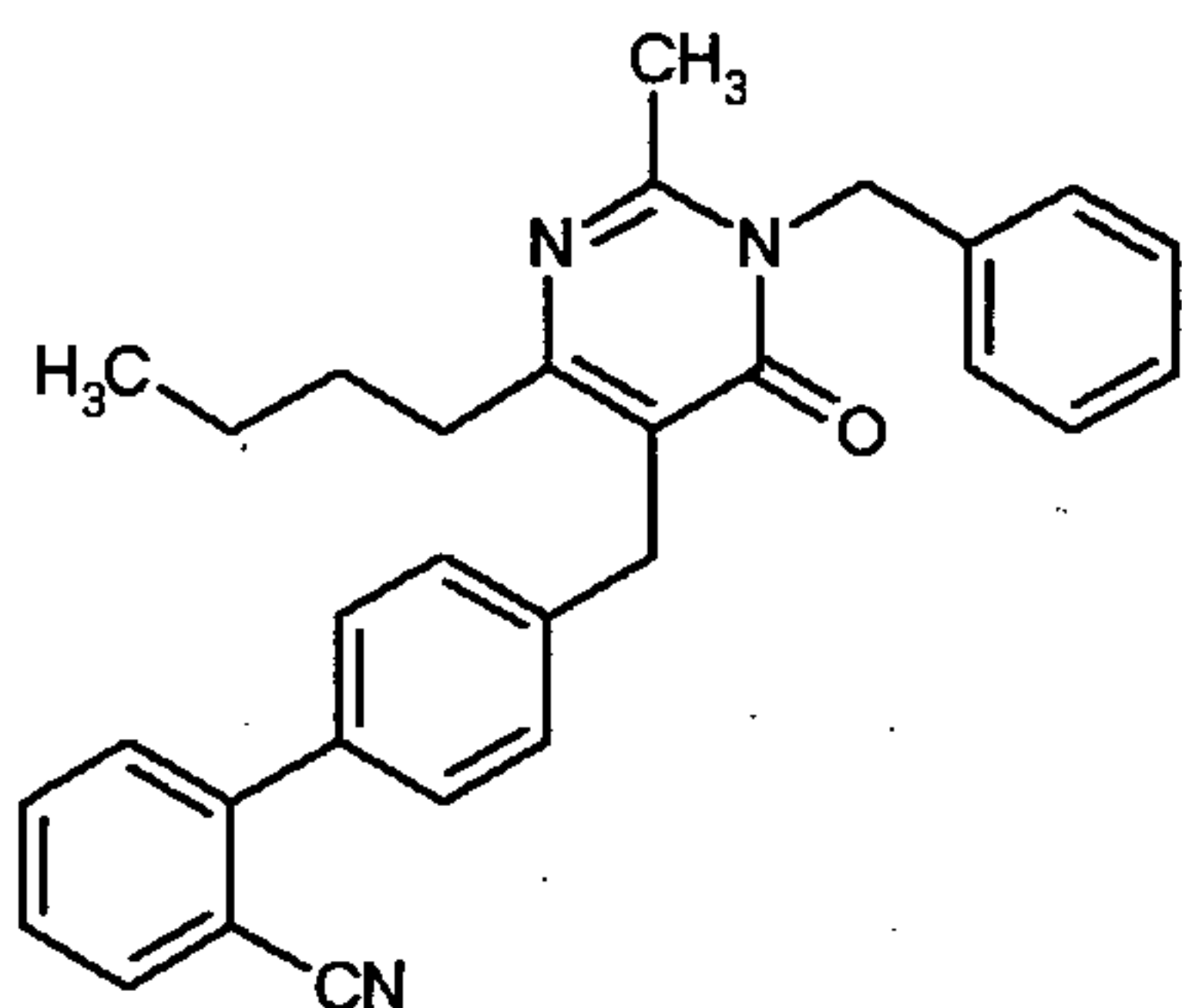
46b) 6-butyl-3-(4-fluorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (1.7 g), sodium hydrogen carbonate (2.74 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(4-fluorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.76 g) was added, and the mixture was stirred
 10 at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole
 15 (0.32 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.27 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over
 20 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.55 g, 65%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.4), 1.21-1.36
 25 (2H, m), 1.38-1.56 (2H, m), 2.39 (3H, s), 2.43-2.51 (2H, m), 3.90 (2H, s), 5.26 (2H, s), 7.14-7.36 (8H, m), 7.44-7.59 (2H, m), 7.60-7.76 (2H, m), 12.40 (1H, s)

Example 47

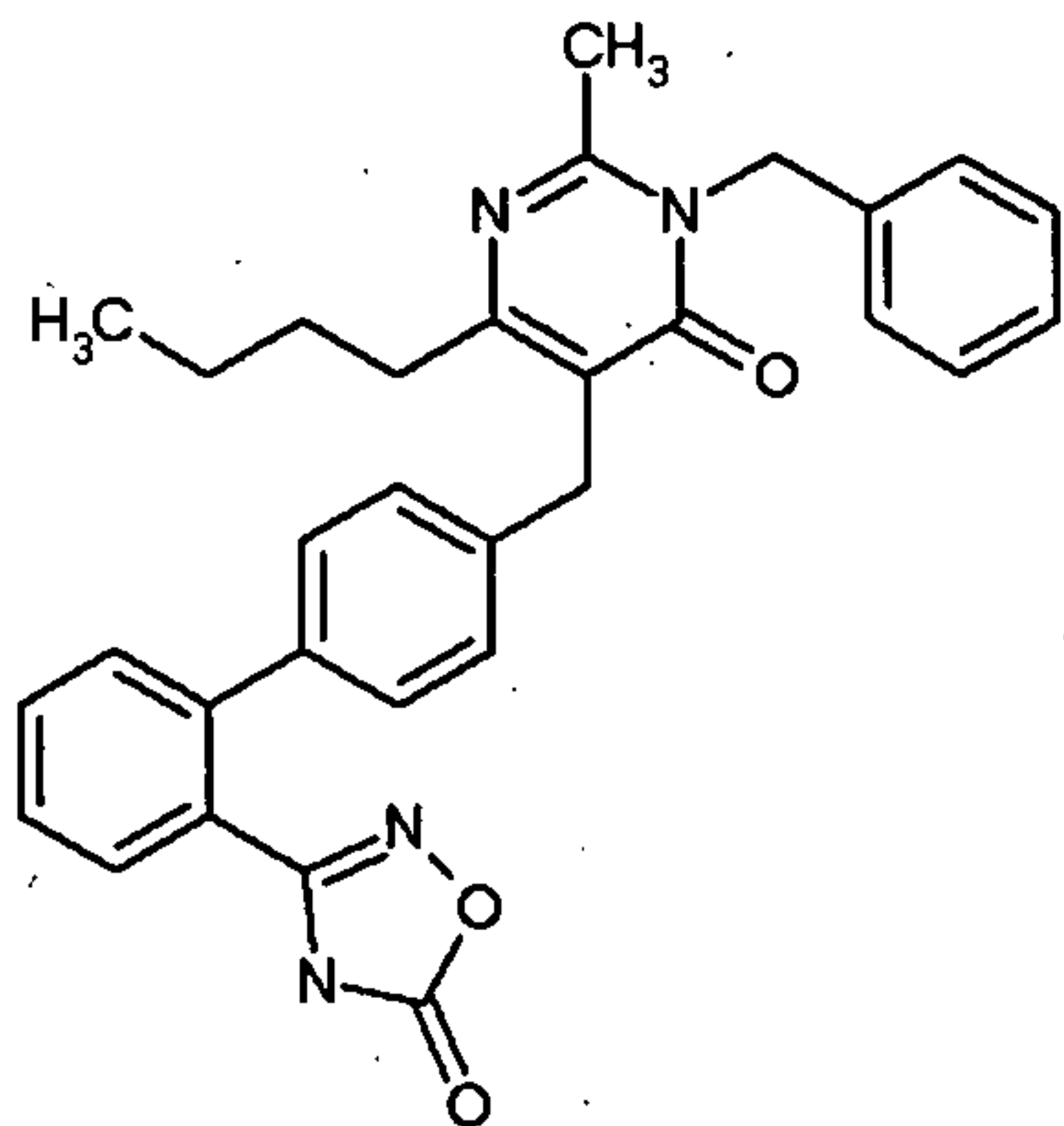
3-benzyl-6-butyl-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one



47a) 4'-[(1-benzyl-4-butyl-2-methyl-6-oxo-1,6-
 5 dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, (bromomethyl)benzene
 10 (0.67 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under
 15 reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.64 g, 51%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.32-1.45 (2H, m), 1.52-1.62 (2H, m), 2.45 (3H, s), 2.55-2.67 (2H, m), 4.01
 20 (2H, s), 5.30 (2H, s), 7.16-7.23 (2H, m), 7.26-7.41 (6H, m), 7.43-7.51 (3H, m), 7.61 (1H, dd, J = 7.6, 1.2), 7.74 (1H, dd, J = 7.7, 0.9)



47b) 3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.49 g), sodium hydrogen carbonate (2.40 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-[(1-benzyl-4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (0.64 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.28 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.24 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.36 g, 49%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.23-1.38 (2H, m), 1.37-1.56 (2H, m), 2.38 (3H, s), 2.46-2.57 (2H, m), 3.91 (2H, s), 5.29 (2H, s), 7.13-7.42 (9H, m), 7.47-7.61 (2H, m), 7.61-7.74 (2H, m), 12.39 (1H, s)

3-Benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one sodium salt

3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one potassium salt

3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-

oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one 0.5
calcium salt

3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-
oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

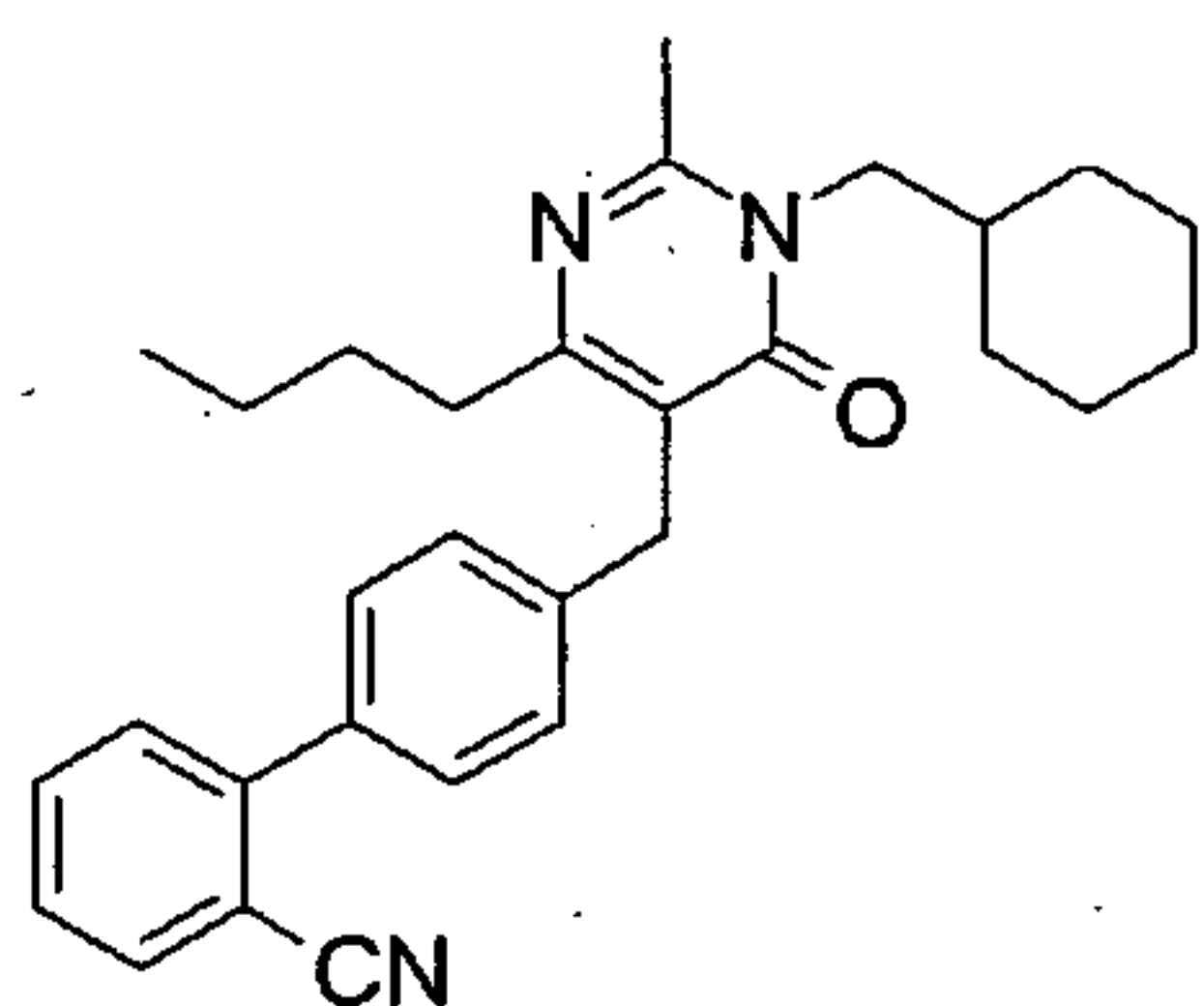
5 hydrochloride

3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-
oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

hydrobromide

Example 48

10 6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-
dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
4(3H)-one

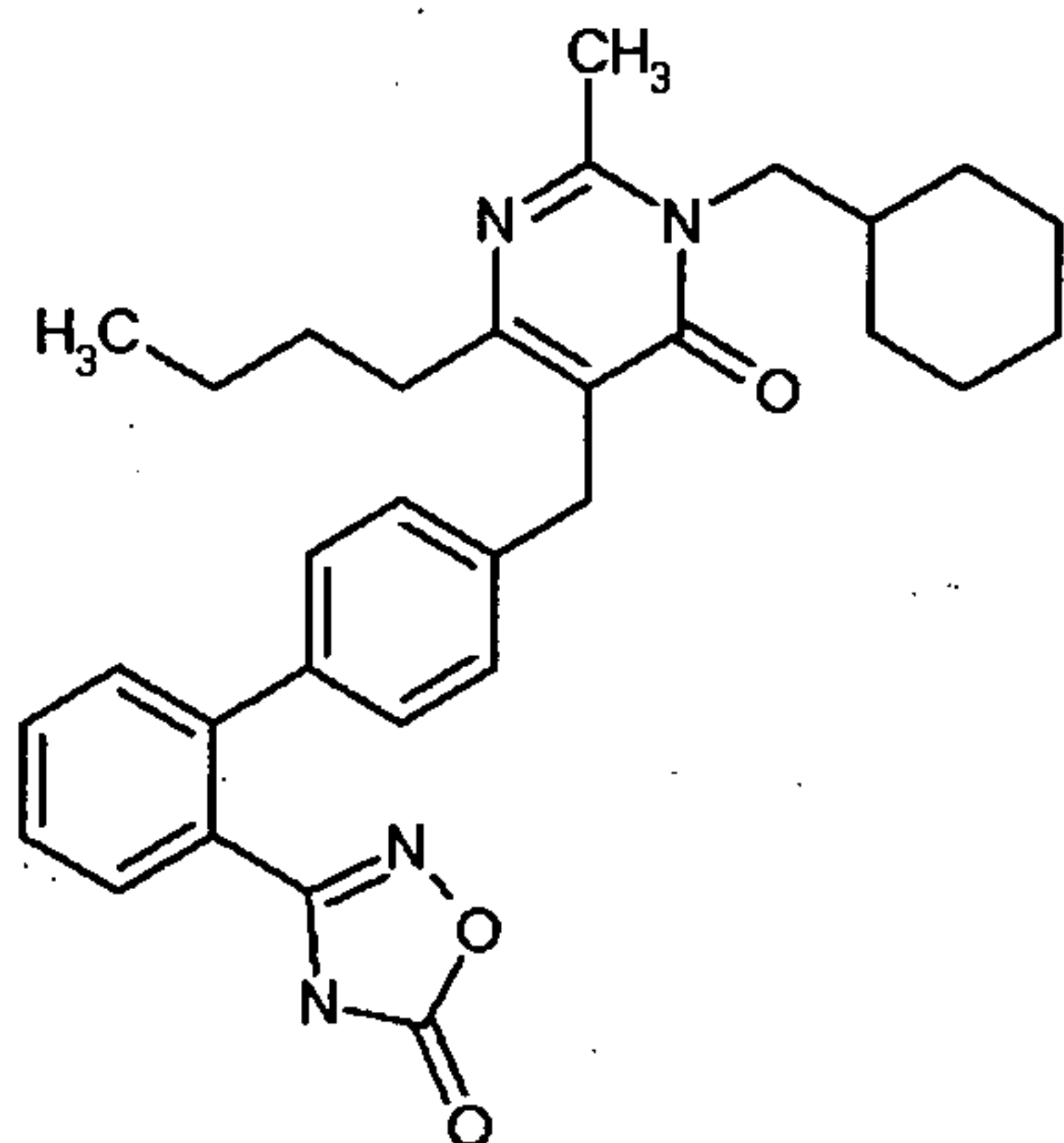


15 48a) 4'-{[4-butyl-1-(cyclohexylmethyl)-2-methyl-6-oxo-1,6-
dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min,
 20 (bromomethyl)cyclohexane (0.70 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent
 25 was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.38 g, 30%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.2), 0.99-1.26 (4H, m), 1.32-1.43 (2H, m), 1.50-1.78 (8H, m), 1.79-1.92 (1H, m),
 30 2.53 (3H, s), 2.54-2.61 (2H, m), 3.86 (2H, d, J = 7.0), 3.95 (2H, s), 7.31-7.49 (6H, m), 7.57-7.65 (1H, m), 7.74 (1H, dd, J

= 7.7, 0.9)



48b) 6-butyl-3-(cyclohexylmethyl)-2-methyl-5-([2'-(5-oxo-4,5-
dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-
 5 4(3H)-one

A mixture of hydroxylammonium chloride (0.88 g), sodium hydrogen carbonate (1.41 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(cyclohexylmethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-
 10 carbonitrile (0.38 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was
 15 dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.16 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.14 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate
 20 solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.14 g, 33%).

25 ¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.3), 0.97-1.90 (15H, m), 2.40-2.50 (5H, m), 3.84 (4H, s), 7.03-7.27 (4H, m), 7.43-7.58 (2H, m), 7.60-7.72 (2H, m), 12.37 (1H, s)

6-Butyl-3-(cyclohexylmethyl)-2-methyl-5-([2'-(5-oxo-4,5-

dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

5 6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one sodium salt

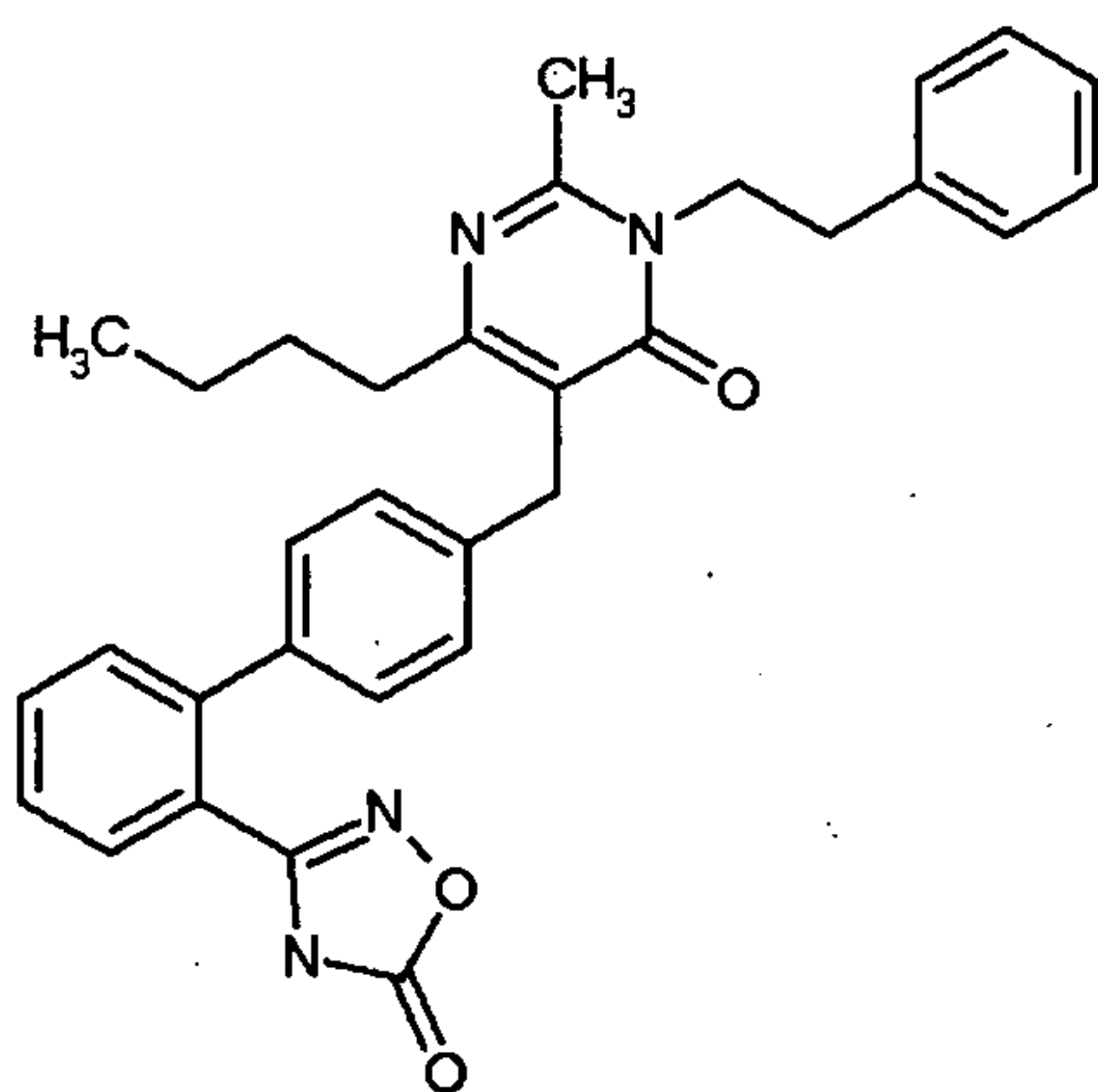
6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one potassium salt

10 6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one 0.5 calcium salt

6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-
15 4(3H)-one dihydrochloride

6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one dihydrobromide

Example 49.



20

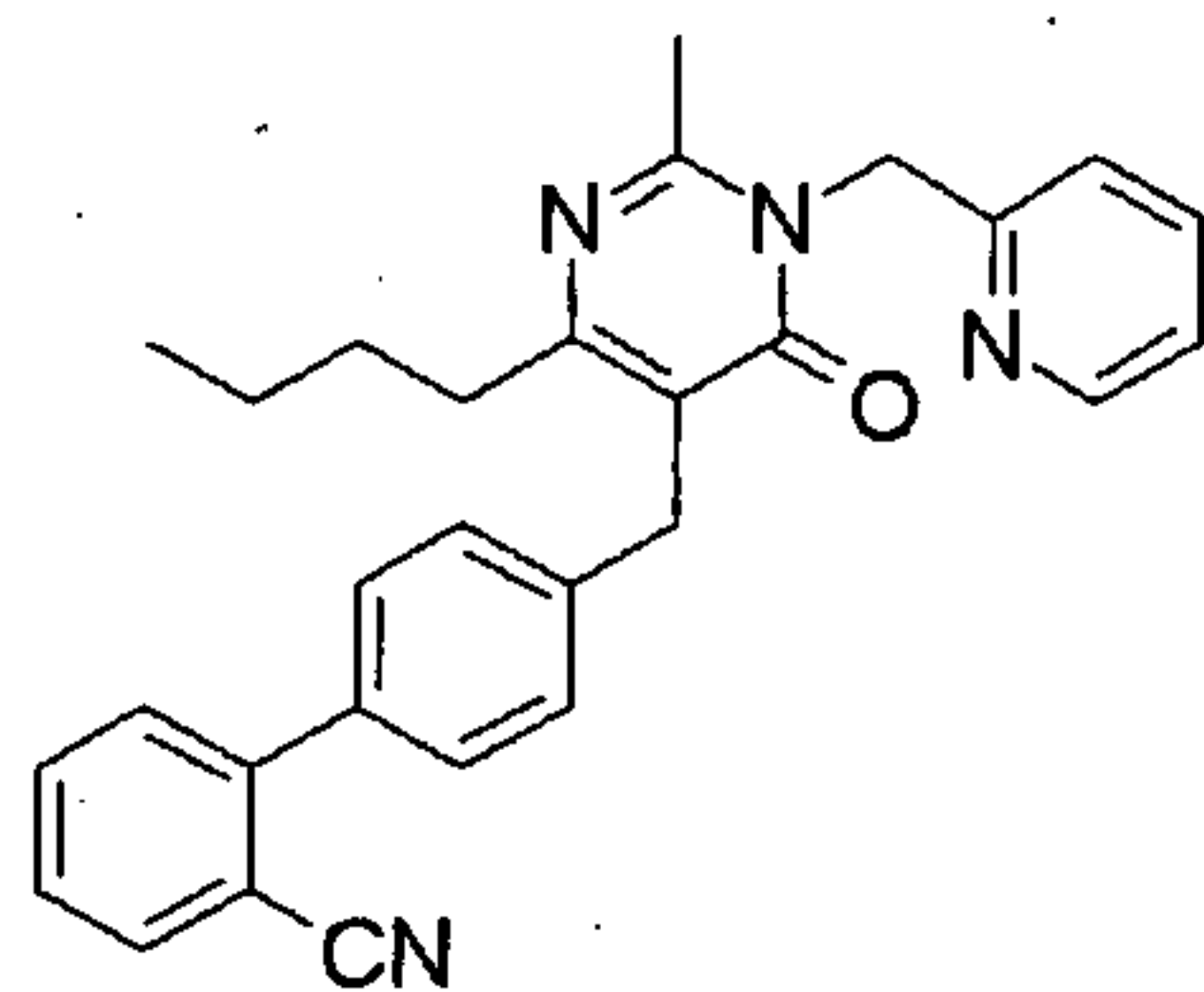
6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-3-(2-phenylethyl)pyrimidin-4(3H)-one

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g),
25 sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, (2-bromoethyl)benzene (0.76 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with

ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.9 g), sodium hydrogen carbonate (1.45 g) and dimethyl sulfoxide (10 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.17 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.14 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.14 g, 31%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.2), 1.17-1.33 (2H, m), 1.35-1.50 (2H, m), 2.37 (3H, s), 2.41-2.48 (2H, m), 2.94 (2H, t, J = 7.5), 3.87 (2H, s), 4.14 (2H, t, J = 8.1), 7.18-7.36 (9H, m), 7.47-7.57 (2H, m), 7.61-7.73 (2H, m), 12.38 (1H, br)

Example 50

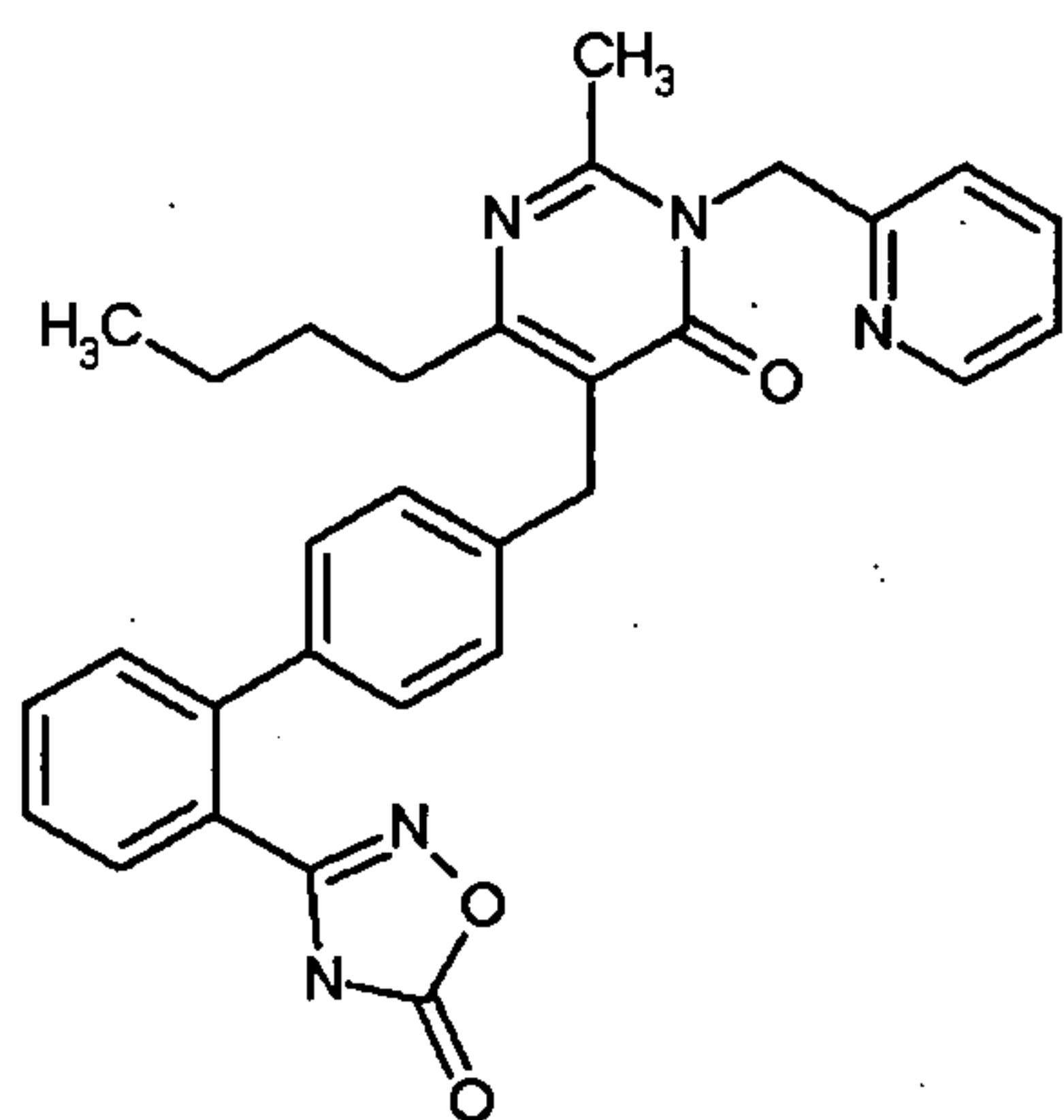
6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one



50a) 4'-{[4-butyl-2-methyl-6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), potassium carbonate (0.77 g), 2-(bromomethyl)pyridine hydrobromide (1.06 g) and N,N-dimethylformamide (10 mL) was stirred at 50°C for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.87 g, 69%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.4), 1.30-1.44 (2H, m), 1.49-1.64 (2H, m), 2.56-2.65 (5H, m), 3.98 (2H, s), 5.38 (2H, s), 7.16-7.29 (2H, m), 7.32-7.52 (6H, m), 7.56-7.69 (2H, m), 7.74 (1H, dd, J = 7.7, 0.9), 8.51-8.57 (1H, m)



50b) 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (2.02 g), sodium hydrogen carbonate (3.24 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-2-methyl-6-oxo-1-

(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile (0.87 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then
 5 with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.24 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.2 mL) were added, and the
 10 mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under
 15 reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.076 g, 8%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (3H, t, J = 7.3), 1.22-1.38 (2H, m), 1.39-1.54 (2H, m), 2.42-2.52 (5H, m), 3.85 (2H, s),
 20 5.34 (2H, s), 7.13-7.25 (4H, m), 7.25-7.40 (2H, m), 7.44-7.60 (2H, m), 7.59-7.76 (2H, m), 7.74-7.86 (1H, m), 8.42-8.55 (1H, m), 12.38 (1H, s)

6-Butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one obtained above is subjected to a
 25 conventional method of salt formation to give the following salts.

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-3-(pyridin-2-ylmethyl)pyrimidin-
 30 4(3H)-one sodium salt

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-3-(pyridin-2-ylmethyl)pyrimidin-
4(3H)-one potassium salt

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-3-(pyridin-2-ylmethyl)pyrimidin-
 35 4(3H)-one sodium salt

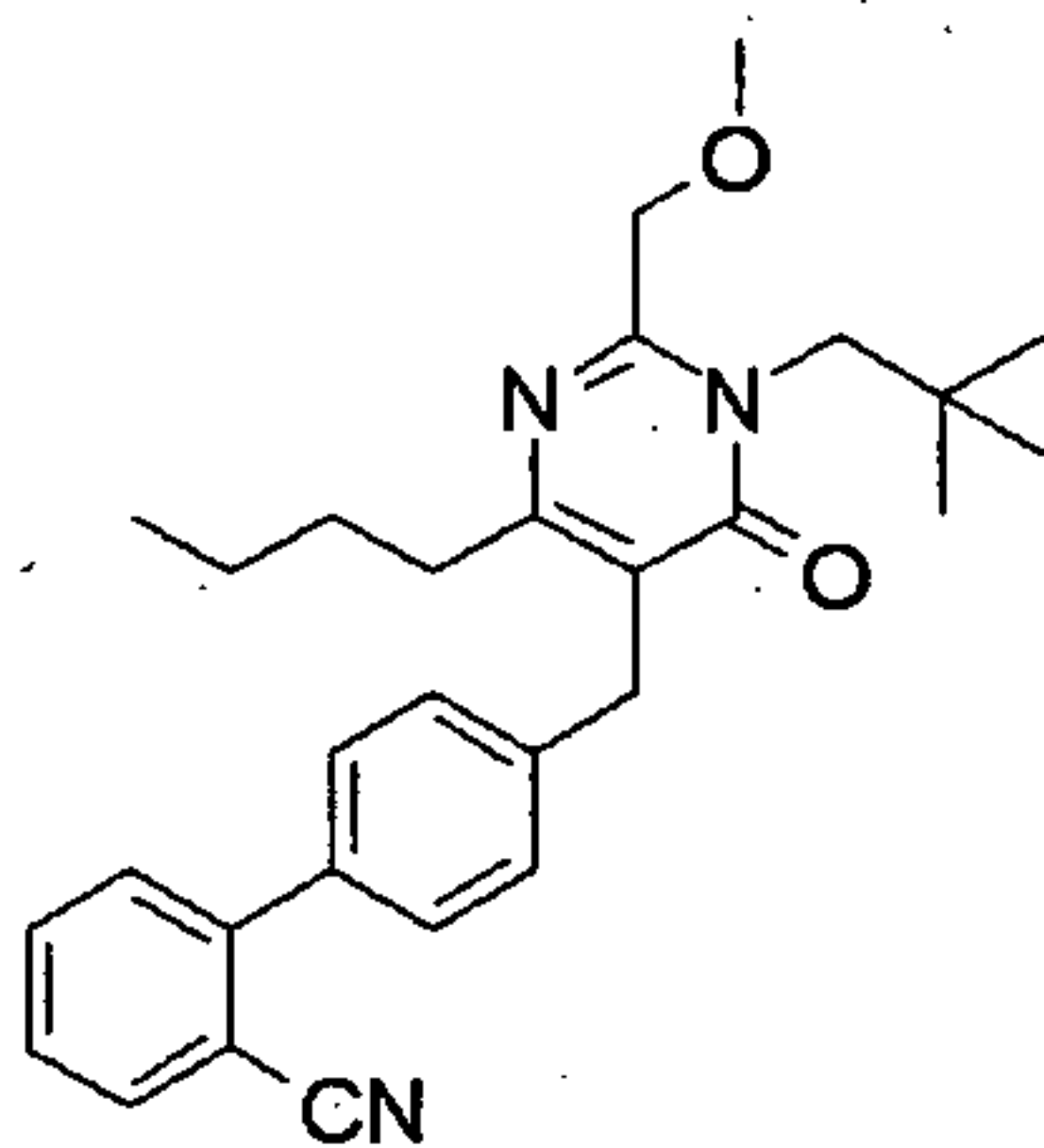
4(3H)-one 0.5 calcium salt

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one hydrochloride

5 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one hydrobromide

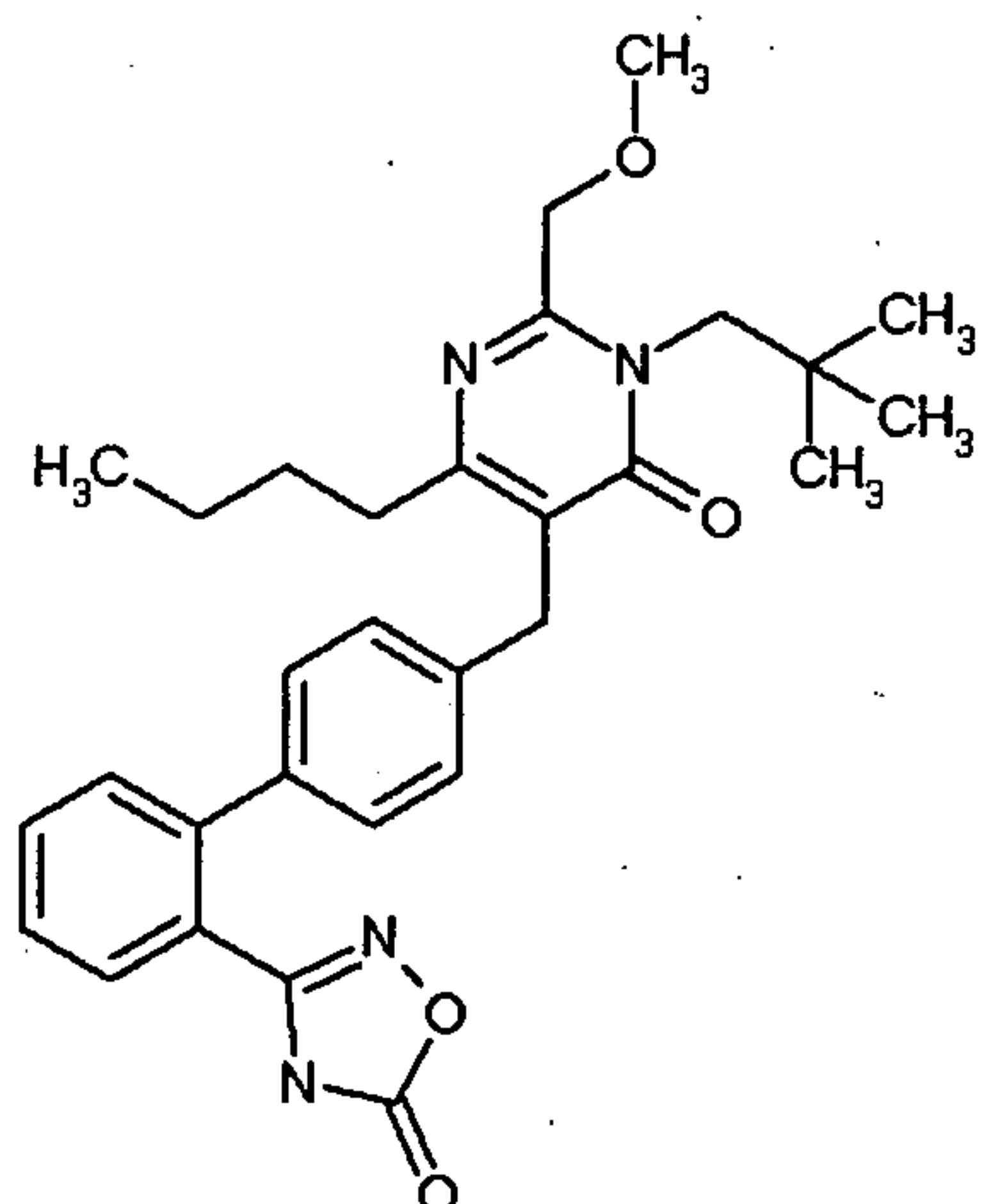
Example 51

10 6-butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



51a) 4'-{[4-butyl-1-(2,2-dimethylpropyl)-2-(methoxymethyl)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

15 A mixture of 4'-{[4-butyl-2-(methoxymethyl)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (5 g), cesium carbonate (8.4 g), 1-iodo-2,2-dimethylpropane (3.4 mL) and N,N-dimethylacetamide (50 mL) was stirred at 130°C for 2 hr. The reaction mixture was diluted with ethyl acetate, washed
20 with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (1.76 g, 30%).
25 ¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.4), 0.98 (9H, s), 1.30-1.45 (2H, m), 1.52-1.67 (2H, m), 2.57-2.66 (2H, m), 3.38 (3H, s), 3.97 (2H, s), 4.13 (2H, br), 4.54 (2H, br), 7.31-7.50 (6H, m), 7.57-7.65 (1H, m), 7.74 (1H, dd, J = 7.7, 0.8)



51b) 6-butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (4.01 g), sodium hydrogen carbonate (6.50 g) and dimethyl sulfoxide (30 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(2,2-dimethylpropyl)-2-(methoxymethyl)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1.76 g) was added, and
 10 the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (40 mL), N,N'-
 15 carbonyldiimidazole (0.75 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.63 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
 20 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.78 g, 39%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 0.90 (9H, s),
 25 1.20-1.36 (2H, m), 1.41-1.55 (2H, m), 2.45-2.59 (5H, m), 3.88 (2H, s), 4.00 (2H, s), 4.47 (2H, s), 7.15-7.29 (4H, m), 7.52 (2H, dd, J = 18.3, 7.5), 7.61-7.75 (2H, m), 12.37 (1H, s)

6-Butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

6-butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one sodium salt

6-butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one potassium salt

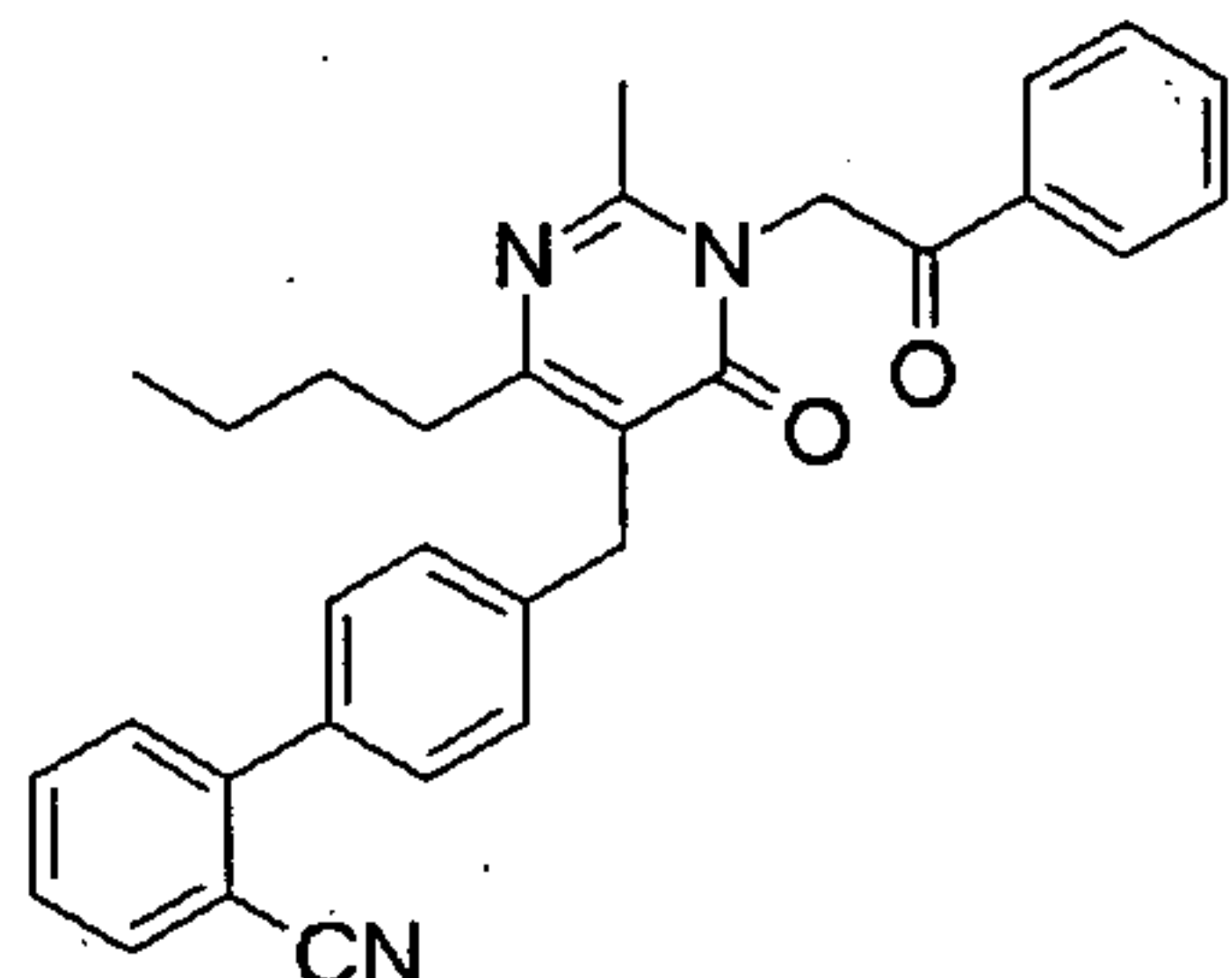
6-butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one 0.5 calcium salt

6-butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrochloride

6-butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrobromide

Example 52

6-butyl-3-(2-hydroxy-2-phenylethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

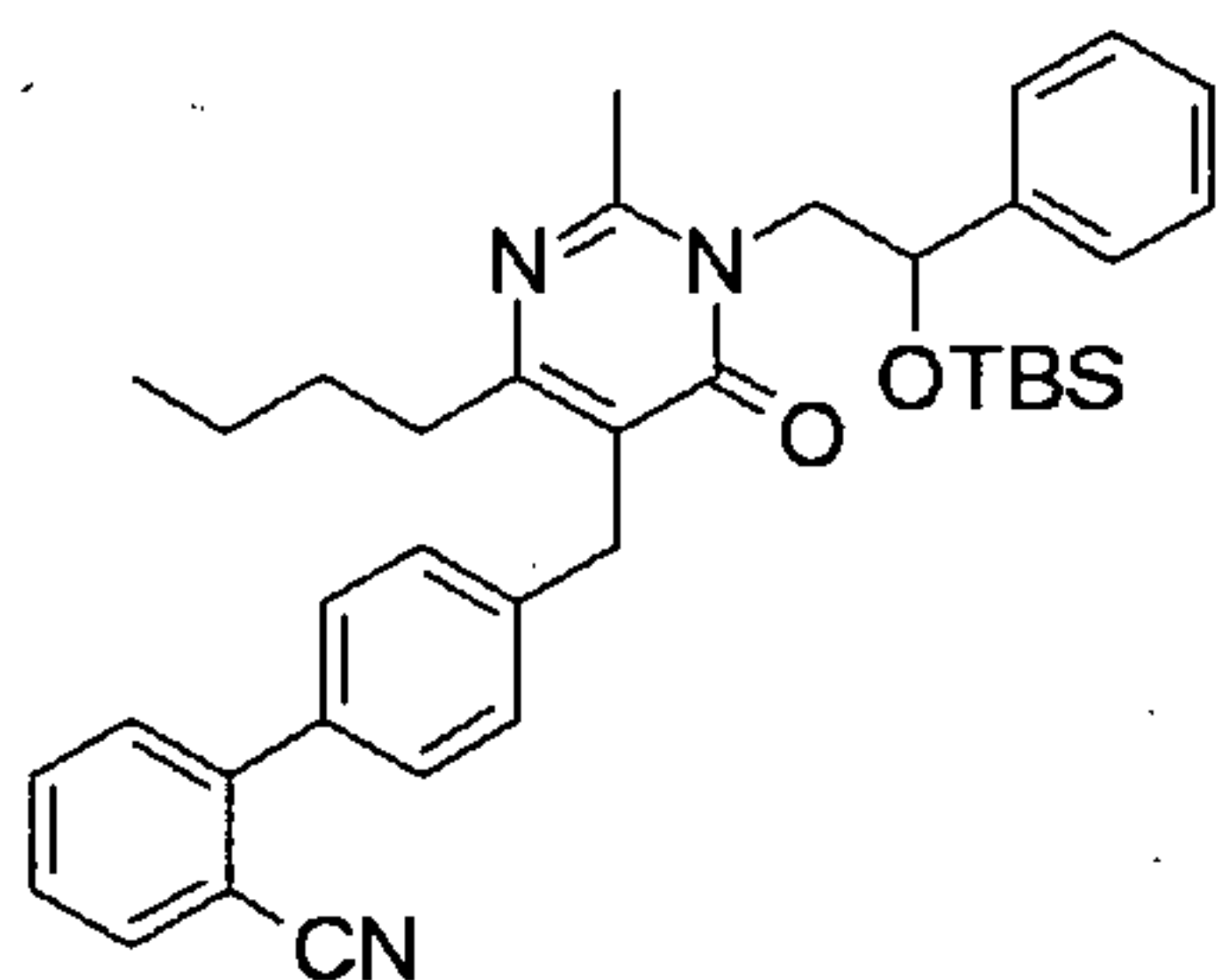


52a) 4'-{[4-butyl-2-methyl-6-oxo-1-(2-oxo-2-phenylethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1.5 g), sodium hydride (0.25 g) and N,N-dimethylformamide (30 mL) was

stirred at room temperature for 10 min, 2-bromo-1-phenylethanone (1.25 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.87 g, 43%).

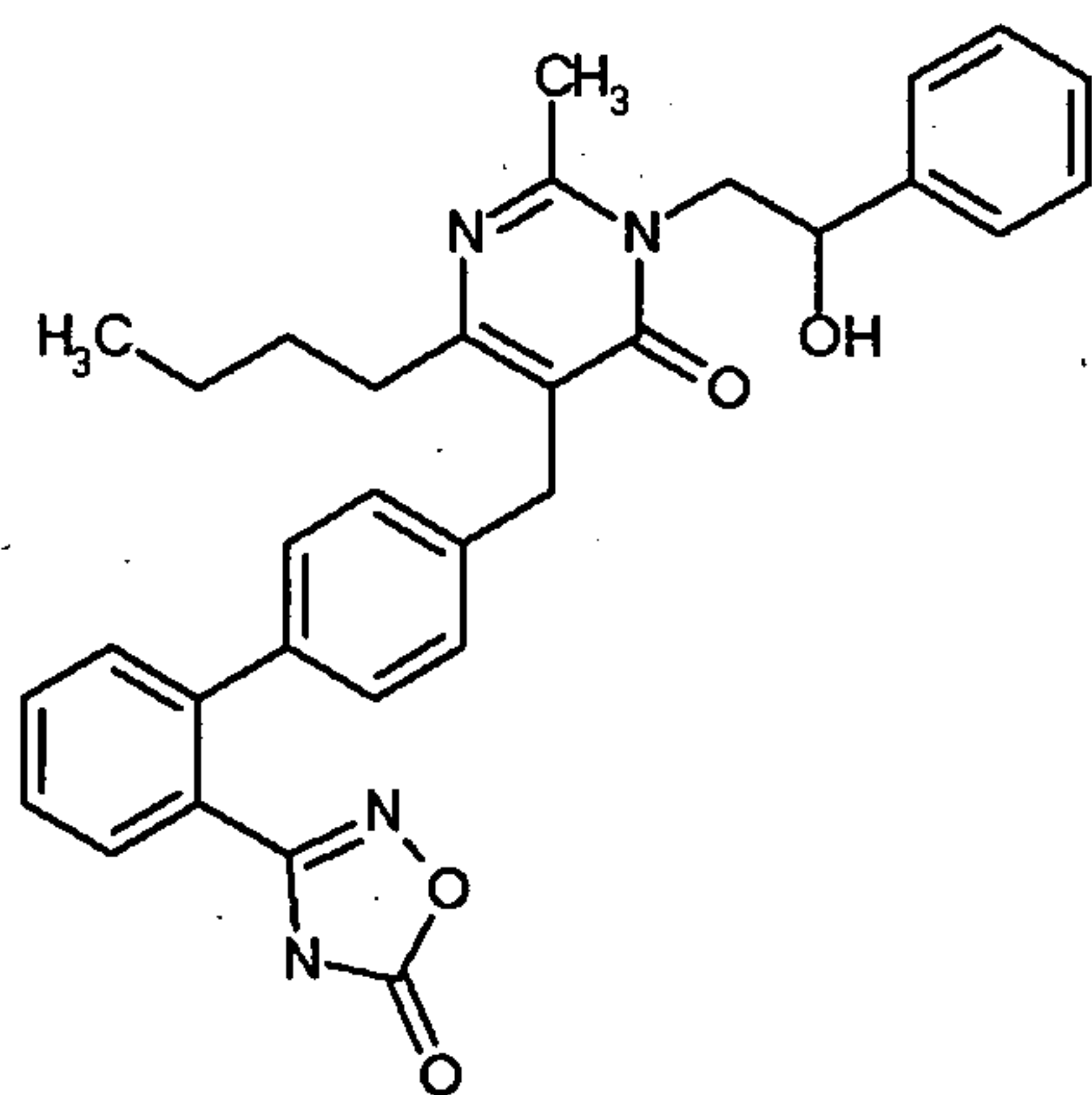
¹H NMR (300 MHz, CDCl₃) δ 0.92 (3H, t, J = 7.3), 1.31-1.49 (2H, m), 1.53-1.68 (2H, m), 2.41 (3H, s), 2.58-2.67 (2H, m), 3.97 (2H, s), 5.51 (2H, s), 7.31-7.68 (10H, m), 7.73 (1H, dd, J = 7.7, 1.3), 8.00-8.08 (2H, m)



52b) 4'-{[4-butyl-1-(2-{[tert-butyl(dimethyl)silyl]oxy}-2-phenylethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-{[4-butyl-2-methyl-6-oxo-1-(2-oxo-2-phenylethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.87 g), sodium borohydride (0.21 g) and methanol (25 mL) was stirred at room temperature for 3 hr. The reaction mixture was concentrated. The residue was extracted with ethyl acetate and saturated aqueous ammonium chloride solution. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was dissolved in tetrahydrofuran (20 mL), and 2,6-lutidine (0.50 mL) and tert-butyl(dimethyl)silyl trifluoromethanesulfonate (0.98 mL) were added at 0°C. The reaction mixture was stirred at 0°C for 3 hr, and diluted with

ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.73 g, 29%).
¹H NMR (300 MHz, CDCl₃) δ -0.29-0.22 (6H, m), 0.78 (9H, s), 0.92 (3H, t, J = 7.3), 1.32-1.45 (2H, m), 1.50-1.64 (2H, m), 2.51-2.75 (5H, m), 3.75 (1H, br), 3.98 (2H, dd, J = 25.6, 15.1), 4.33-4.43 (1H, m), 5.22 (1H, dd, J = 9.9, 2.9), 7.28-7.50 (11H, m), 7.58-7.65 (1H, m), 7.74 (1H, dd, J = 7.7, 0.9)



52c) 6-butyl-3-(2-hydroxy-2-phenylethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

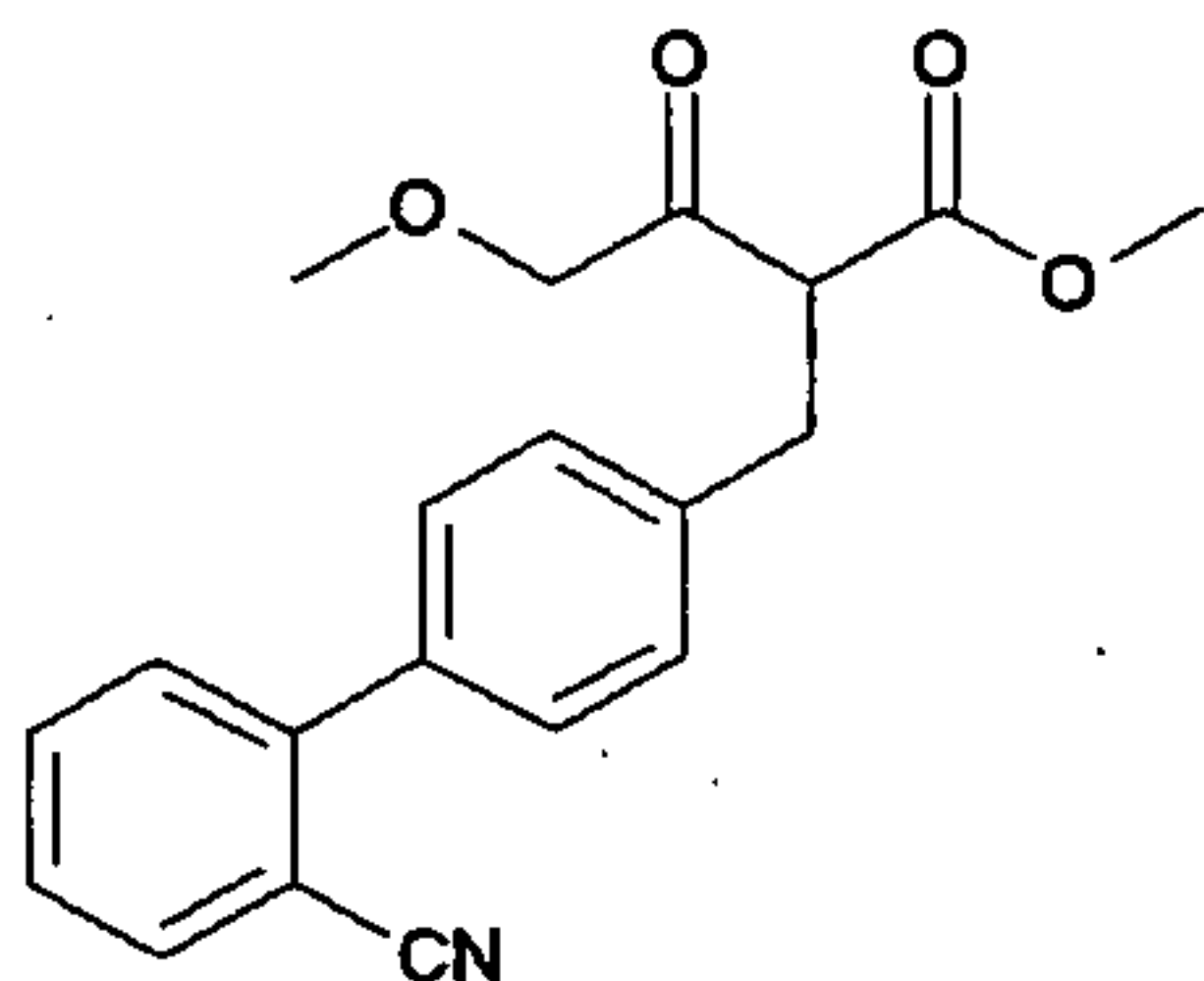
A mixture of hydroxylammonium chloride (1.29 g), sodium hydrogen carbonate (2.07 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(2-{[tert-butyl(dimethyl)silyl]oxy}-2-phenylethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.73 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.24 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.20 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated

aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution, 3.7 mL) was added, and the mixture was stirred at 70°C for 6 hr. The reaction mixture was extracted with 1 M hydrochloric acid and ethyl acetate, and the ethyl acetate layer was washed with saturated brine and concentrated. The residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.37 g, 56%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.20-1.36 (2H, m), 1.35-1.53 (2H, m), 2.39-2.62 (5H, m), 3.78-3.99 (3H, m), 4.16 (1H, dd, J = 13.7, 3.1), 4.86-5.07 (1H, m), 5.77 (1H, d, J = 4.5), 7.16-7.33 (5H, m), 7.34-7.47 (4H, m), 7.46-7.59 (2H, m), 7.62-7.77 (2H, m), 12.39 (1H, s)

Example 53

6-(methoxymethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one

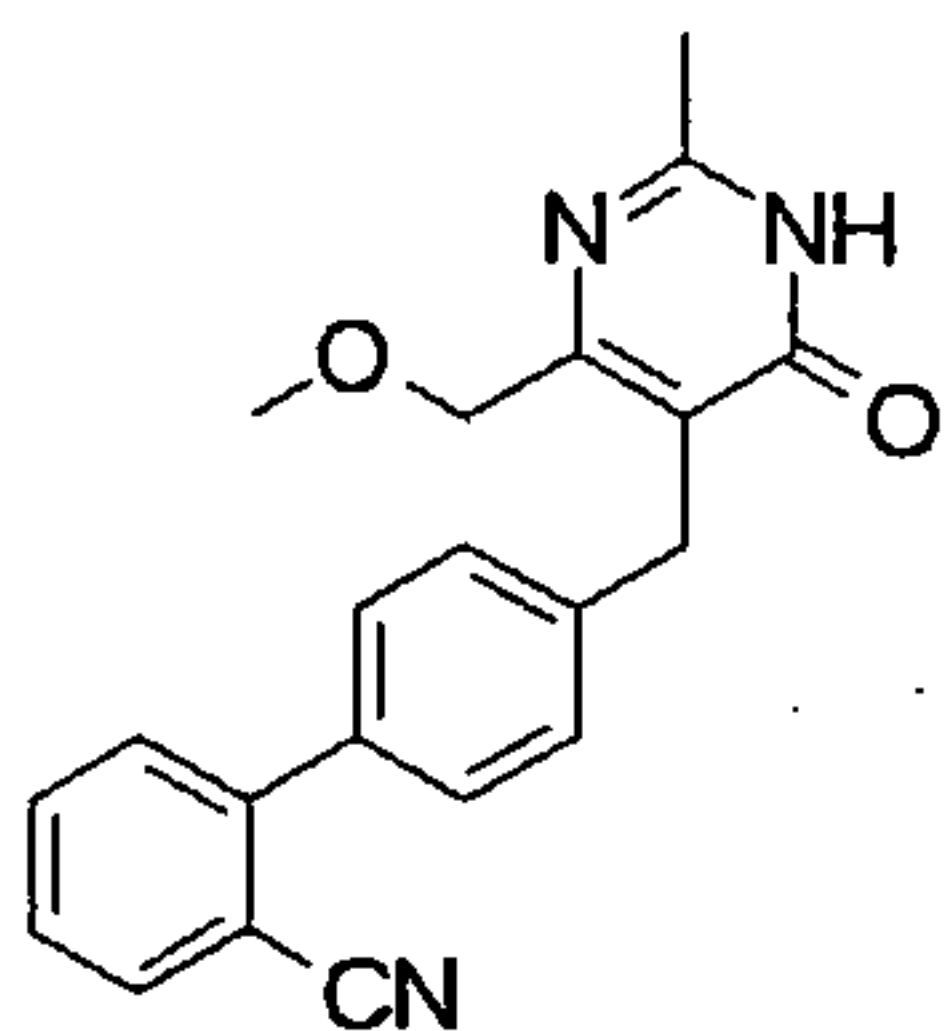


53a) methyl 2-[(2'-cyanobiphenyl-4-yl)methyl]-4-methoxy-3-oxobutanoate

A solution of methyl 4-methoxy-3-oxobutyrates (10.7 g) in tetrahydrofuran (150 mL) was added to a mixture of sodium hydride (1.91 g) and tetrahydrofuran (150 mL) at room temperature, and the mixture was stirred at room temperature for 30 min. 4'-(Bromomethyl)biphenyl-2-carbonitrile (10 g) was added to the reaction mixture, and the reaction mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated. To the residue were added 5% aqueous

potassium hydrogen sulfate solution and then ethyl acetate, and the mixture was extracted. The ethyl acetate layer was washed with saturated brine and concentrated. The residue was purified by silica gel column chromatography to give the title
 5 compound as a colorless oil (12.1 g, 98%).

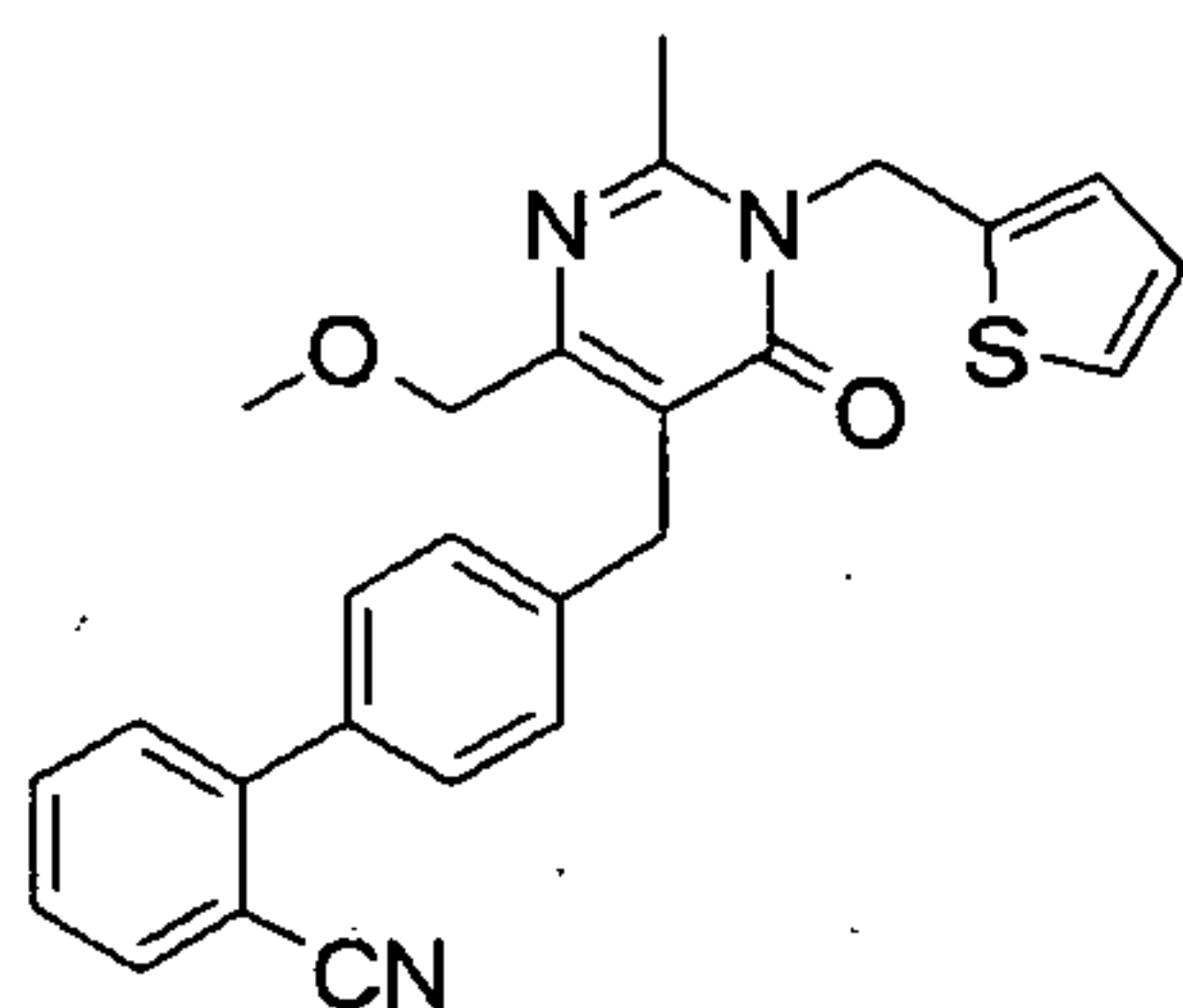
¹H NMR (300 MHz, CDCl₃) δ 3.25 (2H, t, J = 7.4), 3.34 (3H, s), 3.71 (3H, s), 3.88-4.12 (3H, m), 7.25-7.34 (2H, m), 7.39-7.51 (4H, m), 7.60-7.67 (1H, m), 7.75 (1H, d, J = 7.7)



10 53b) 4'-{[4-(methoxymethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

To a solution of acetamidine hydrochloride (3.4 g) in methanol (30 mL) was added sodium methoxide (28% methanol solution, 10.3 g) at 0°C, a solution of methyl 2-[(2'-
 15 cyanobiphenyl-4-yl)methyl]-4-methoxy-3-oxobutanoate in methanol (60 mL) - 1,4-dioxane (20 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated, and water (50 mL) and 50%
 20 aqueous acetic acid solution were added to the residue and adjusted to pH 5. The obtained crystallized product was collected by filtration and washed with water to give the title compound as colorless crystals (5.27 g, 86%).

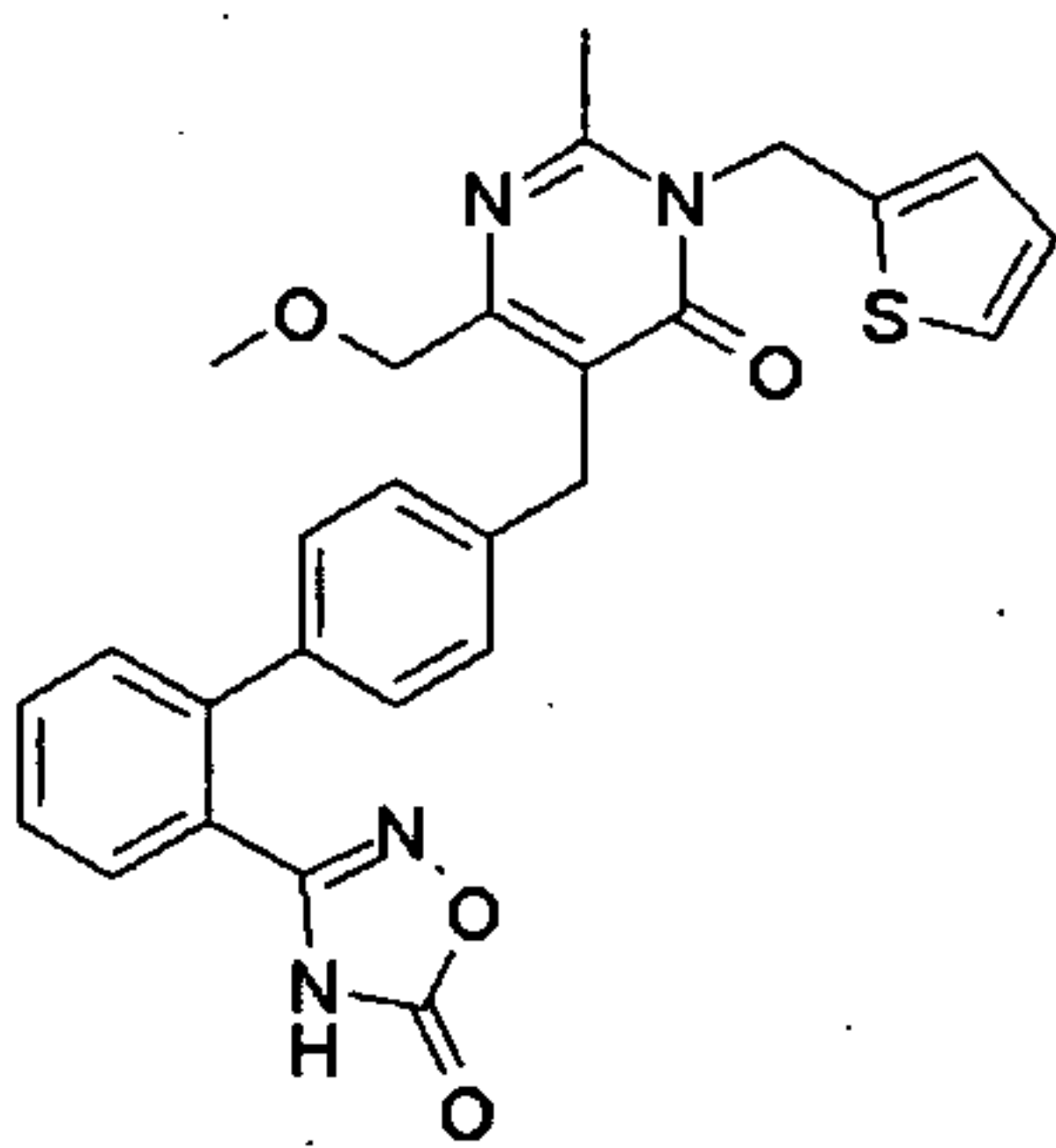
¹H NMR (300 MHz, DMSO-d₆) δ 2.27 (3H, s), 3.27 (3H, s), 3.89 (2H, s), 4.30 (2H, s), 7.33-7.39 (2H, m), 7.45-7.51 (2H, m),
 25 7.53-7.61 (2H, m), 7.77 (1H, dt, J = 7.7, 1.0), 7.93 (1H, d, J = 7.7), 12.49 (1H, s)



53c) 4'-{[4-(methoxymethyl)-2-methyl-6-oxo-1-(2-thienylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-{[4-(methoxymethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 2-(bromomethyl)thiophene (4.5 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.68 g, 53%).

¹H NMR (300 MHz, CDCl₃) δ 2.66 (3H, s), 3.44 (3H, s), 4.06 (2H, s), 4.38 (2H, s), 5.39 (2H, s), 6.95 (1H, dd, J = 5.1, 3.4), 7.06 (1H, dd, J = 3.5, 1.0), 7.22-7.29 (1H, m), 7.37-7.43 (3H, m), 7.43-7.50 (3H, m), 7.62 (1H, dt, J = 7.7, 1.4), 7.74 (1H, dd, J = 7.7, 0.9)

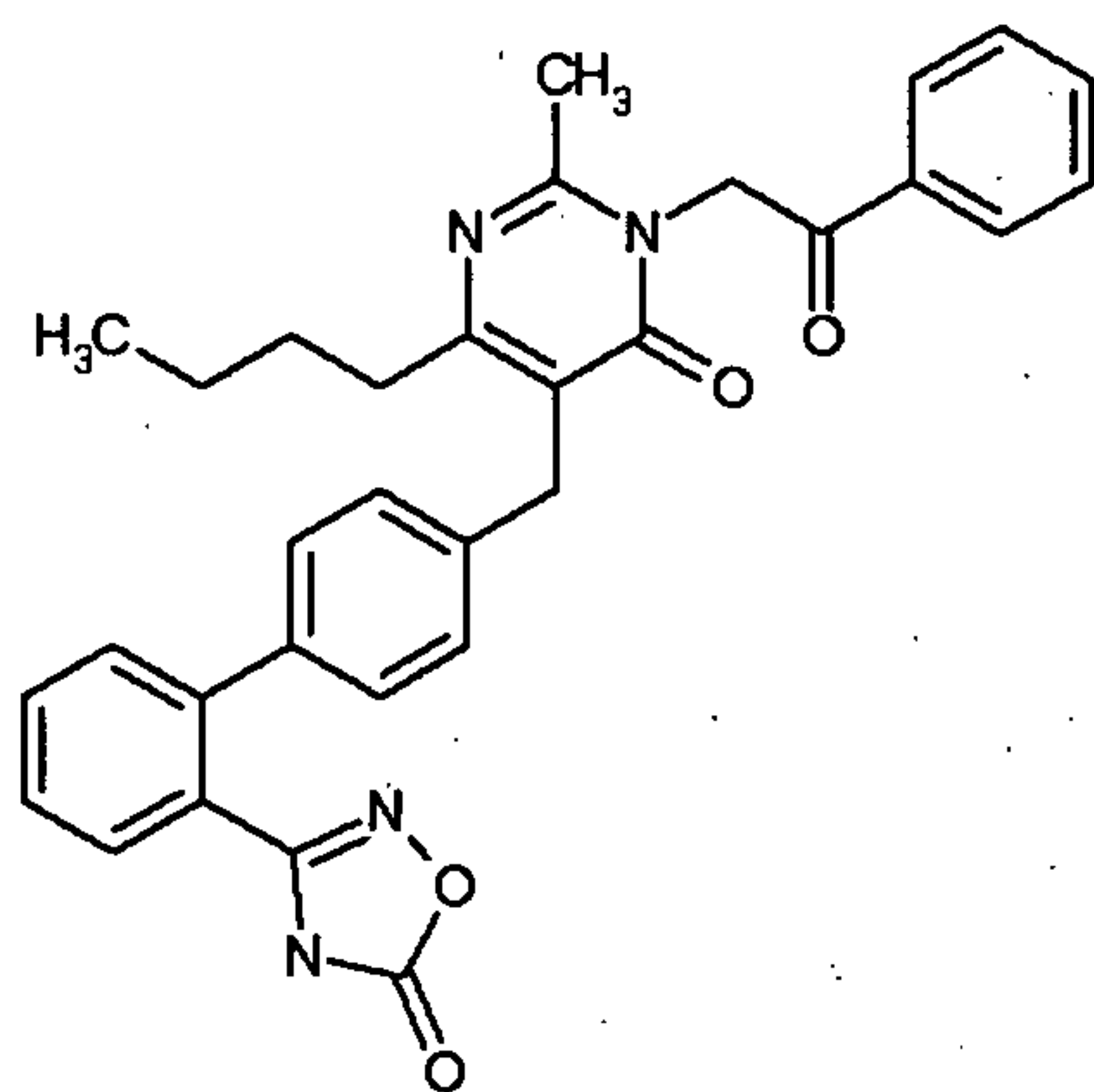


53d) 6-(methoxymethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.29 g), sodium hydrogen carbonate (1.94 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-(methoxymethyl)-2-methyl-6-oxo-1-(2-thienylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.68 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture

was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (15 mL), N,N'-
 5 carbonyldiimidazole (0.3 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.25 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
 10 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.4 g, 52%).
¹H NMR (300 MHz, DMSO-d₆) δ 2.56 (3H, s), 3.23 (3H, s), 3.93 (2H, s), 4.27 (2H, s), 5.39 (2H, s), 6.99 (1H, dd, J = 5.1, 3.4), 7.14-7.24 (3H, m), 7.26-7.32 (2H, m), 7.43-7.58 (3H, m), 7.62-7.73 (2H, m), 12.39 (1H, s)

Example 54



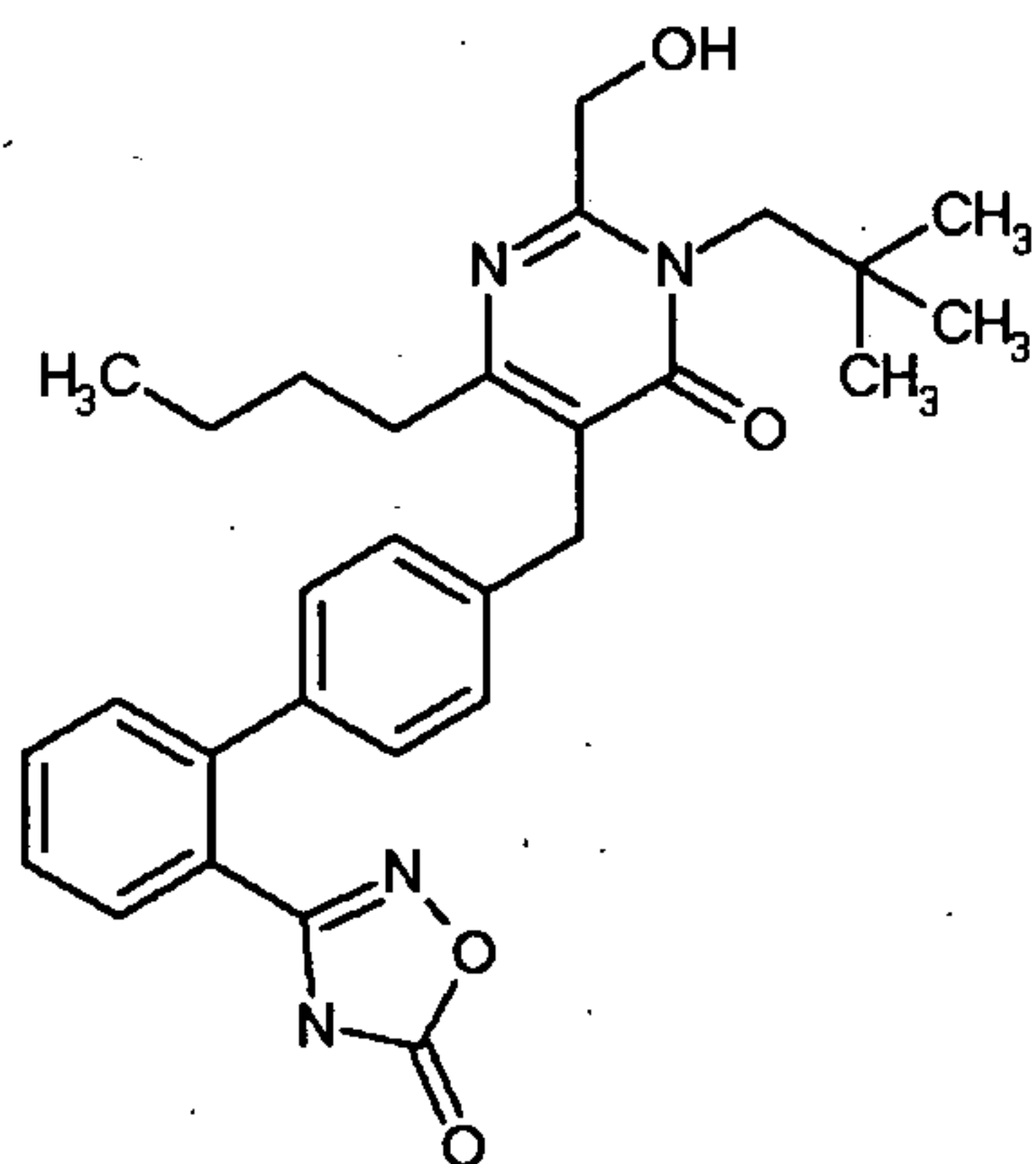
20 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-oxo-2-phenylethyl)pyrimidin-4(3H)-one

A mixture of 6-butyl-3-(2-hydroxy-2-phenylethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (0.25 g), 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (0.3 g) and methylene chloride (10 mL) was stirred at room temperature for 2 hr. A saturated aqueous sodium hydrogen carbonate

solution and sodium thiosulfate were added to the reaction mixture, and the mixture was stirred at room temperature for 2 hr and extracted with chloroform. The chloroform layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.2 g, 78%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.3), 1.22-1.39 (2H, m), 1.39-1.58 (2H, m), 2.37 (3H, s), 2.51-2.56 (2H, m), 3.85 (2H, s), 5.65 (2H, s), 7.21 (4H, s), 7.43-7.83 (7H, m), 8.02-8.15 (2H, m), 12.37 (1H, s)

Example 55



6-butyl-3-(2,2-dimethylpropyl)-2-(hydroxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

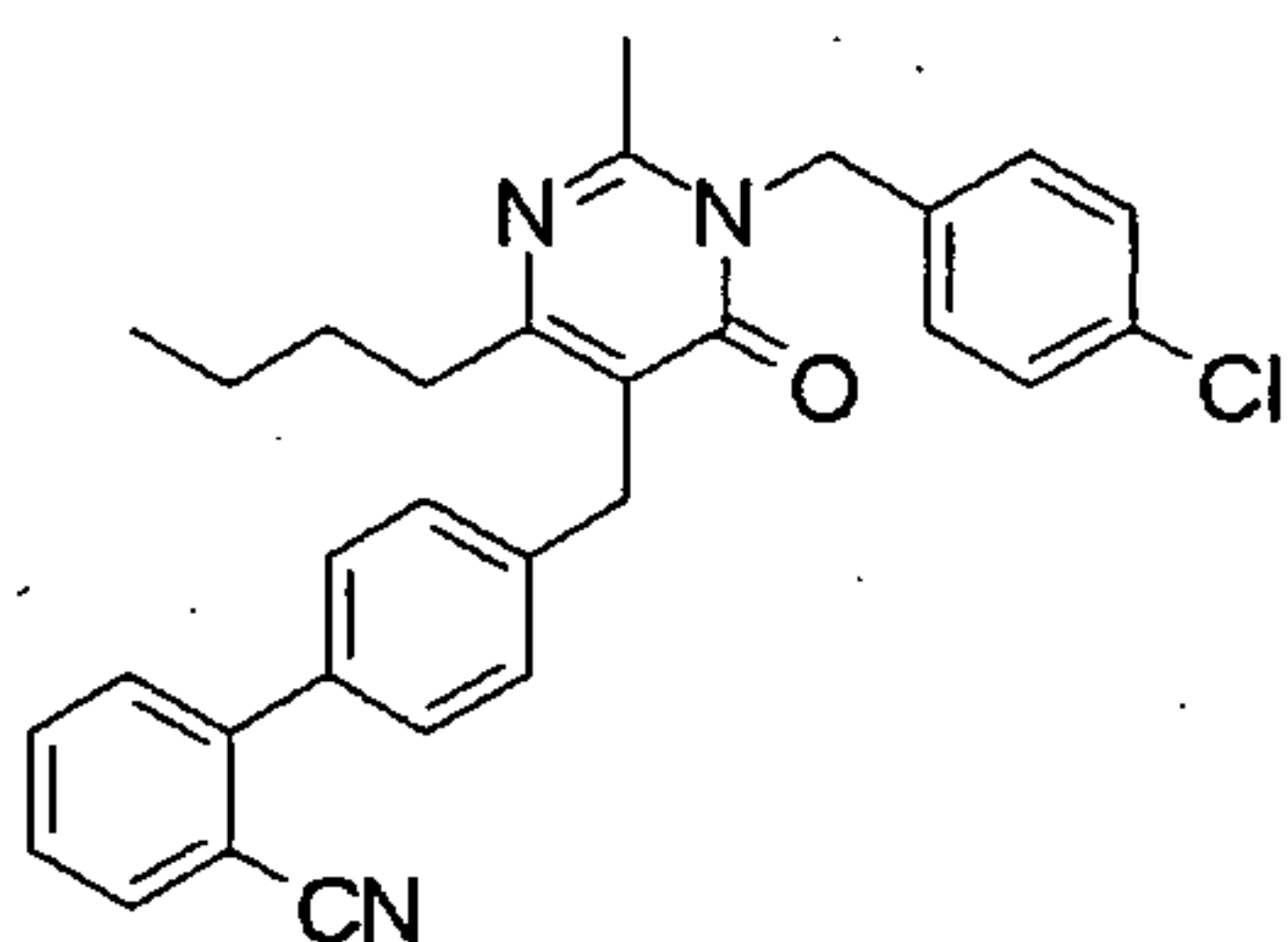
A mixture of 6-butyl-3-(2,2-dimethylpropyl)-2-(methoxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one (0.5 g), boron tribromide (1.0 M dichloromethane solution, 2.9 mL) and dichloromethane (20 mL) was stirred at room temperature for 3 hr, 0.5 M aqueous sodium hydroxide solution (10 mL) was added, and the mixture was further stirred for 1 hr. To the reaction mixture was added 1 M hydrochloric acid and adjusted to pH 5. Ethyl acetate was added, and the mixture was extracted. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated

under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.48 g, 98%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (3H, t, J = 7.3), 0.90 (9H, s),
 5 1.21-1.36 (2H, m), 1.41-1.53 (2H, m), 2.50-2.57 (2H, m), 3.87 (2H, s), 4.03 (2H, s), 4.50 (2H, d, J = 5.3), 5.51 (1H, t, J = 5.7), 7.15-7.28 (4H, m), 7.44-7.60 (2H, m), 7.60-7.74 (2H, m), 12.37 (1H, s)

Example 56

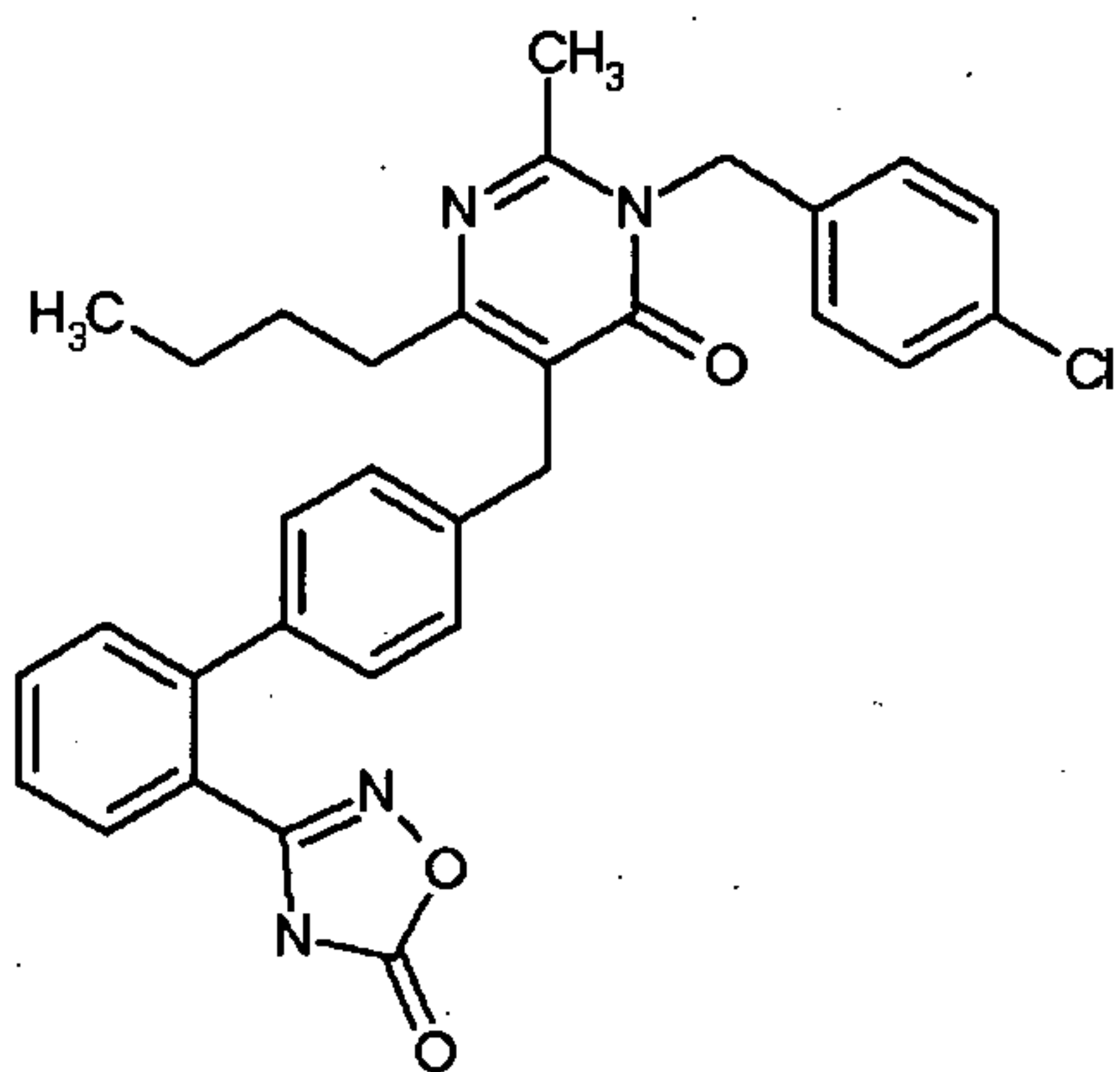
10 6-butyl-3-(4-chlorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



56a) 4'-{[4-butyl-1-(4-chlorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

15 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (15 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)-4-chlorobenzene (0.69 g) was added, and the mixture was stirred
 20 at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified
 25 by silica gel column chromatography to give the title compound as a colorless solid (0.84 g, 62%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.31-1.46 (2H, m), 1.51-1.65 (2H, m), 2.44 (3H, s), 2.56-2.65 (2H, m), 4.00 (2H, s), 5.25 (2H, s), 7.14 (2H, d, J = 8.3), 7.25-7.52 (8H, m),
 30 7.58-7.66 (1H, m), 7.75 (1H, d, J = 7.3)



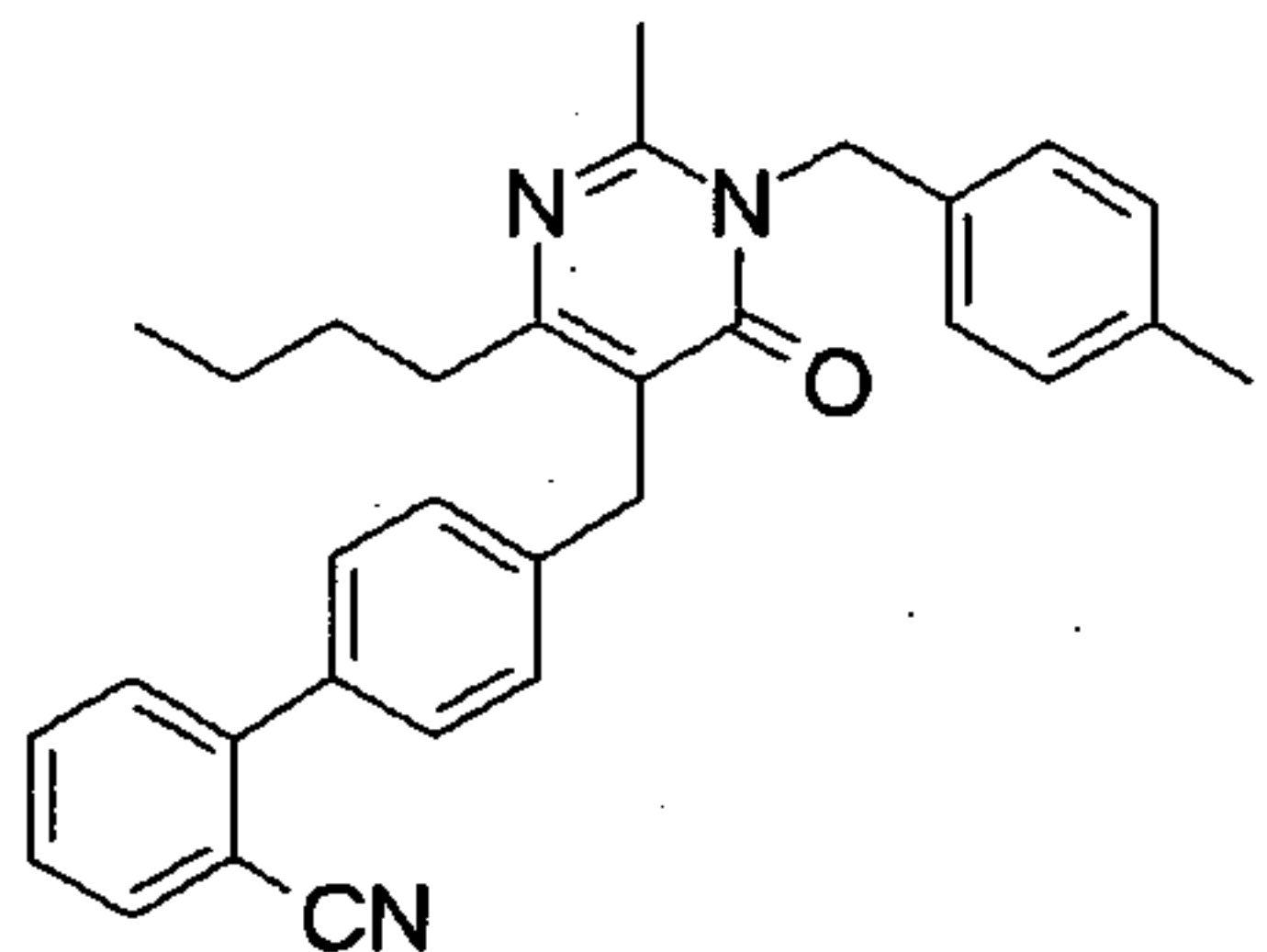
56b) 6-butyl-3-(4-chlorobenzyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (1.81 g), sodium hydrogen carbonate (2.92 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(4-chlorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.84 g) was added, and the mixture was stirred
10 at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole
15 (0.34 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.29 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over
20 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.42 g, 45%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.19-1.36
25 (2H, m), 1.36-1.54 (2H, m), 2.38 (3H, s), 2.43-2.49 (2H, m), 3.90 (2H, s), 5.27 (2H, s), 7.16-7.30 (6H, m), 7.37-7.47 (2H, m), 7.53 (2H, dd, J = 15.6, 7.7), 7.60-7.79 (2H, m), 12.39 (1H, s)

Example 57

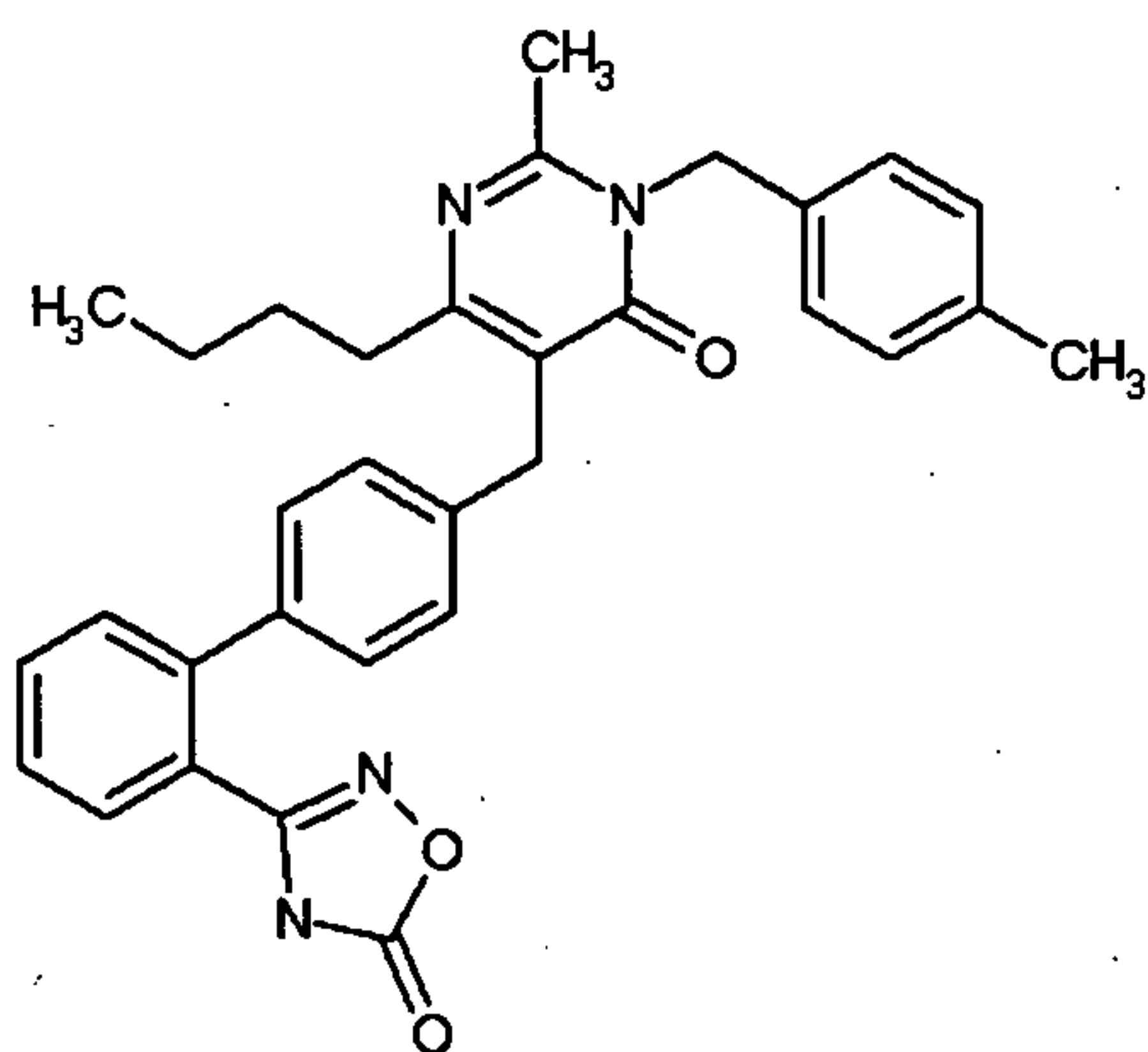
6-butyl-2-methyl-3-(4-methylbenzyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



5 57a) 4'-{[4-butyl-2-methyl-1-(4-methylbenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (15 mL) was
 10 stirred at room temperature for 10 min, 1-(bromomethyl)-4-methylbenzene (0.62 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and
 15 dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.79 g, 61%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.30-1.46 (2H, m), 1.49-1.65 (2H, m), 2.32 (3H, s), 2.45 (3H, s), 2.55-2.64 (2H, m), 4.01 (2H, s), 5.26 (2H, s), 7.11 (4H, q, J = 8.1), 7.34-7.52 (6H, m), 7.58-7.65 (1H, m), 7.75 (1H, d, J = 9.0)



57b) 6-butyl-2-methyl-3-(4-methylbenzyl)-5-{[2'-(5-oxo-4,5-

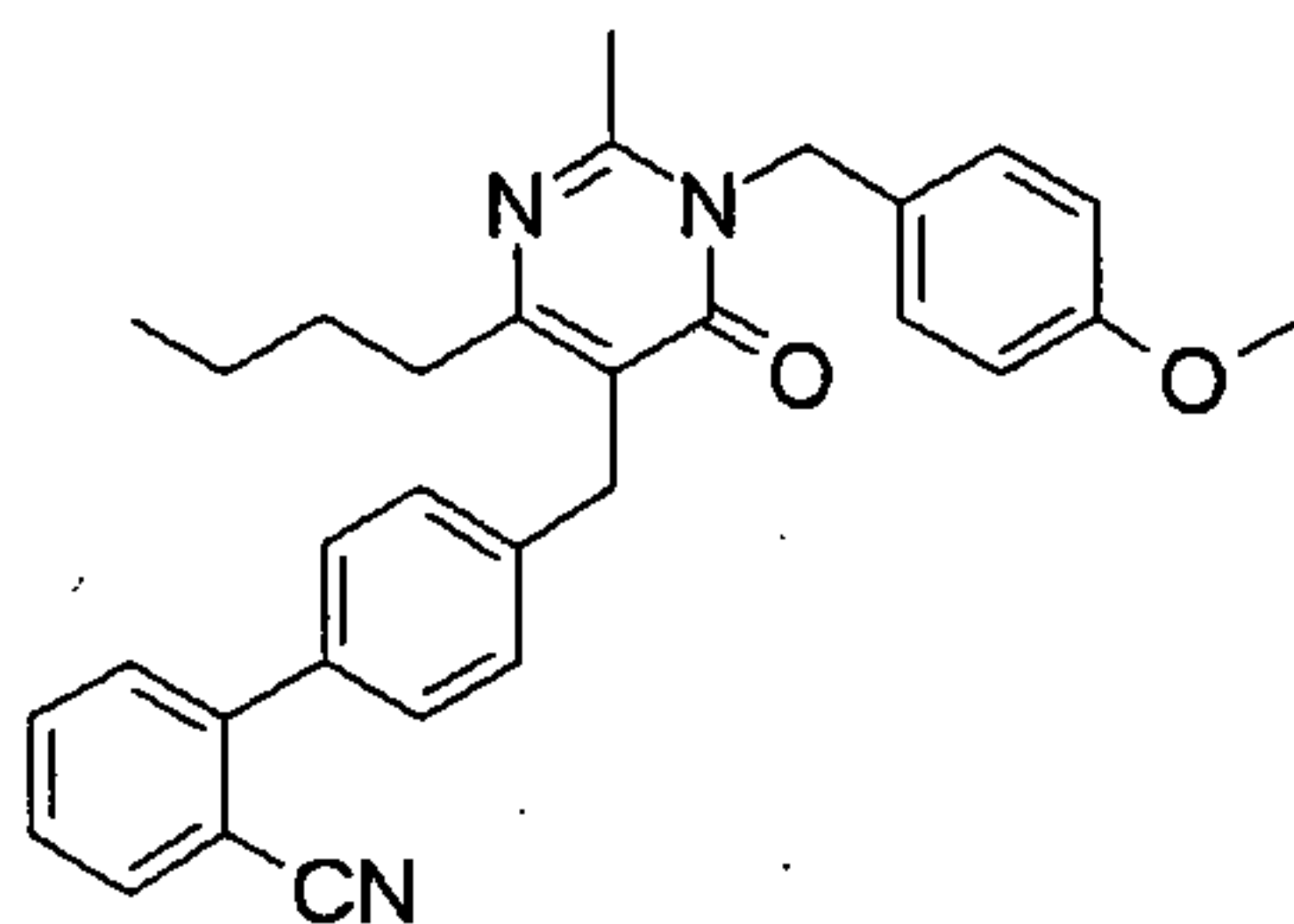
dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.79 g), sodium hydrogen carbonate (2.87 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-2-methyl-1-(4-methylbenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile (0.79 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.33 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.28 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.53 g, 59%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.18-1.37 (2H, m), 1.36-1.53 (2H, m), 2.27 (3H, s), 2.38 (3H, s), 2.44-2.49 (2H, m), 3.90 (2H, s), 5.24 (2H, s), 7.06 (2H, d, J = 8.1), 7.17 (2H, d, J = 7.9), 7.20-7.29 (4H, m), 7.46-7.61 (2H, m), 7.62-7.79 (2H, m), 12.39 (1H, s)

Example 58

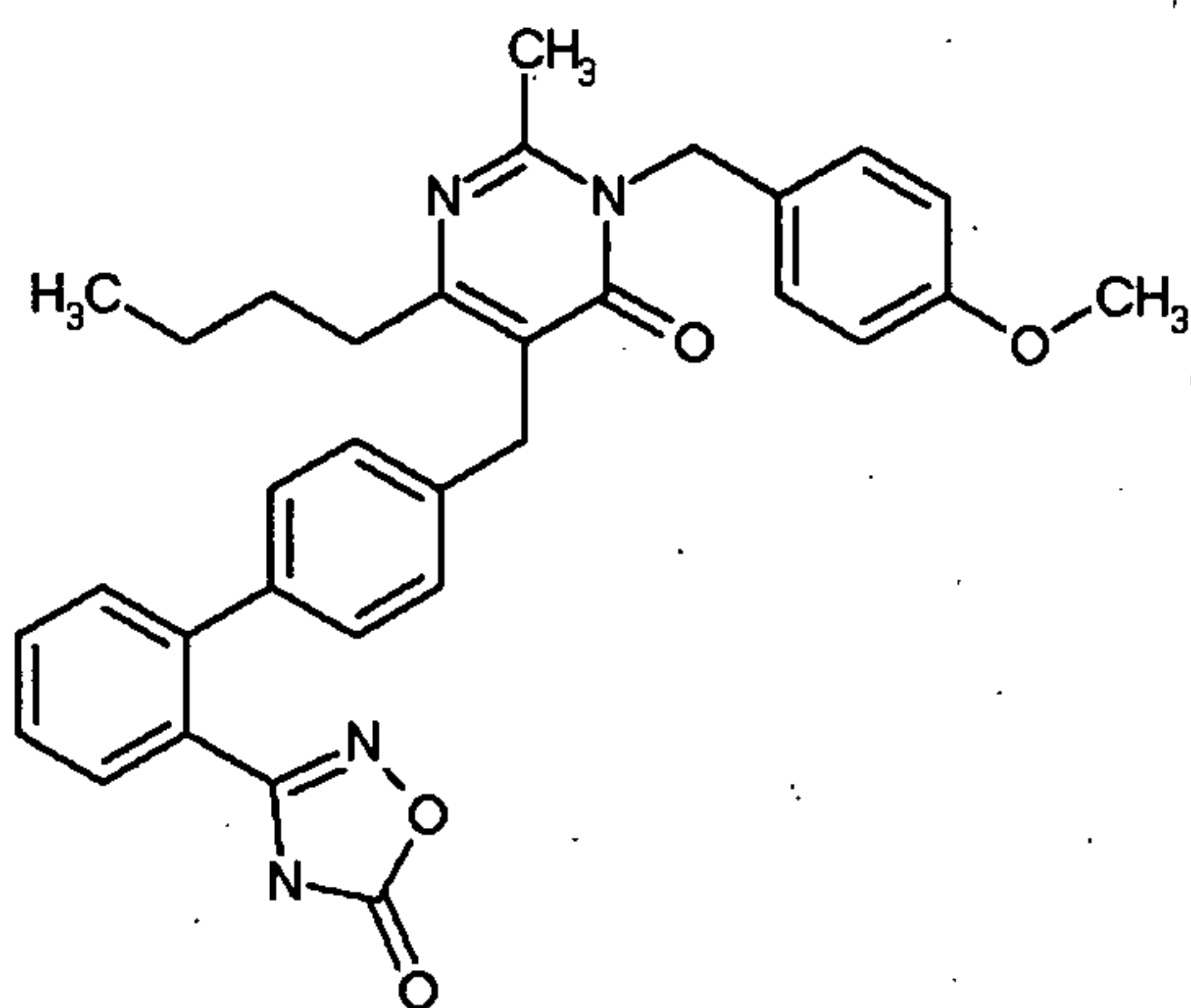
6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one



58a) 4'-{[4-butyl-1-(4-methoxybenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (15 mL) was stirred at room temperature for 10 min, 1-(chloromethyl)-4-methoxybenzene (0.46 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.83 g, 62%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.31-1.45 (2H, m), 1.49-1.66 (2H, m), 2.47 (3H, s), 2.54-2.64 (2H, m), 3.78 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.88 (2H, d, J = 8.7), 7.15 (2H, d, J = 8.7), 7.34-7.52 (6H, m), 7.58-7.69 (1H, m), 7.72-7.79 (1H, m)



58b) 6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.81 g), sodium hydrogen carbonate (2.92 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(4-methoxybenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.83 g) was added, and the mixture was stirred

at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.34 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.29 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.51 g, 54%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.21-1.36 (2H, m), 1.36-1.51 (2H, m), 2.39 (3H, s), 2.45-2.49 (2H, m), 3.73 (3H, s), 3.90 (2H, s), 5.21 (2H, s), 6.92 (2H, d, J = 8.7), 7.14 (2H, d, J = 8.7), 7.19-7.33 (4H, m), 7.47-7.61 (2H, m), 7.60-7.77 (2H, m), 12.39 (1H, s)

6-Butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one sodium salt

6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one potassium salt

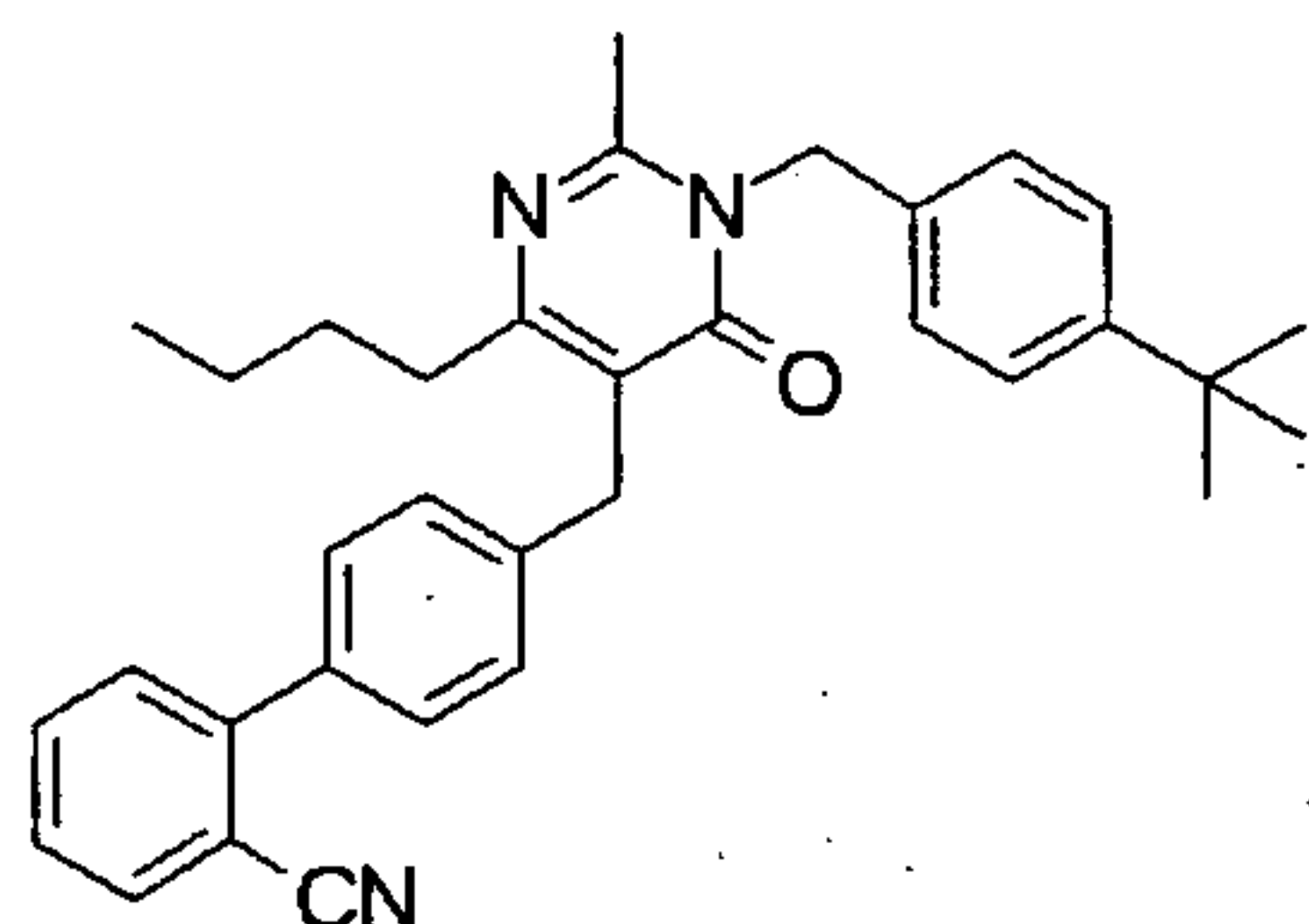
6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one 0.5 calcium salt

6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrochloride

6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrobromide

Example 59

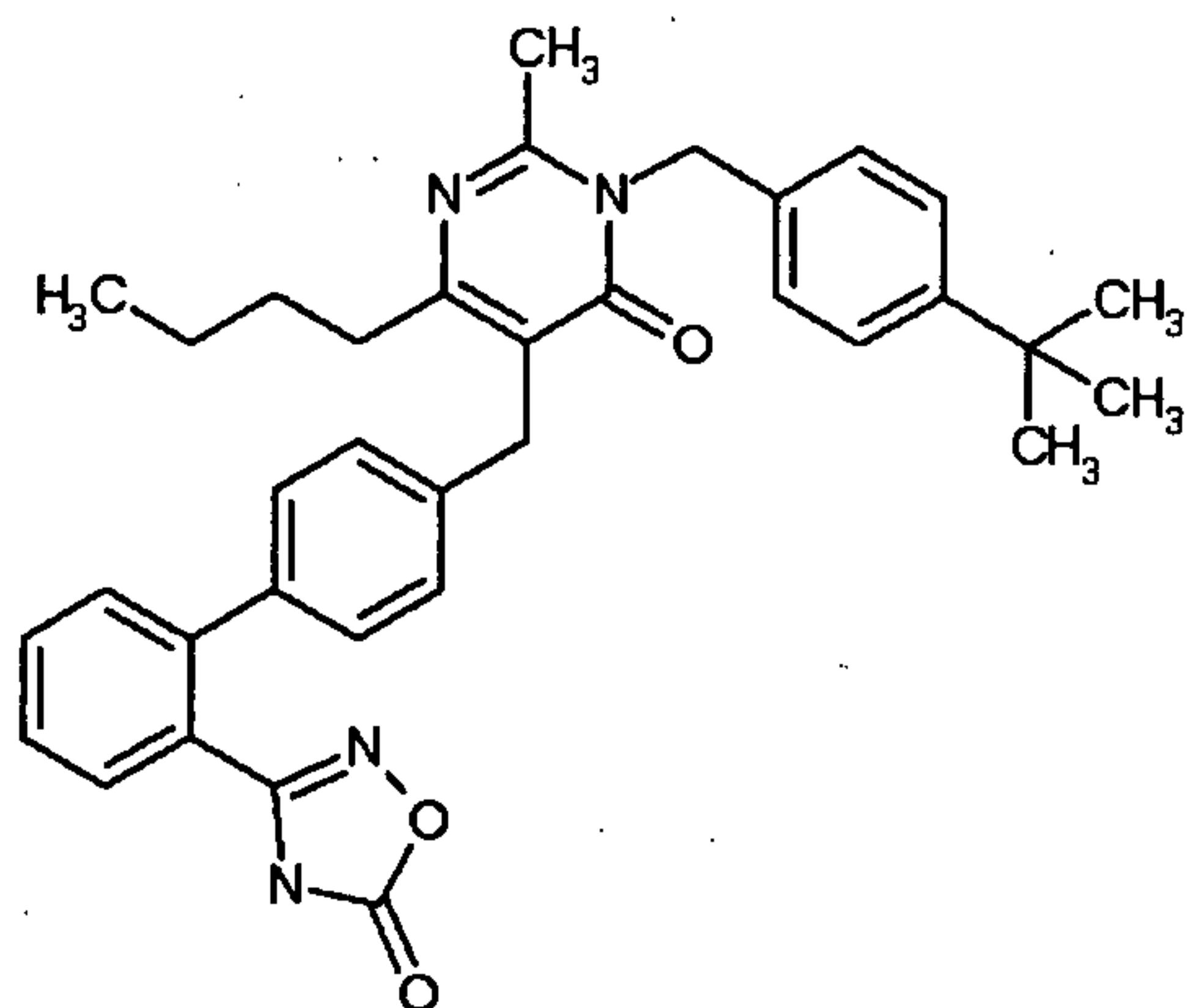
- 5 6-butyl-3-(4-tert-butylbenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



- 59a) 4'-{[4-butyl-1-(4-tert-butylbenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (15 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)-4-tert-butylbenzene (0.62 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.86 g, 61%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.29 (9H, s), 1.34-1.45 (2H, m), 1.49-1.59 (2H, m), 2.47 (3H, s), 2.54-2.65 (2H, m), 4.01 (2H, s), 5.27 (2H, s), 7.13 (2H, d, J = 8.3), 7.31-7.54 (8H, m), 7.55-7.67 (1H, m), 7.75 (1H, dd, J = 7.7, 1.3)

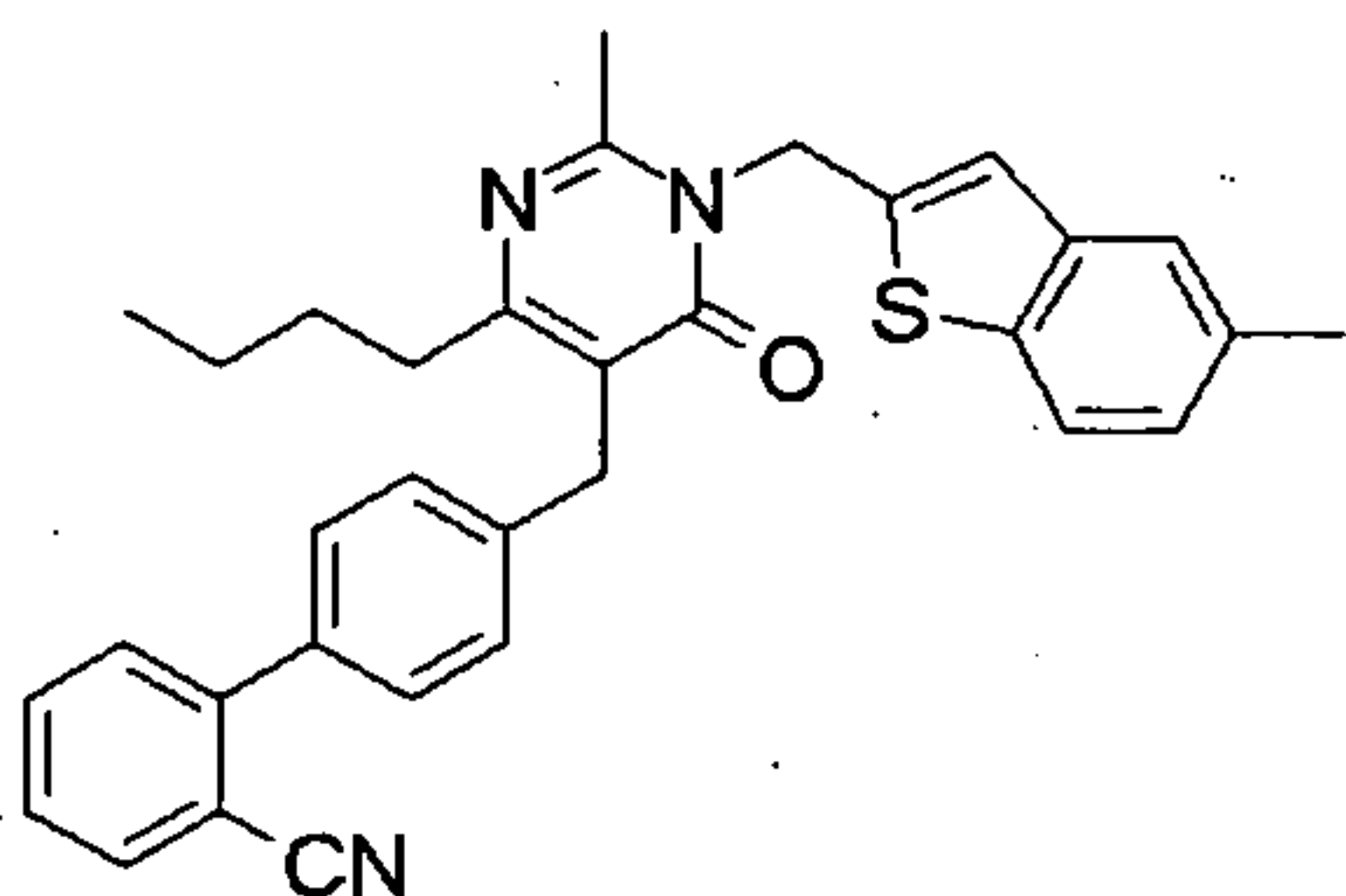


59b) 6-butyl-3-(4-tert-butylbenzyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (1.79 g), sodium hydrogen carbonate (2.87 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(4-tert-butylbenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.86 g) was added, and the
 10 mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-
 15 carbonyldiimidazole (0.33 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.28 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
 20 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.55 g, 57%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.22-1.37 (11H, m), 1.39-1.54 (2H, m), 2.39 (3H, s), 2.45-2.49 (2H, m), 3.90 (2H, s), 5.24 (2H, s), 7.10 (2H, d, J = 8.5), 7.19-7.32 (4H, m), 7.38 (2H, d, J = 8.3), 7.47-7.61 (2H, m), 7.61-7.75 (2H, m), 12.39 (1H, s)

Example 60

6-butyl-2-methyl-3-[(5-methyl-1-benzothien-2-yl)methyl]-5-
 {[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
 yl)methyl}pyrimidin-4(3H)-one

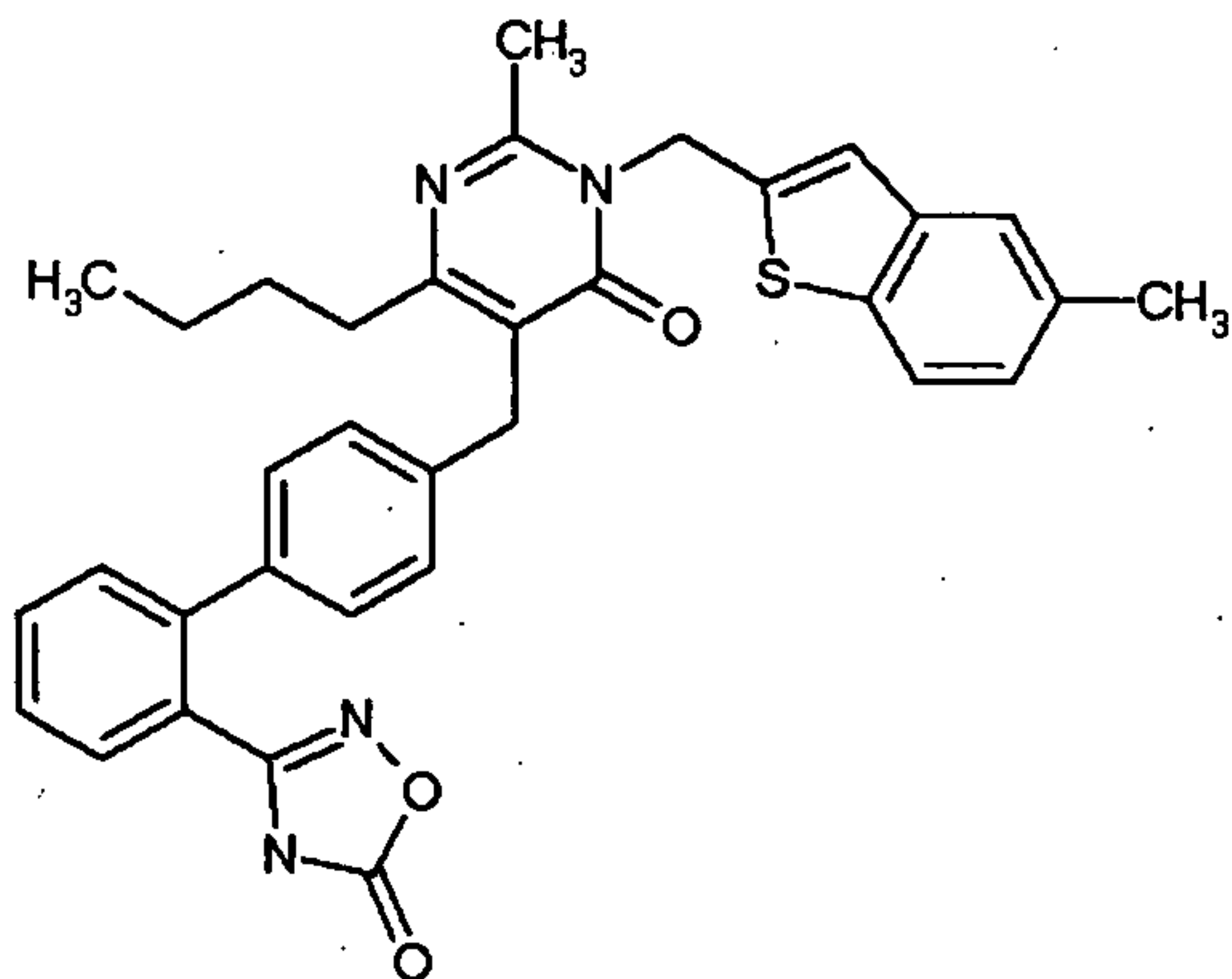


5

60a) 4'-([4-butyl-2-methyl-1-[(5-methyl-1-benzothien-2-
 yl)methyl]-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)biphenyl-2-
 carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-
 10 dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g),
 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine
 (1.56 mL), (5-methyl-1-benzothien-2-yl)methanol (0.75 g) and
 tetrahydrofuran (50 mL) was stirred at room temperature for 4
 hr. The reaction mixture was diluted with ethyl acetate,
 15 washed with 1 M hydrochloric acid and then with saturated
 brine, and dried over anhydrous magnesium sulfate. The solvent
 was evaporated under reduced pressure and the residue was
 purified by silica gel column chromatography to give the title
 compound as a colorless solid (0.63 g, 44%).

20 ¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.4), 1.29-1.43 (2H,
 m), 1.48-1.60 (2H, m), 2.43 (3H, s), 2.54-2.64 (5H, m), 4.02
 (2H, s), 5.45 (2H, s), 7.10-7.19 (2H, m), 7.34-7.53 (7H, m),
 7.56-7.67 (2H, m), 7.74 (1H, dd, J = 7.7, 0.9)

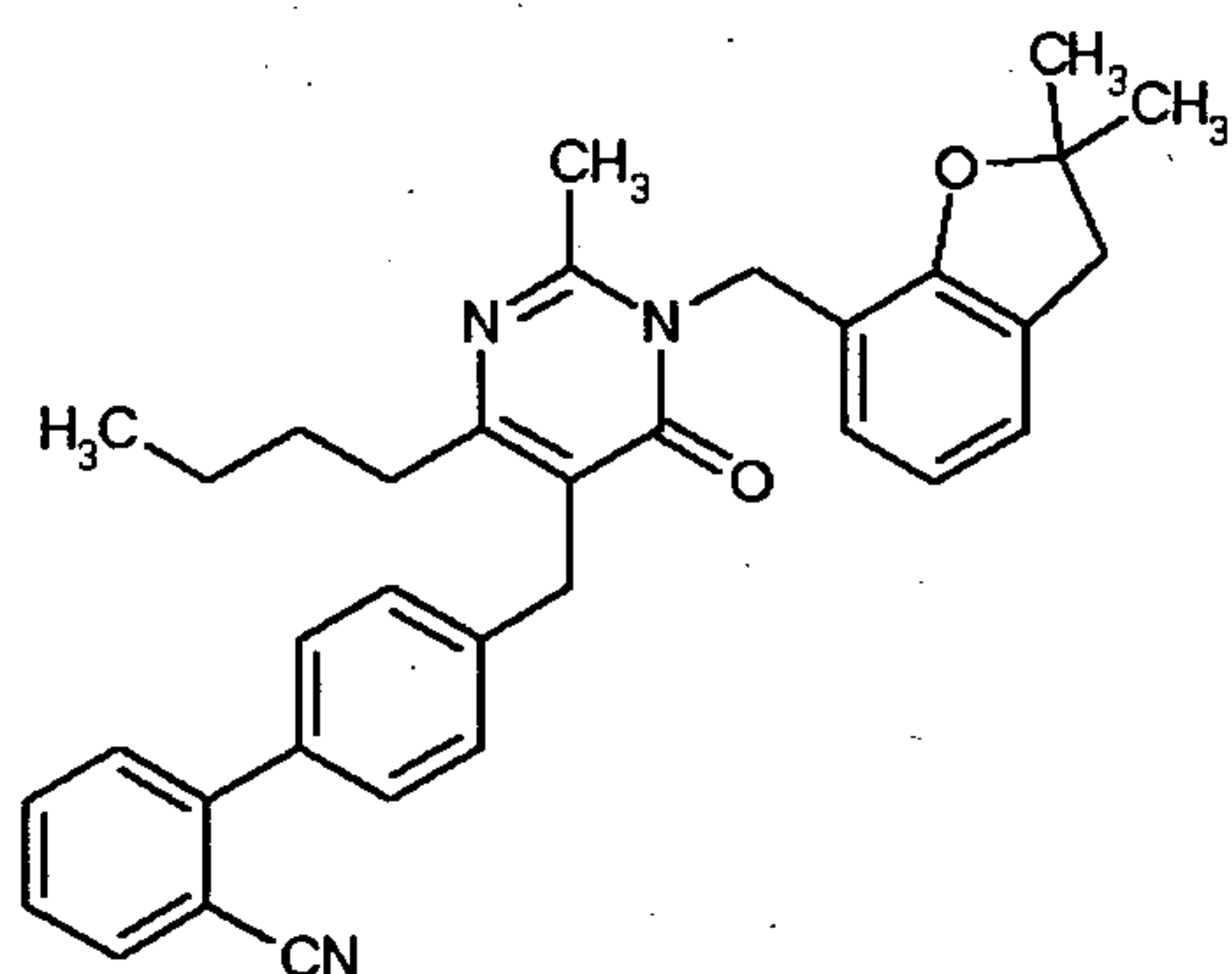


60b) 6-butyl-2-methyl-3-[(5-methyl-1-benzothien-2-yl)methyl]-
5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
yl)methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.28 g), sodium
5 hydrogen carbonate (2.07 g) and dimethyl sulfoxide (15 mL) was
stirred at 40°C for 30 min, 4'-({4-butyl-2-methyl-1-[(5-methyl-
1-benzothien-2-yl)methyl]-6-oxo-1,6-dihydropyrimidin-5-
yl)methyl)biphenyl-2-carbonitrile (0.63 g) was added, and the
mixture was stirred at 90°C for 16 hr. The reaction mixture
10 was diluted with ethyl acetate, washed with water and then
with saturated brine, and dried over anhydrous magnesium
sulfate. The solvent was evaporated under reduced pressure and
the residue was dissolved in tetrahydrofuran (20 mL), N,N'-
carbonyldiimidazole (0.24 g) and then 1,8-
15 diazabicyclo[5.4.0]undec-7-ene (0.2 mL) were added, and the
mixture was stirred at room temperature for 2 hr. The reaction
mixture was diluted with ethyl acetate, washed with saturated
aqueous potassium hydrogen sulfate solution and then with
saturated brine, and dried over anhydrous magnesium sulfate.
20 The solvent was evaporated under reduced pressure and the
residue was purified by silica gel column chromatography to
give the title compound as colorless crystals (0.25 g, 35%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.81 (3H, t, J = 7.2), 1.16-1.34
(2H, m), 1.35-1.53 (2H, m), 2.39 (3H, s), 2.43-2.49 (2H, m),
25 2.56 (3H, s), 3.91 (2H, s), 5.49 (2H, s), 7.12-7.35 (5H, m),
7.38 (1H, s), 7.44-7.74 (5H, m), 7.79 (1H, d, J = 8.1), 12.38
(1H, s)

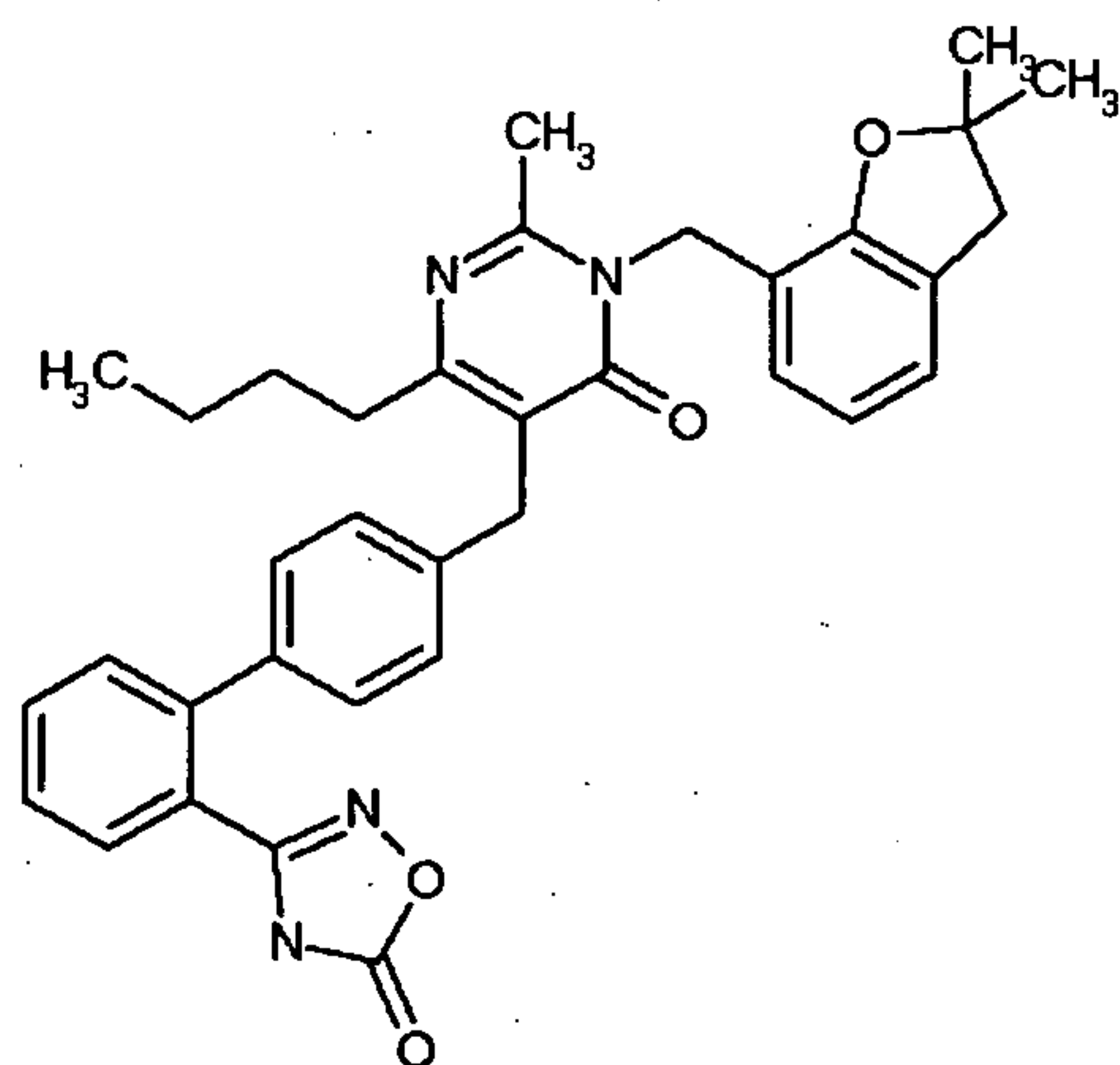
Example 61

6-butyl-3-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-7-
30 yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-
3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one



61a) 4'-({4-butyl-1-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile

5 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine (1.56 mL), (2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl)methanol (0.75 g) and tetrahydrofuran (50 mL) was stirred
10 at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography
15 to give the title compound as a colorless solid (0.67 g, 46%).
¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.3), 1.31-1.42 (2H, m), 1.44 (6H, s), 1.49-1.60 (2H, m), 2.48 (3H, s), 2.55-2.64 (2H, m), 3.01 (2H, s), 4.00 (2H, s), 5.23 (2H, s), 6.76 (1H, t, J = 7.5), 6.92 (1H, d, J = 7.3), 7.04 (1H, dd, J = 7.2, 0.9),
20 7.32-7.52 (6H, m), 7.56-7.66 (1H, m), 7.74 (1H, dd, J = 7.7, 0.8)



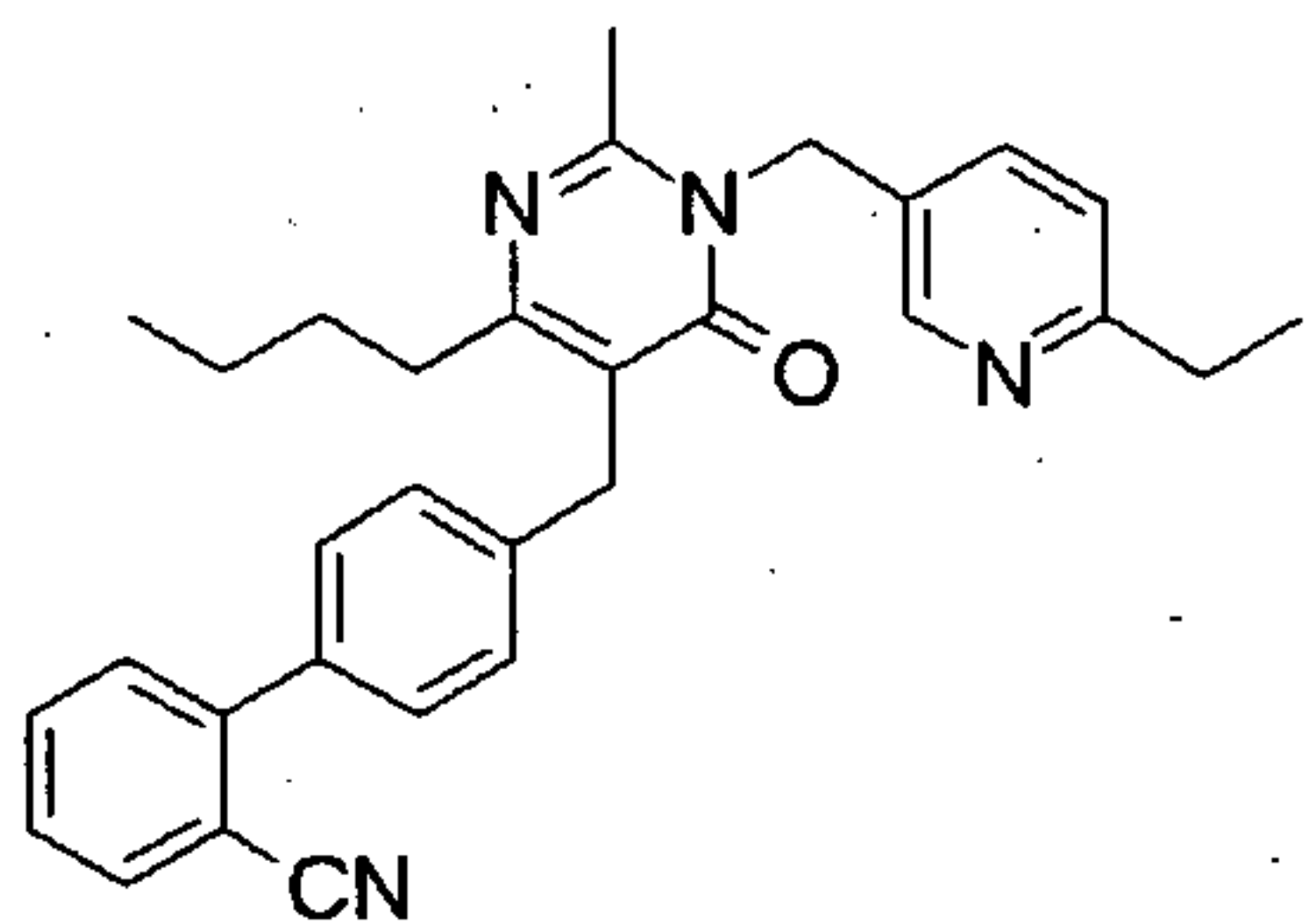
61b) 6-butyl-3-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (1.35 g), sodium hydrogen carbonate (2.17 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-1-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}methyl)biphenyl-2-carbonitrile (0.67 g)
 10 was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20
 15 mL), N,N'-carbonyldiimidazole (0.25 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.21 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
 20 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.16 g, 21%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.2), 1.22-1.33
 25 (2H, m), 1.36-1.51 (8H, m), 2.39 (3H, s), 2.45-2.49 (2H, m), 3.01 (2H, s), 3.88 (2H, s), 5.13 (2H, s), 6.67-6.81 (2H, m), 7.10 (1H, d, J = 7.0), 7.18-7.27 (4H, m), 7.46-7.59 (2H, m),

7.61-7.72 (2H, m), 12.39 (1H, br)

Example 62

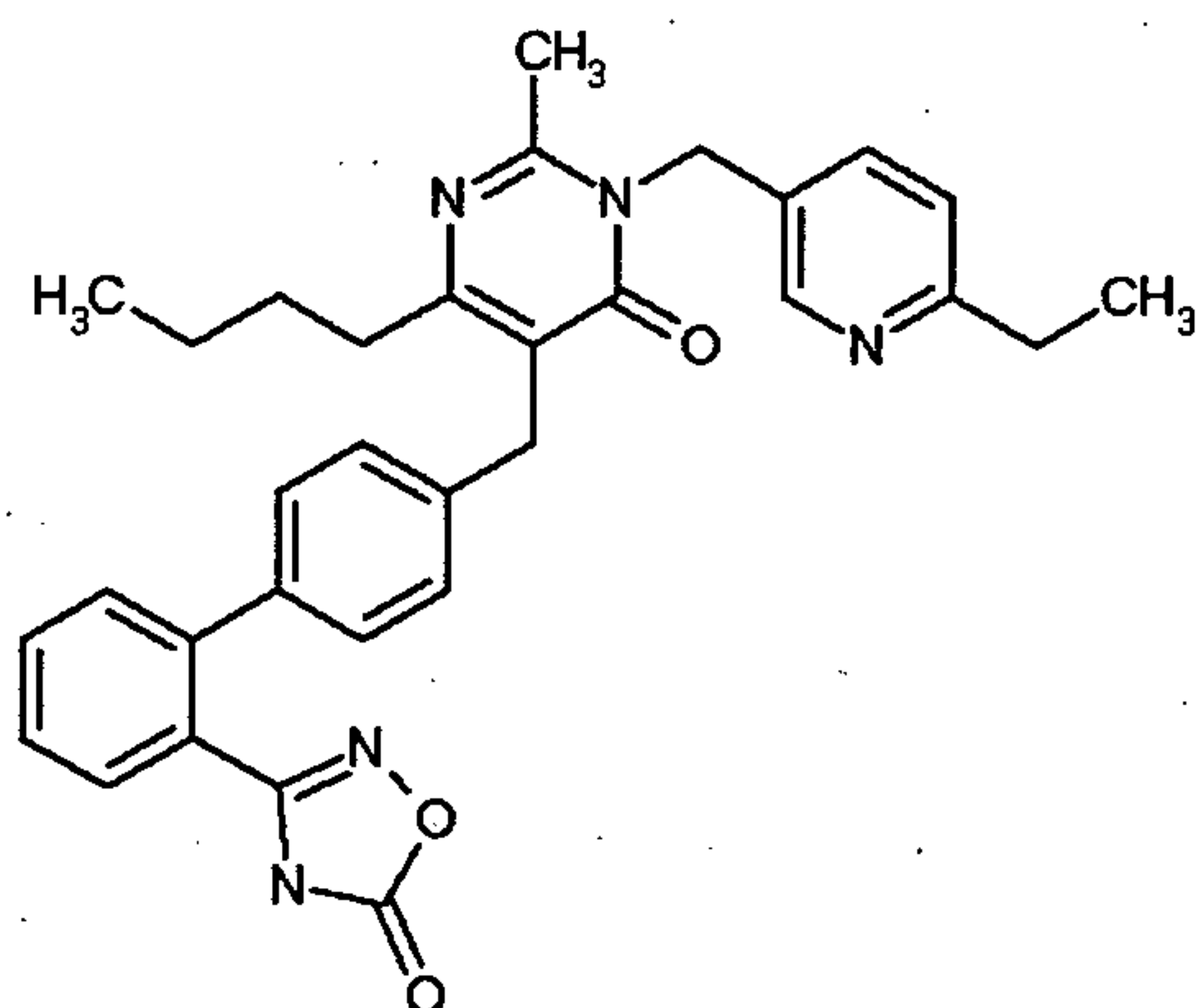
6-butyl-3-[(6-ethylpyridin-3-yl)methyl]-2-methyl-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one



62a) 4'-([4-butyl-1-[(6-ethylpyridin-3-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile

A mixture of (6-ethylpyridin-3-yl)methanol hydrochloride (0.74 g) and saturated potassium carbonate (10 mL) was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL), 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.41 g) and tributylphosphine (1.56 mL) were added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.93 g, 70%).

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t), 1.22-1.45 (7H, m), 2.49 (3H, s), 2.57-2.65 (2H, m), 2.75-2.89 (2H, m), 3.99 (2H, s), 5.26 (2H, s), 7.15 (1H, d, J = 8.1), 7.32-7.53 (7H, m), 7.58-7.66 (1H, m), 7.74 (1H, dd, J = 7.7, 0.8), 8.44 (1H, d, J = 2.3)



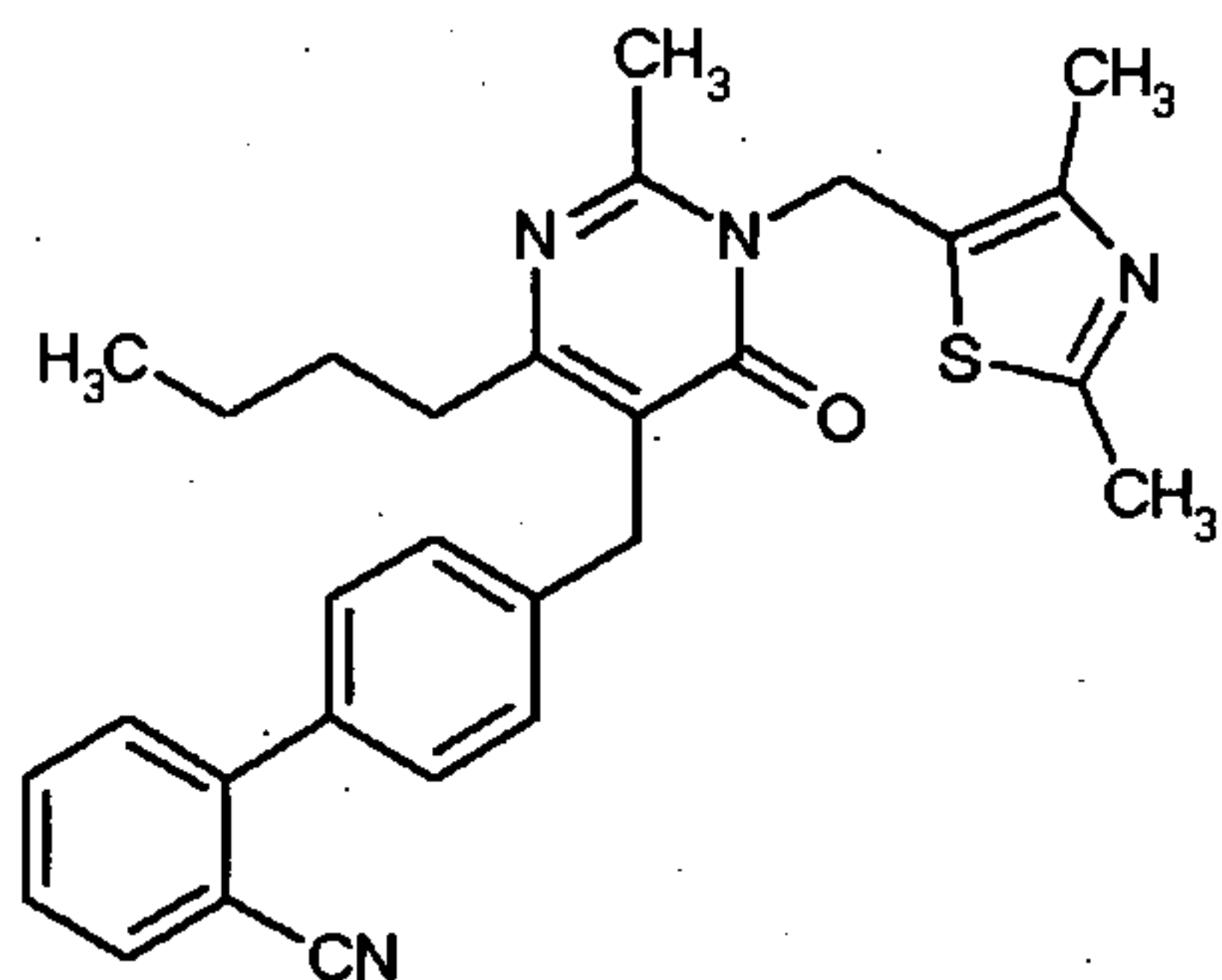
62b) 6-butyl-3-[(6-ethylpyridin-3-yl)methyl]-2-methyl-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (2.04 g), sodium hydrogen carbonate (3.28 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-1-[(6-ethylpyridin-3-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)biphenyl-2-carbonitrile (0.93 g) was added, and the
10 mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-
15 carbonyldiimidazole (0.38 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.32 mL) were added, and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and 1 M hydrochloric acid was added and adjusted to pH 5, and the mixture was extracted with
20 ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.38 g, 36%).
25 ¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.15-1.36 (5H, m), 1.37-1.55 (2H, m), 2.36-2.51 (5H, m), 2.72 (2H, q, J = 7.5), 3.90 (2H, s), 5.26 (2H, s), 7.17-7.35 (5H, m), 7.45-7.58 (3H, m), 7.62-7.75 (2H, m), 8.40 (1H, d, J = 1.9), 12.40

(1H, s)

Example 63

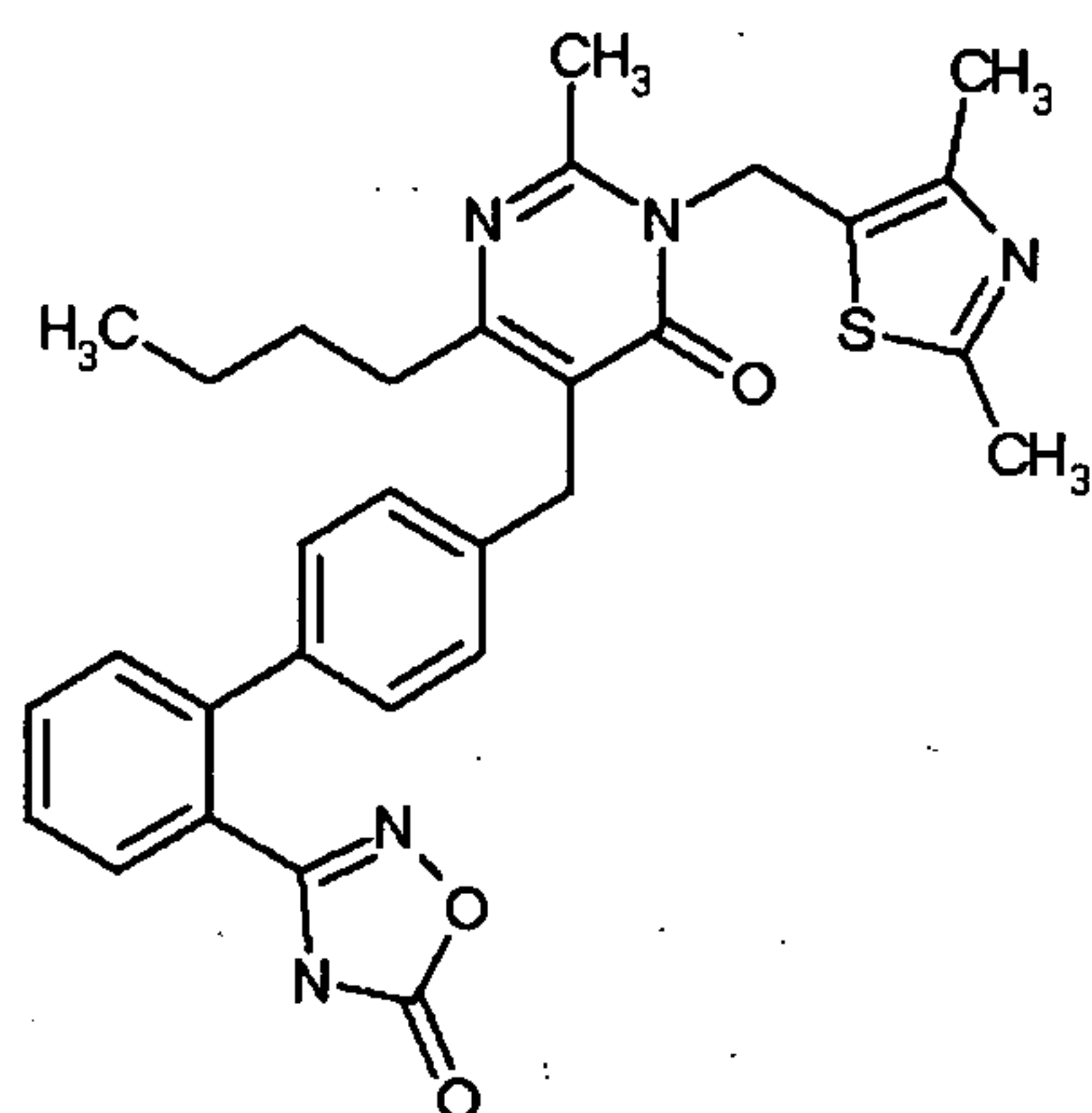
6-butyl-3-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-2-methyl-5-
 {[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
 5. yl)methyl}pyrimidin-4(3H)-one



63a) 4'-[(4-butyl-1-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-2-
 methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-
 carbonitrile

10 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-
 dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g),
 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine
 (1.56 mL), (2,4-dimethyl-1,3-thiazol-5-yl)methanol (0.6 g) and
 tetrahydrofuran (50 mL) was stirred at room temperature for 4
 15 hr. The reaction mixture was diluted with ethyl acetate,
 washed with water and then with saturated brine, and dried
 over anhydrous magnesium sulfate. The solvent was evaporated
 under reduced pressure and the residue was purified by silica
 gel column chromatography to give the title compound as a
 20 colorless solid (1.33 g, 99%).

¹H NMR (300 MHz, CDCl₃) δ 0.89 (3H, t, J = 7.4), 1.31-1.74 (4H,
 m), 2.47 (3H, s), 2.51-2.57 (5H, m), 2.59 (3H, s), 4.00 (2H,
 s), 5.26 (2H, s), 7.33-7.51 (6H, m), 7.58-7.66 (1H, m), 7.74
 (1H, dd, J = 7.7, 0.9)

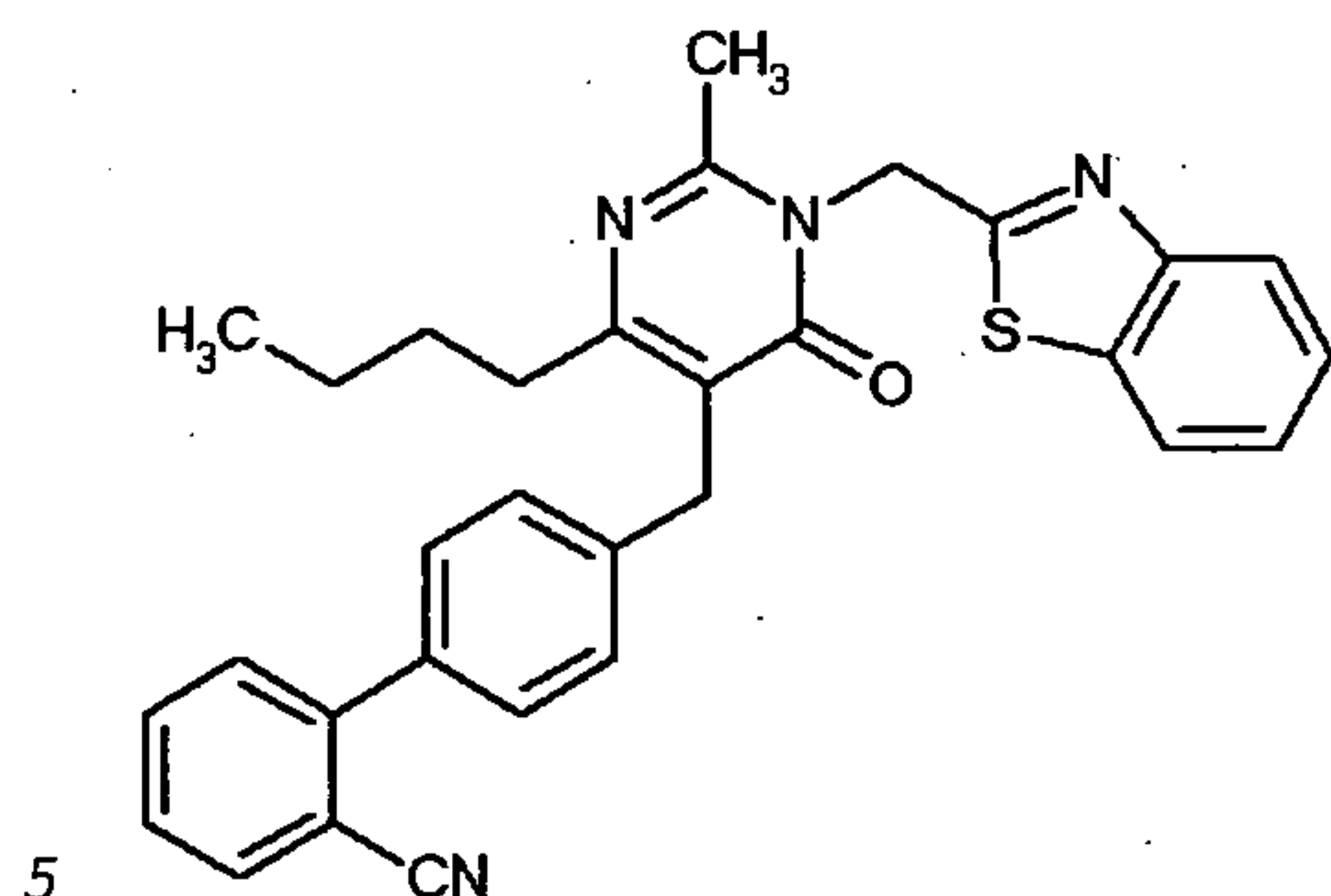


63b) 6-butyl-3-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (2.9 g), sodium hydrogen carbonate (4.7 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-1-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)biphenyl-2-carbonitrile (1.33 g) was added, and the
10 mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-
15 carbonyldiimidazole (0.49 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.41 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
20 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.42 g, 27%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.3), 1.15-1.35 (2H, m), 1.34-1.52 (2H, m), 2.39 (3H, s), 2.41-2.48 (2H, m), 2.49 (3H, s), 2.52 (3H, s), 3.89 (2H, s), 5.29 (2H, s), 7.17-7.32 (4H, m), 7.43-7.61 (2H, m), 7.61-7.80 (2H, m), 12.39 (1H, s)

Example 64

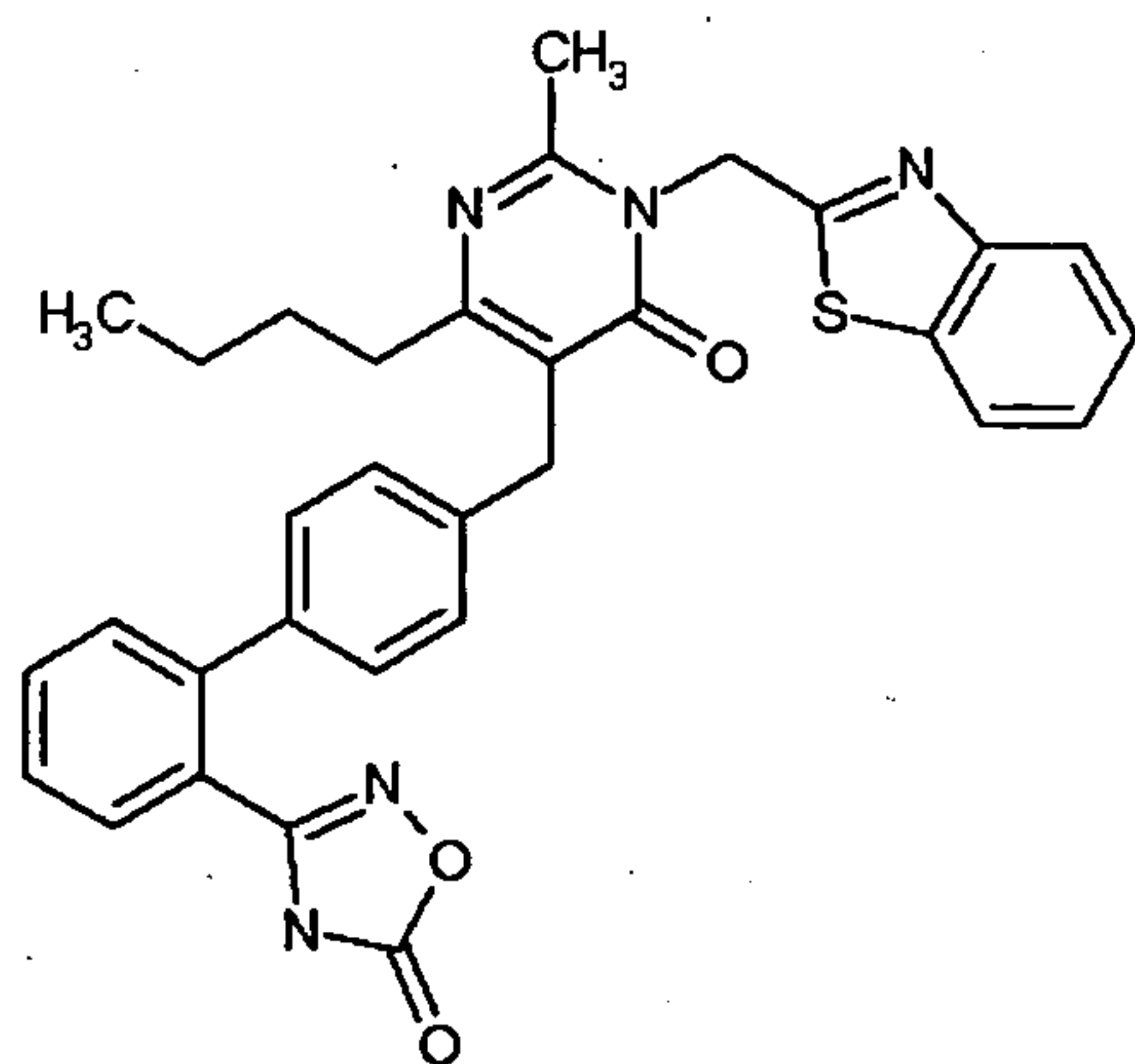
3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



64a) 4'-{[1-(1,3-benzothiazol-2-ylmethyl)-4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g),
 10 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine (1.56 mL), 1,3-benzothiazol-2-ylmethanol (0.69 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried
 15 over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.63 g, 45%).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.3), 1.30-1.43 (2H, m), 1.48-1.63 (2H, m), 2.52-2.66 (2H, m), 2.70 (3H, s), 4.02 (2H, s), 5.63 (2H, s), 7.36-7.53 (8H, m), 7.57-7.66 (1H, m), 7.74 (1H, d, J = 7.7), 7.87 (1H, d, J = 7.3), 8.01 (1H, d, J = 8.1)



64b) 3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

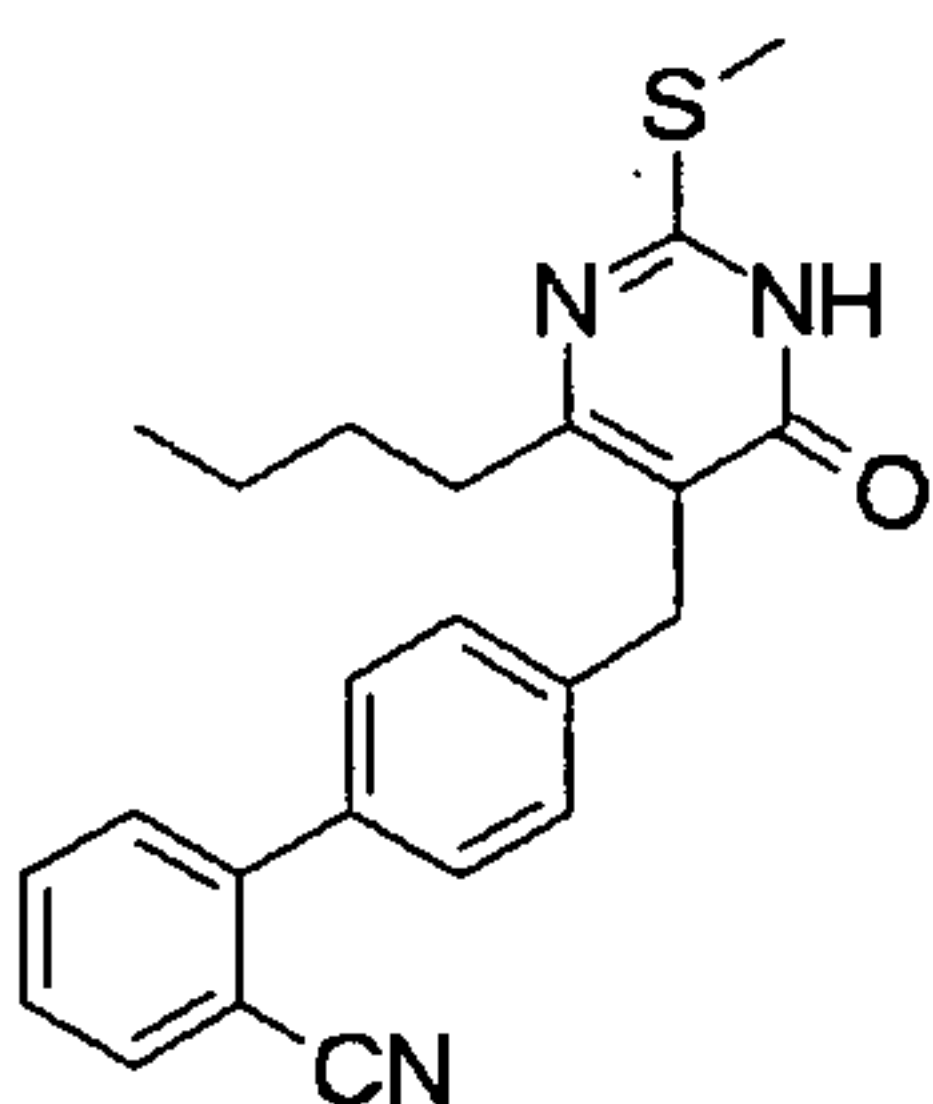
5 A mixture of hydroxylammonium chloride (1.31 g), sodium hydrogen carbonate (2.1 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[1-(1,3-benzothiazol-2-ylmethyl)-4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.63 g) was added, and the
10 mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-
15 carbonyldiimidazole (0.24 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.21 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
20 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.2 g, 28%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.22-1.36 (2H, m), 1.38-1.52 (2H, m), 2.51-2.55 (2H, m), 2.58 (3H, s), 3.89 (2H, s), 5.66 (2H, s), 7.17-7.29 (4H, m), 7.41-7.58 (4H, m), 7.62-7.72 (2H, m), 8.02 (1H, d, J = 8.7), 8.11 (1H, d, J = 8.7), 12.38 (1H, s)

3-(1,3-Benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

- 3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}pyrimidin-4(3H)-one sodium salt
- 3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}pyrimidin-4(3H)-one potassium salt
- 3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}pyrimidin-4(3H)-one 0.5 calcium salt
- 3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}pyrimidin-4(3H)-one hydrochloride
- 3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}pyrimidin-4(3H)-one hydrobromide

Example 65

6-butyl-3-(4-fluorobenzyl)-5-{{2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl}methyl}pyrimidin-4(3H)-one

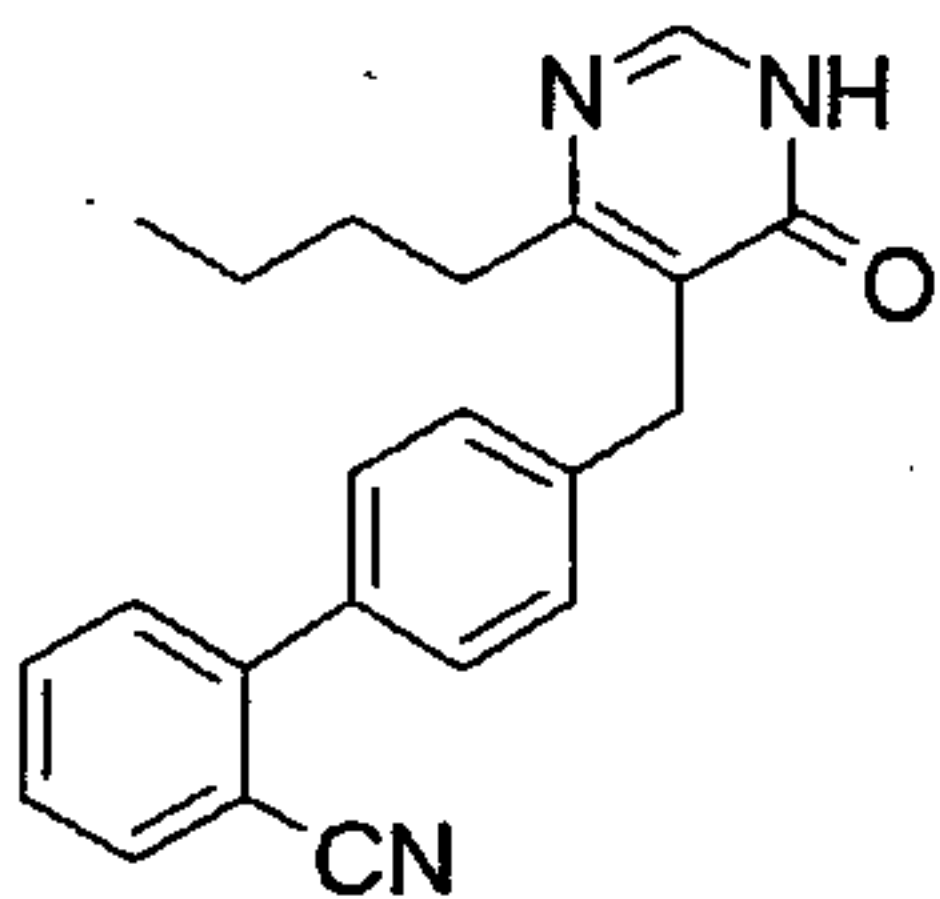


- 65a) 4'-{{[4-butyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-mercapto-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (2.3 g), iodomethane (0.54 mL), potassium hydroxide (0.44 g) and methanol (20 mL) was stirred at room temperature for 3 hr. The obtained crystallized product was collected by filtration and

washed with water and diethyl ether to give the title compound as colorless crystals (1.98 g, 83%).

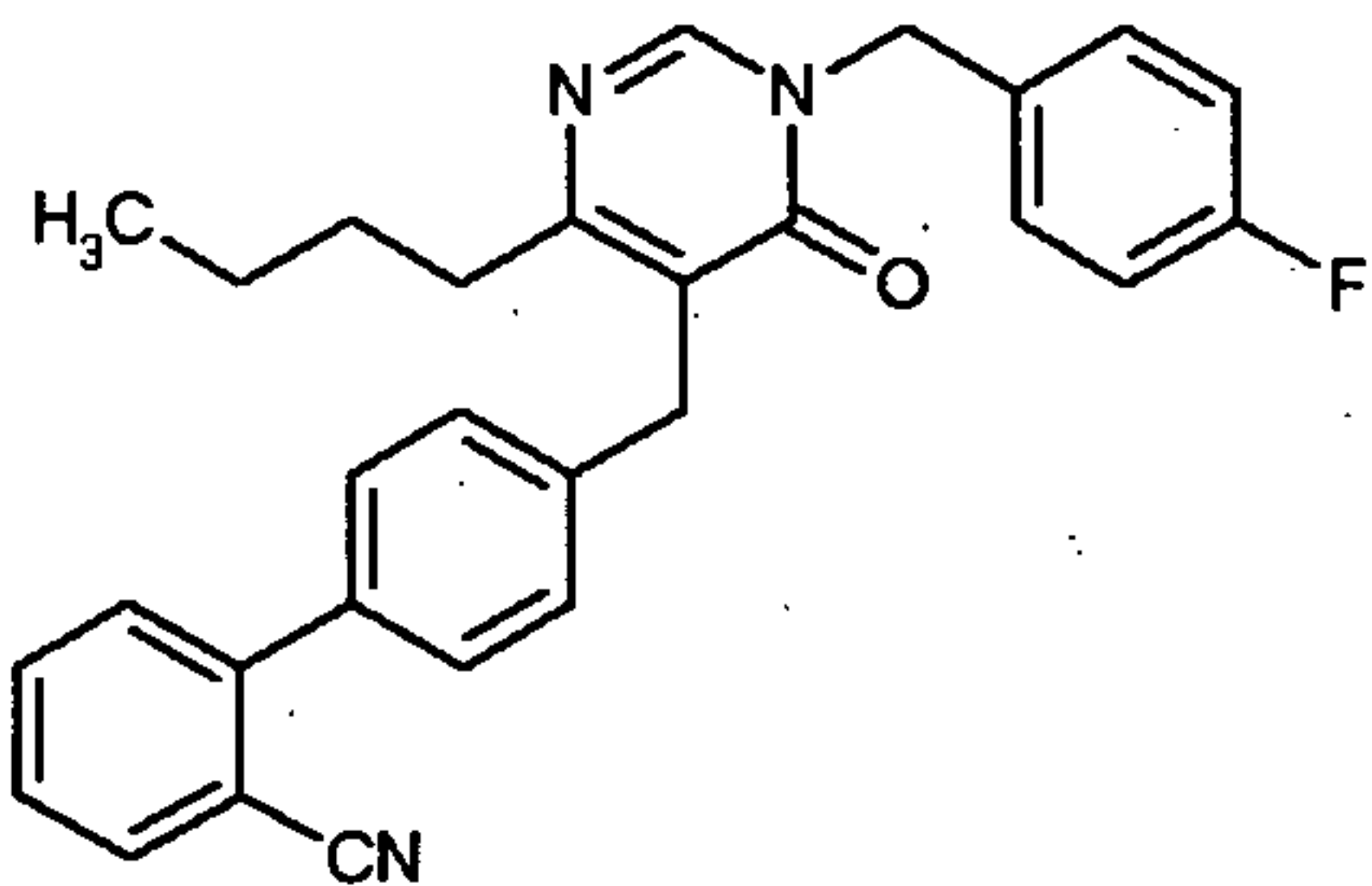
¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.4), 1.26-1.42 (2H, m), 1.51-1.66 (2H, m), 2.52-2.64 (5H, m), 3.95 (2H, s), 7.37-7.50 (6H, m), 7.57-7.65 (1H, m), 7.74 (1H, dd, J = 7.7, 1.3), 12.56 (1H, br)



65b) 4'-[(4-butyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile

10 A mixture of 4'-{[4-butyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1.98 g), Raney-nickel (15 g) and 1-methoxy-2-(2-methoxyethoxy)ethane (25 mL) was stirred at 160°C for 16 hr. The insoluble material was filtrated, and the filtrate was concentrated to give the
15 title compound as colorless crystals (1.09 g, 63%).

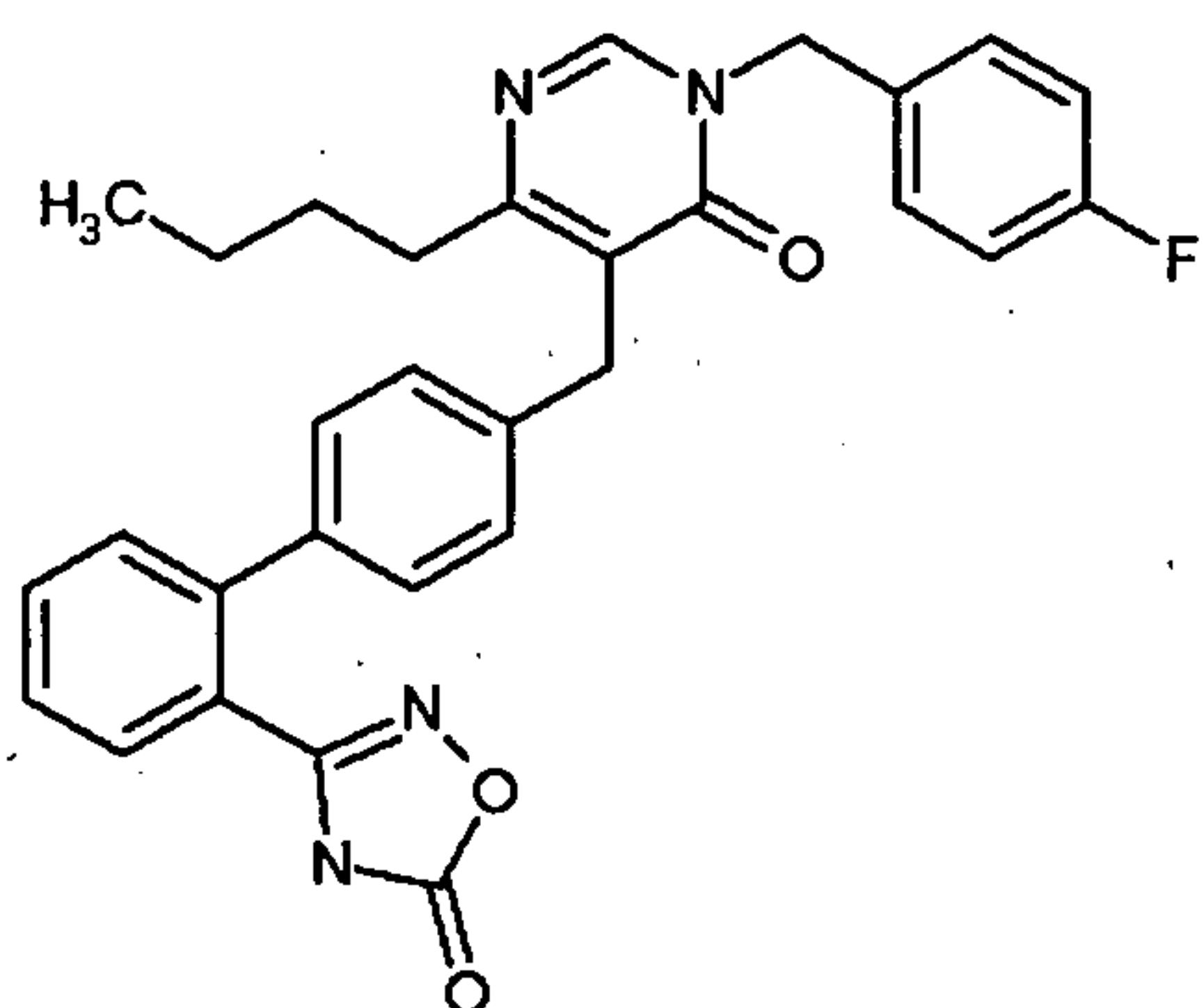
¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.3), 1.19-1.35 (2H, m), 1.35-1.56 (2H, m), 2.51-2.58 (2H, m), 3.89 (2H, s), 7.34 (2H, d, J = 8.3), 7.43-7.64 (4H, m), 7.71-7.82 (1H, m), 7.93 (1H, d, J = 7.7), 8.06 (1H, s), 12.42 (1H, br)



20 65c) 4'-{[4-butyl-1-(4-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (0.5 g), sodium hydride
25 (0.07 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)-4-fluorobenzene (0.22 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate,

washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.54 g, 82%).
¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.4), 1.29-1.42 (2H, m), 1.51-1.63 (2H, m), 2.57-2.68 (2H, m), 3.99 (2H, s), 5.06 (2H, s), 7.01-7.10 (2H, m), 7.30-7.50 (8H, m), 7.57-7.67 (1H, m), 7.74 (1H, dd, J = 7.7, 0.9), 8.06 (1H, s)



10

65d) 6-butyl-3-(4-fluorobenzyl)-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

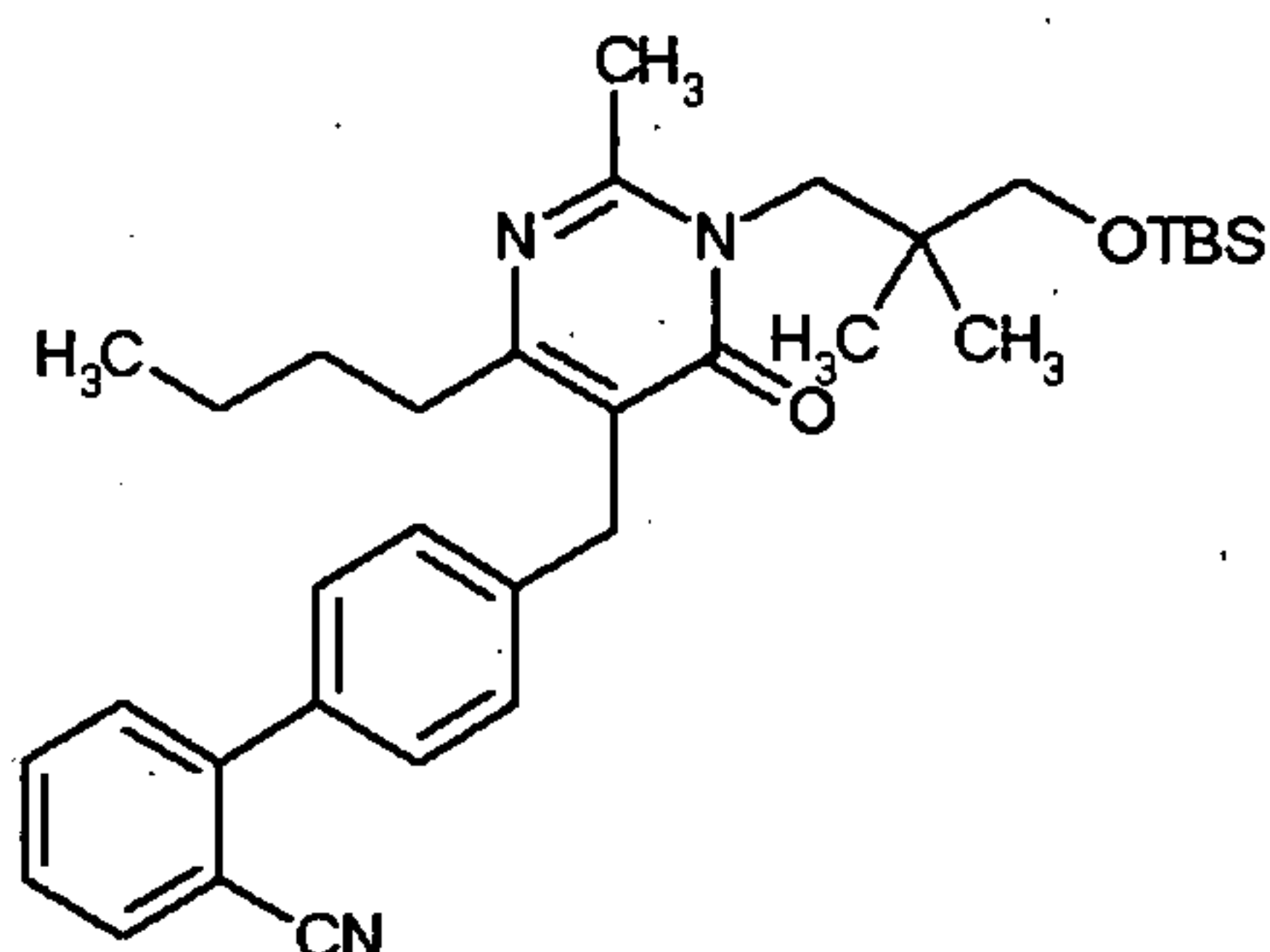
A mixture of hydroxylammonium chloride (1.25 g), sodium hydrogen carbonate (2.02 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(4-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.54 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.23 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.2 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography

to give the title compound as colorless crystals (0.38 g, 62%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.4), 1.20-1.33 (2H, m), 1.37-1.55 (2H, m), 2.51-2.56 (2H, m), 3.87 (2H, s), 5.09 (2H, s), 7.14-7.27 (6H, m), 7.37-7.45 (2H, m), 7.46-7.59 (2H, m), 7.62-7.73 (2H, m), 8.55 (1H, s), 12.37 (1H, s)

Example 66

6-butyl-3-(3-hydroxy-2,2-dimethylpropyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

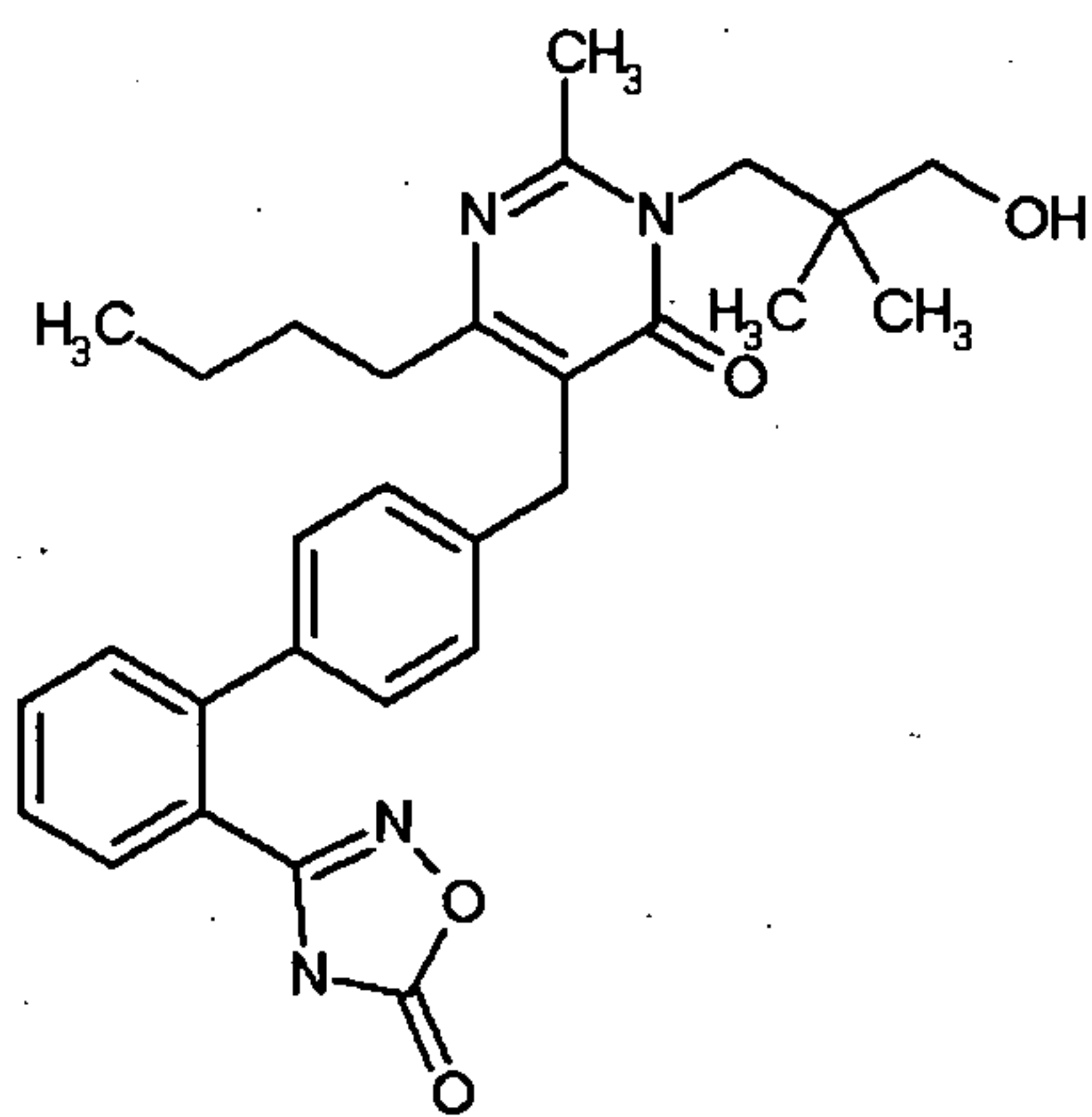


10

66a) 4'-{[4-butyl-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), cesium carbonate (4.1 g), (3-bromo-2,2-dimethylpropoxy)(tert-butyl)dimethylsilane (2.36 g) and N,N-dimethylacetamide (10 mL) was stirred at 130°C for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.63 g, 27%).

¹H NMR (300 MHz, CDCl₃) δ 0.03-0.11 (6H, m), 0.86-0.99 (18H, m), 1.32-1.46 (2H, m), 1.49-1.62 (2H, m), 2.50-2.65 (5H, m), 3.33 (2H, s), 3.95 (2H, s), 4.13 (2H, br), 7.31-7.40 (2H, m), 7.40-7.52 (4H, m), 7.57-7.67 (2H, m), 7.74 (2H, dd, J = 7.7, 0.9)



66b) 6-butyl-3-(3-hydroxy-2,2-dimethylpropyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

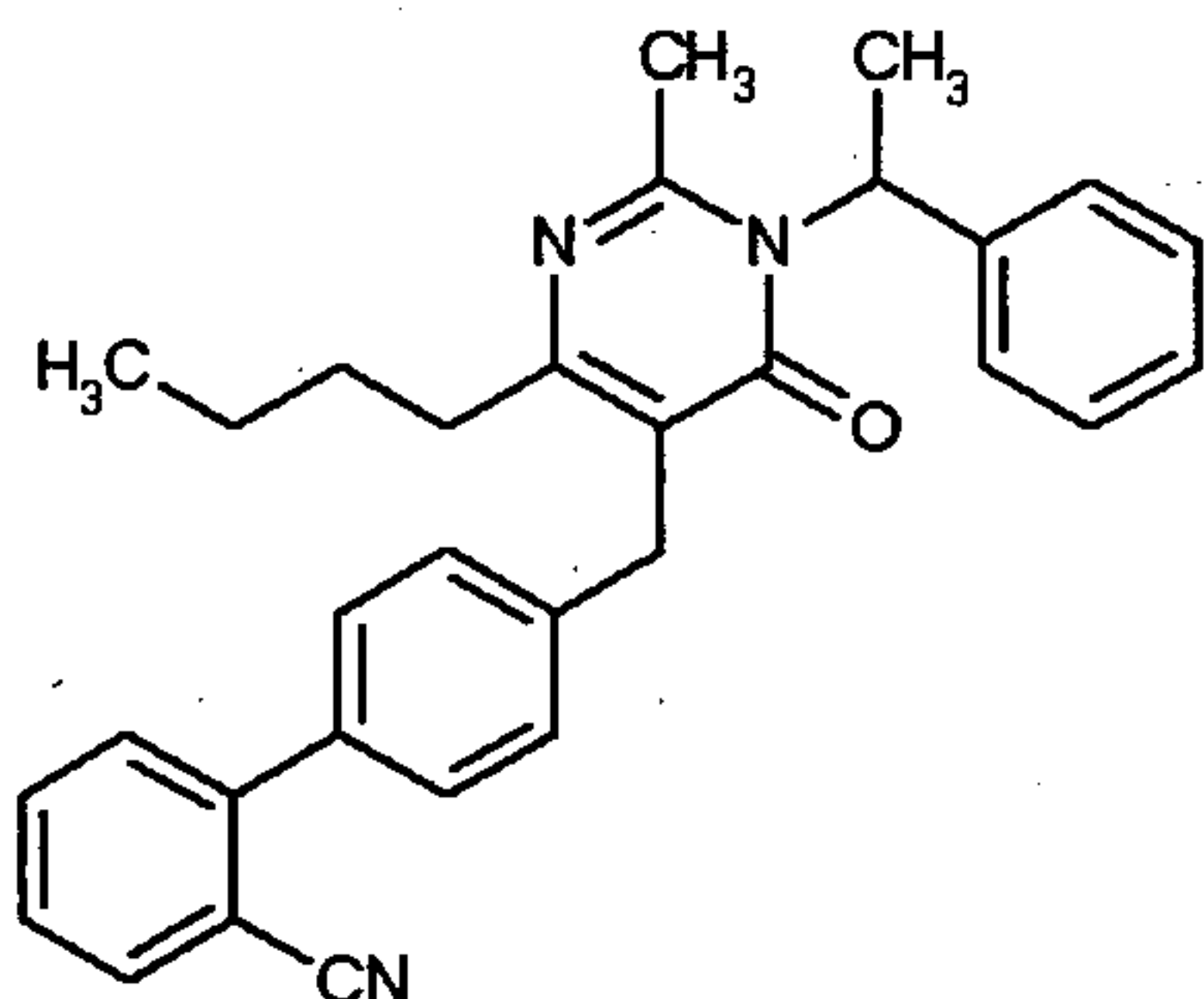
5 A mixture of hydroxylammonium chloride (1.17 g), sodium hydrogen carbonate (1.88 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.63
10 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in
15 tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.22 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.18 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then
20 with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution, 3.7 mL) was added, and the mixture was stirred at 70°C for 6 hr.
25 The reaction mixture was extracted with 1 M hydrochloric acid and ethyl acetate, and the ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the

residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.24 g, 48%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.74-0.90 (9H, m), 1.19-1.35 (2H, m), 1.36-1.53 (2H, m), 2.41-2.48 (2H, m), 2.54 (3H, s), 3.09 (2H, d, J = 4.7), 3.85 (2H, s), 3.97 (2H, s), 4.84 (1H, t, J = 5.2), 7.12-7.27 (4H, m), 7.43-7.58 (2H, m), 7.61-7.74 (2H, m), 12.37 (1H, s)

Example 67

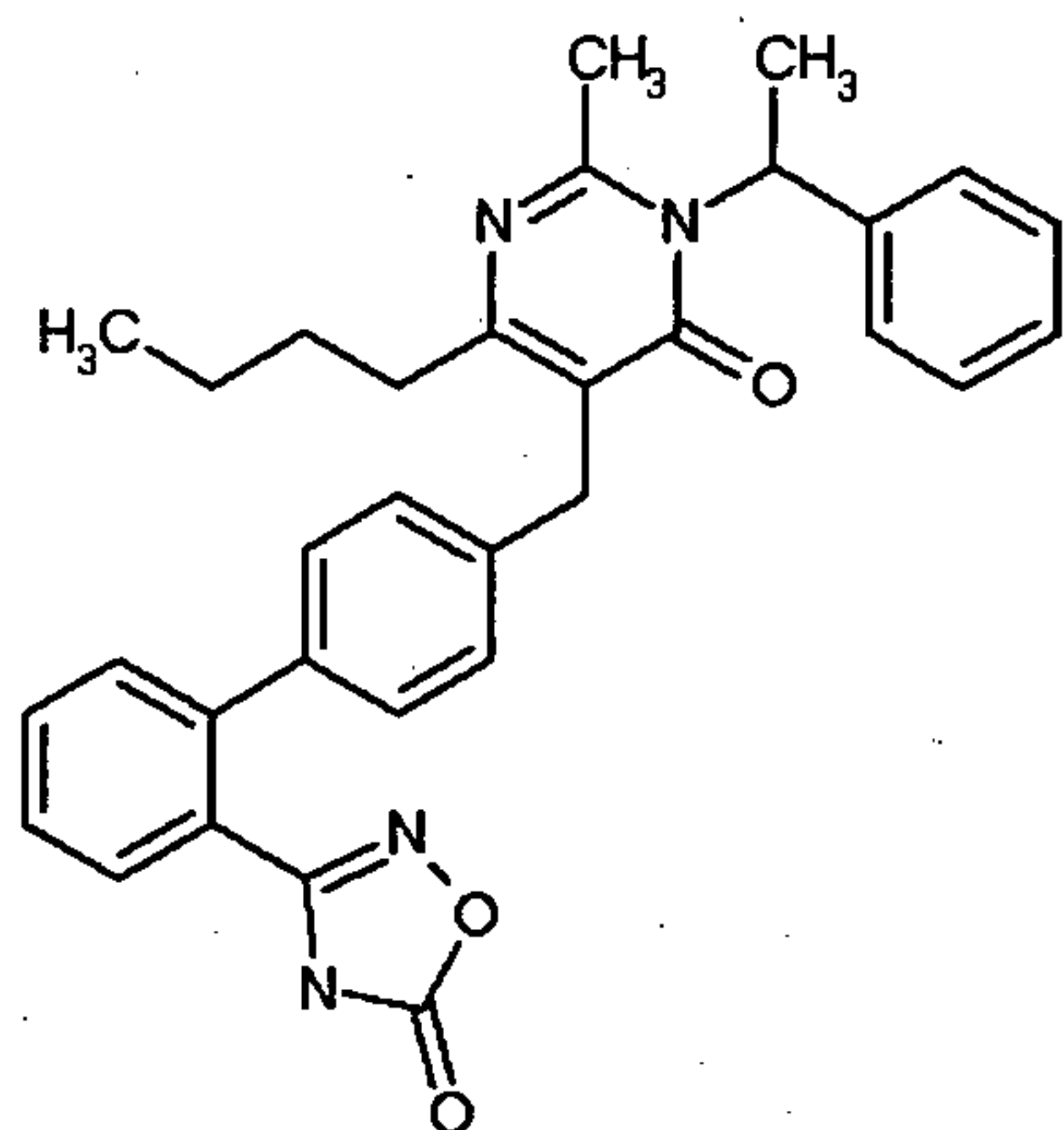
6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(1-phenylethyl)pyrimidin-4(3H)-one



67a) 4'-{[4-butyl-2-methyl-6-oxo-1-(1-phenylethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1-(1-phenylethyl)-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), cesium carbonate (2.73 g), (1-bromoethyl)benzene (1.15 mL) and N,N-dimethylacetamide (10 mL) was stirred at 130°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.24 g, 19%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.30-1.43 (2H, m), 1.48-1.63 (2H, m), 1.91 (3H, d, J = 7.2), 2.27 (3H, s), 2.49-2.59 (2H, m), 3.98 (2H, s), 6.51 (1H, br), 7.16-7.51 (11H, m), 7.58-7.67 (1H, m), 7.74 (1H, dd, J = 7.7, 0.9)



67b) 6-butyl-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-3-(1-phenylethyl)pyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (0.54 g), sodium hydrogen carbonate (0.87 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-2-methyl-6-oxo-1-(1-phenylethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.24 g) was added, and the mixture was stirred
10 at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.1 g)
15 and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.09 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over
20 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.07 g, 26%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.21-1.34
25 (2H, m), 1.36-1.50 (2H, m), 1.86 (3H, d, J = 7.0), 2.33-2.47 (5H, m), 3.81 (2H, s), 6.09 (1H, br), 7.14-7.30 (7H, m), 7.32-7.39 (2H, m), 7.52 (2H, dd, J = 17.6, 7.6), 7.62-7.72 (2H, m), 12.38 (1H, br)

6-Butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(1-phenylethyl)pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(1-phenylethyl)pyrimidin-4(3H)-one sodium salt

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(1-phenylethyl)pyrimidin-4(3H)-one potassium salt

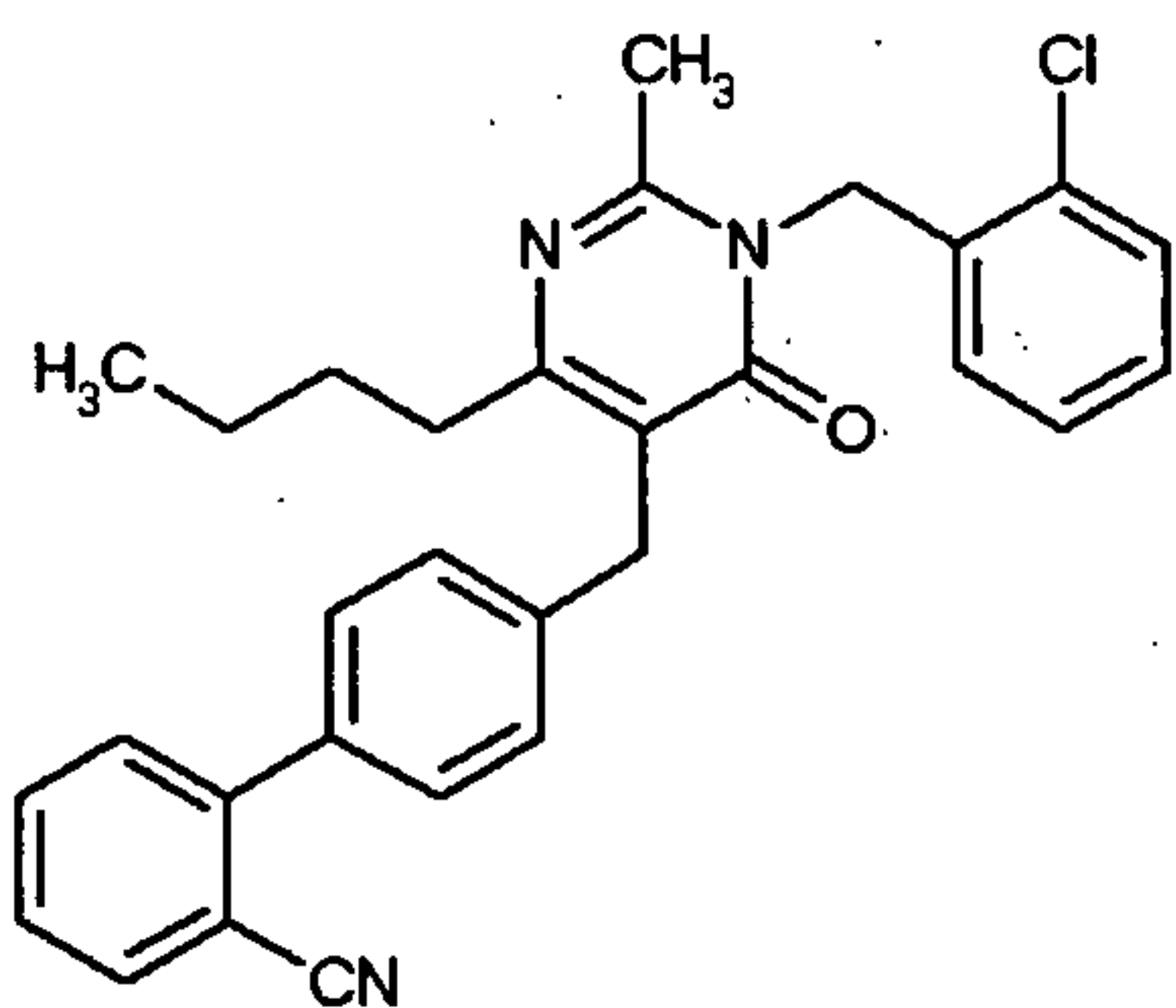
6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(1-phenylethyl)pyrimidin-4(3H)-one 0.5 calcium salt

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(1-phenylethyl)pyrimidin-4(3H)-one hydrochloride

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(1-phenylethyl)pyrimidin-4(3H)-one hydrobromide

Example 68

6-butyl-3-(2-chlorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

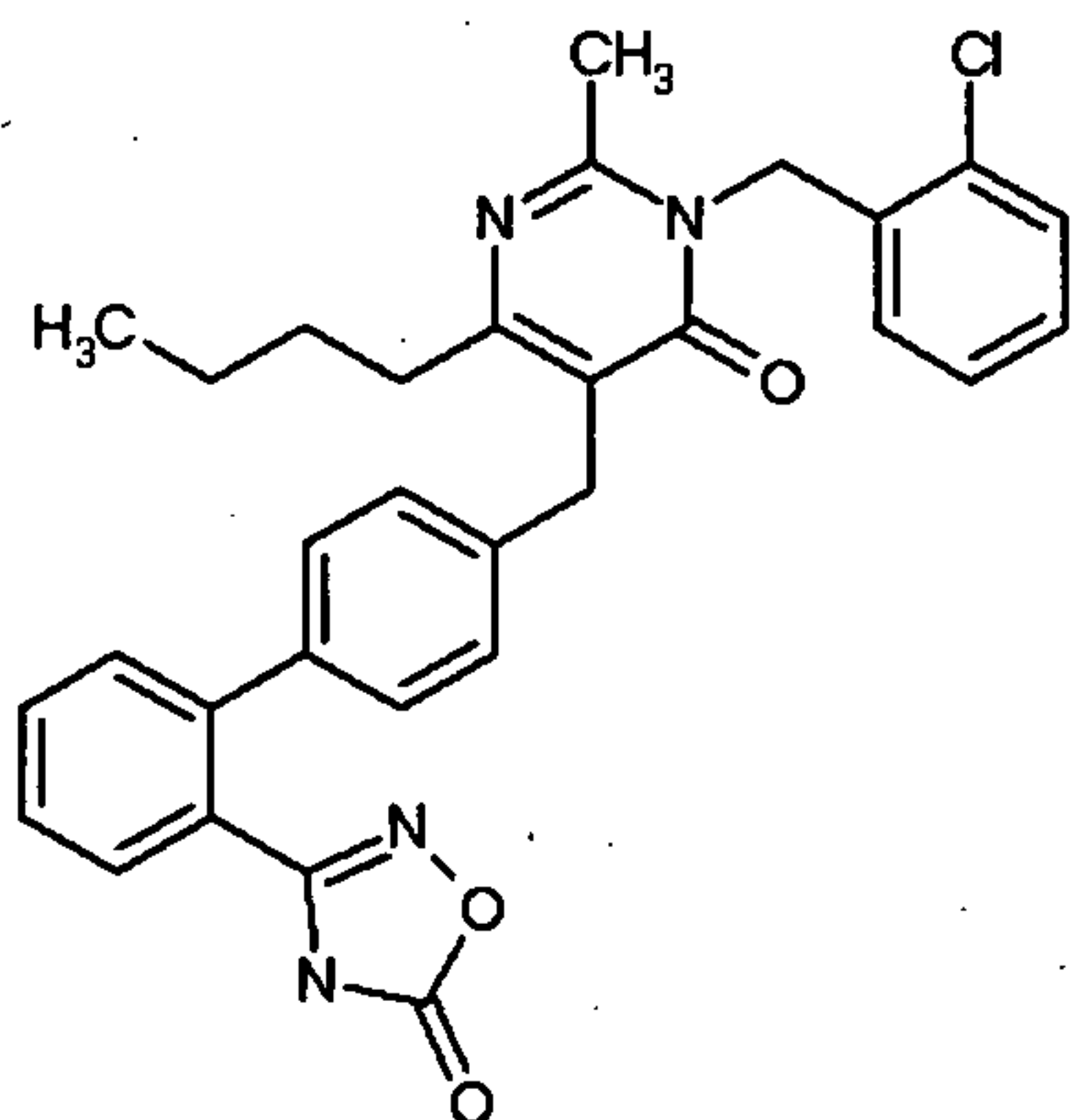


68a) 4'-{[4-butyl-1-(2-chlorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-{[4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1 g), sodium hydride (0.13 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)-2-

chlorobenzene (0.44 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and
 5 dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.6 g, 45%).

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.3), 1.31-1.48 (2H, m), 1.54-1.69 (2H, m), 2.39 (3H, s), 2.59-2.70 (2H, m), 4.01
 10 (2H, s), 5.39 (2H, s), 6.74-6.82 (1H, m), 7.17-7.25 (2H, m), 7.36-7.51 (7H, m), 7.62 (1H, t, J = 7.6), 7.74 (1H, d, J = 7.7)



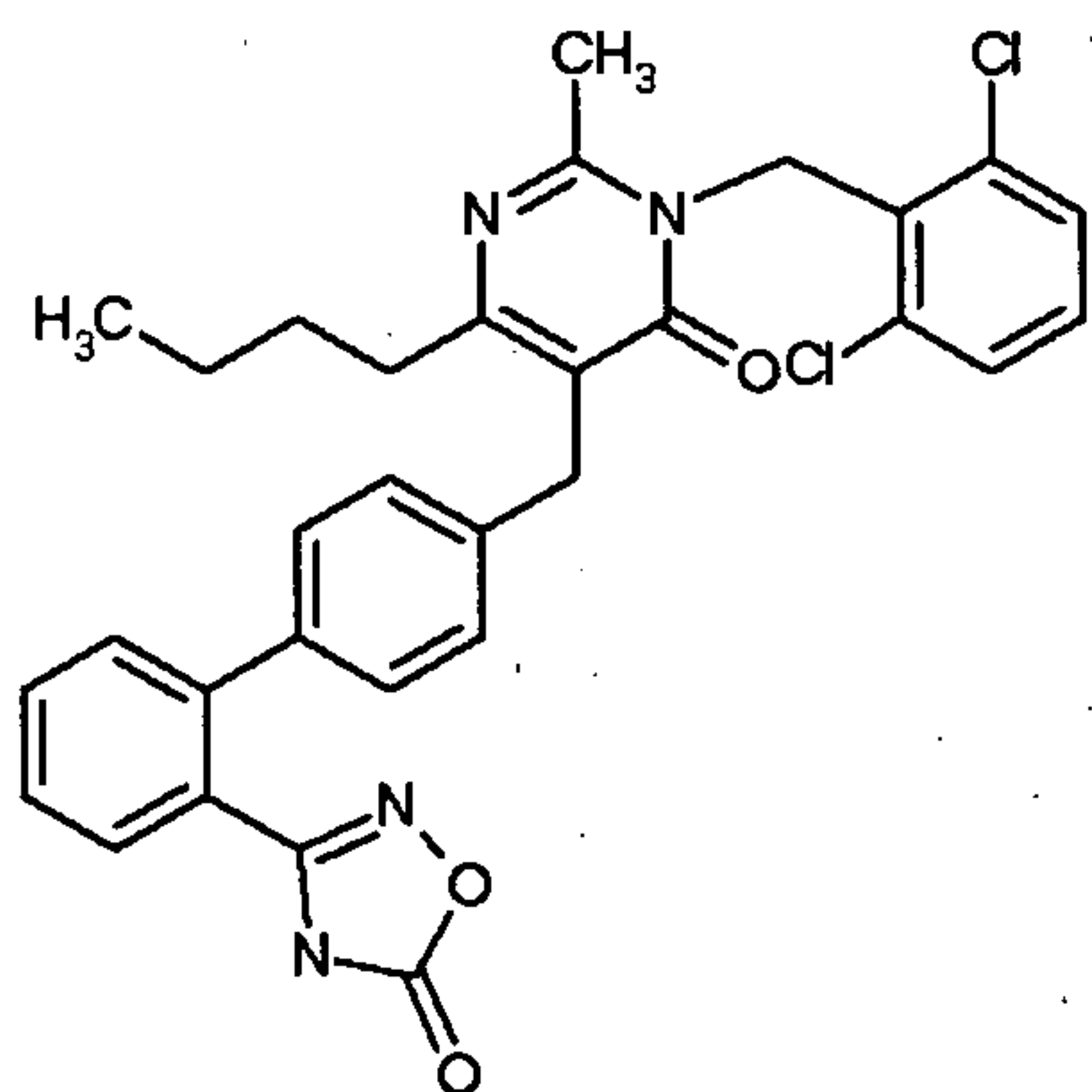
15 68b) 6-butyl-3-(2-chlorobenzyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.3 g), sodium hydrogen carbonate (2.1 g) and dimethyl sulfoxide (15 mL) was
 20 stirred at 40°C for 30 min, 4'-{[4-butyl-1-(2-chlorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.6 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and
 25 dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.24 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.21 mL)

were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over
 5 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.45 g, 67%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.2), 1.24-1.35
 10 (2H, m), 1.41-1.55 (2H, m), 2.36 (3H, s), 2.52-2.58 (2H, m), 3.89 (2H, s), 5.30 (2H, s), 6.68-6.74 (1H, m), 7.17-7.28 (4H, m), 7.30-7.38 (2H, m), 7.46-7.58 (3H, m), 7.62-7.71 (2H, m), 12.39 (1H, s)

Example 69



15

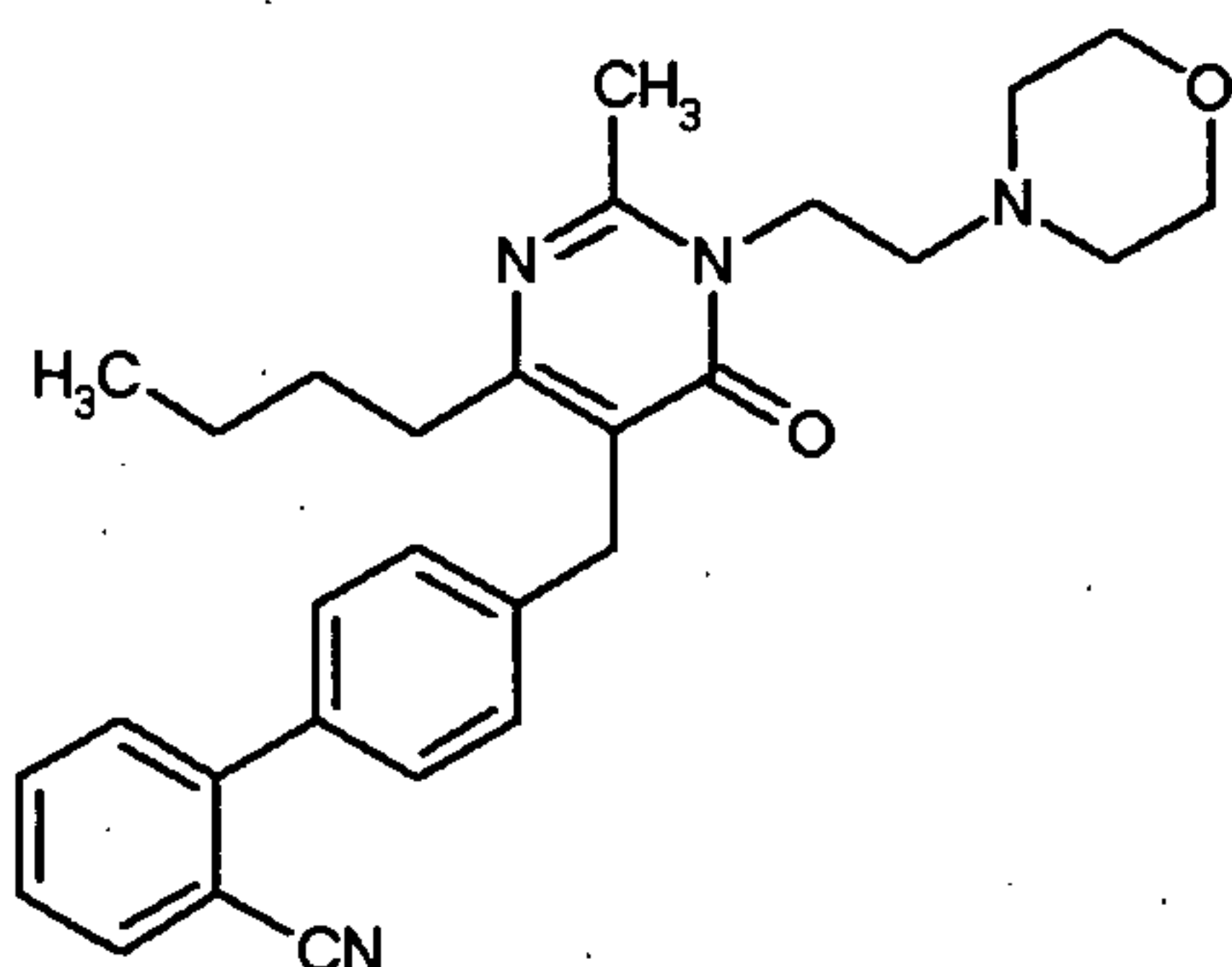
6-butyl-3-(2,6-dichlorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-
 20 dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.13 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 2-(bromomethyl)-1,3-dichlorobenzene (0.81 mL) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture
 25 was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by

silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.4 g), sodium hydrogen carbonate (0.65 g) and dimethyl sulfoxide (10 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL),
 10 N,N'-carbonyldiimidazole (0.075 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.064 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
 15 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.047 g, 3%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.4), 1.16-1.31 (2H, m), 1.36-1.51 (2H, m), 2.41-2.49 (5H, m), 3.79 (2H, s), 5.46 (2H, s), 7.10-7.20 (4H, m), 7.27-7.37 (1H, m), 7.41-7.58 (4H, m), 7.61-7.71 (2H, m), 12.39 (1H, br)

Example 70

6-butyl-2-methyl-3-(2-morpholin-4-ylethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

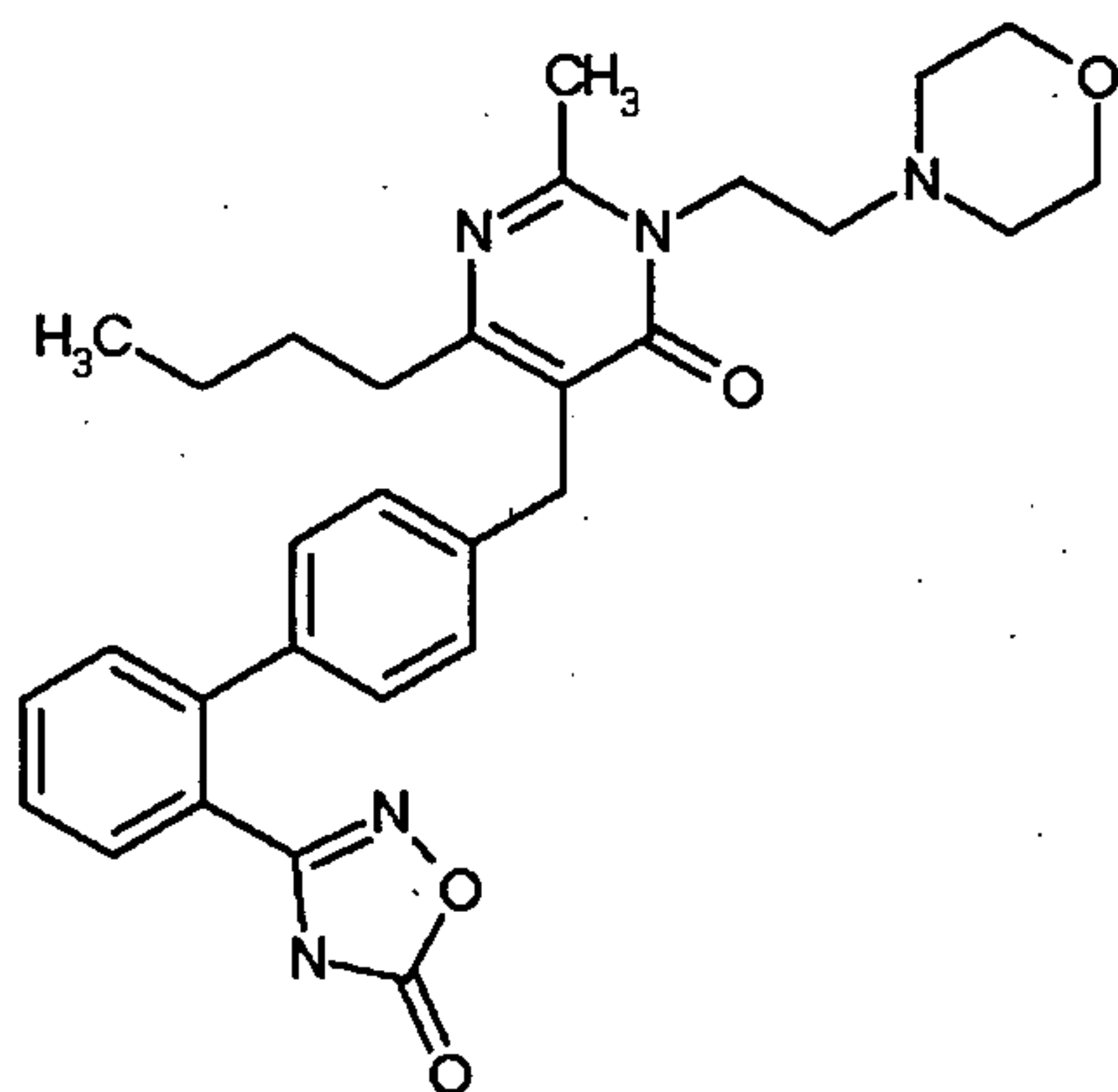


70a) 4'-{[4-butyl-2-methyl-1-(2-morpholin-4-ylethyl)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

30 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-

dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g),
 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine
 (1.56 mL), 2-morpholin-4-ylethanol (0.51 mL) and
 tetrahydrofuran (50 mL) was stirred at room temperature for 4
 5 hr. The reaction mixture was diluted with ethyl acetate,
 washed with water and then with saturated brine, and dried
 over anhydrous magnesium sulfate. The solvent was evaporated
 under reduced pressure and the residue was purified by silica
 gel column chromatography to give the title compound as a
 10 colorless solid (1.34 g, 100%).

¹H NMR (300 MHz, CDCl₃) δ 0.89 (3H, t, J = 7.3), 1.31-1.49 (4H,
 m), 2.44-2.50 (4H, m), 2.57 (3H, s), 2.65-2.75 (4H, m), 3.59-
 3.69 (4H, m), 4.01 (2H, s), 4.50 (2H, t, J = 5.7), 7.22-7.29
 (2H, m), 7.38-7.50 (4H, m), 7.59-7.67 (1H, m), 7.75 (1H, d, J
 15 = 7.7)



70b) 6-butyl-2-methyl-3-(2-morpholin-4-ylethyl)-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]pyrimidin-4(3H)-one

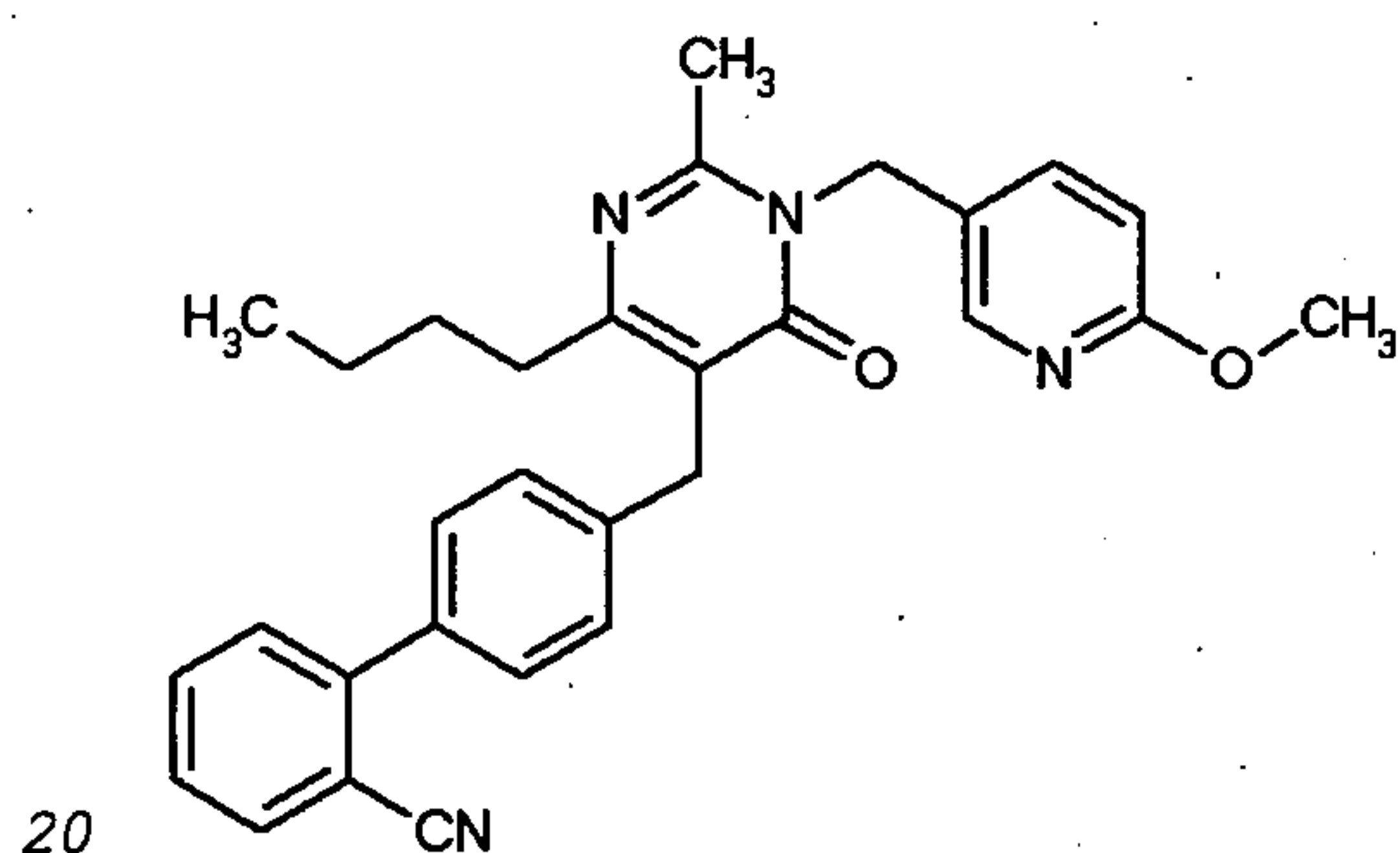
20 A mixture of hydroxylammonium chloride (2.9 g), sodium
 hydrogen carbonate (4.77 g) and dimethyl sulfoxide (30 mL) was
 stirred at 40°C for 30 min, 4'-{[4-butyl-2-methyl-1-(2-
 morpholin-4-ylethyl)-6-oxo-1,6-dihydropyrimidin-5-
 yl)methyl]biphenyl-2-carbonitrile (1.34 g) was added, and the
 25 mixture was stirred at 90°C for 16 hr. The reaction mixture
 was diluted with ethyl acetate, washed with water and then
 with saturated brine, and dried over anhydrous magnesium
 sulfate. The solvent was evaporated under reduced pressure.

The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.55 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.47 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.58 g, 39%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.4), 1.19-1.37 (2H, m), 1.41-1.54 (2H, m), 2.37-2.48 (7H, m), 2.58-2.71 (4H, m), 3.44-3.53 (4H, m), 3.95 (2H, s), 4.45 (2H, t, J = 5.6), 7.18-7.26 (4H, m), 7.44-7.61 (2H, m), 7.58-7.74 (2H, m)

Example 71

6-butyl-3-[(6-methoxypyridin-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

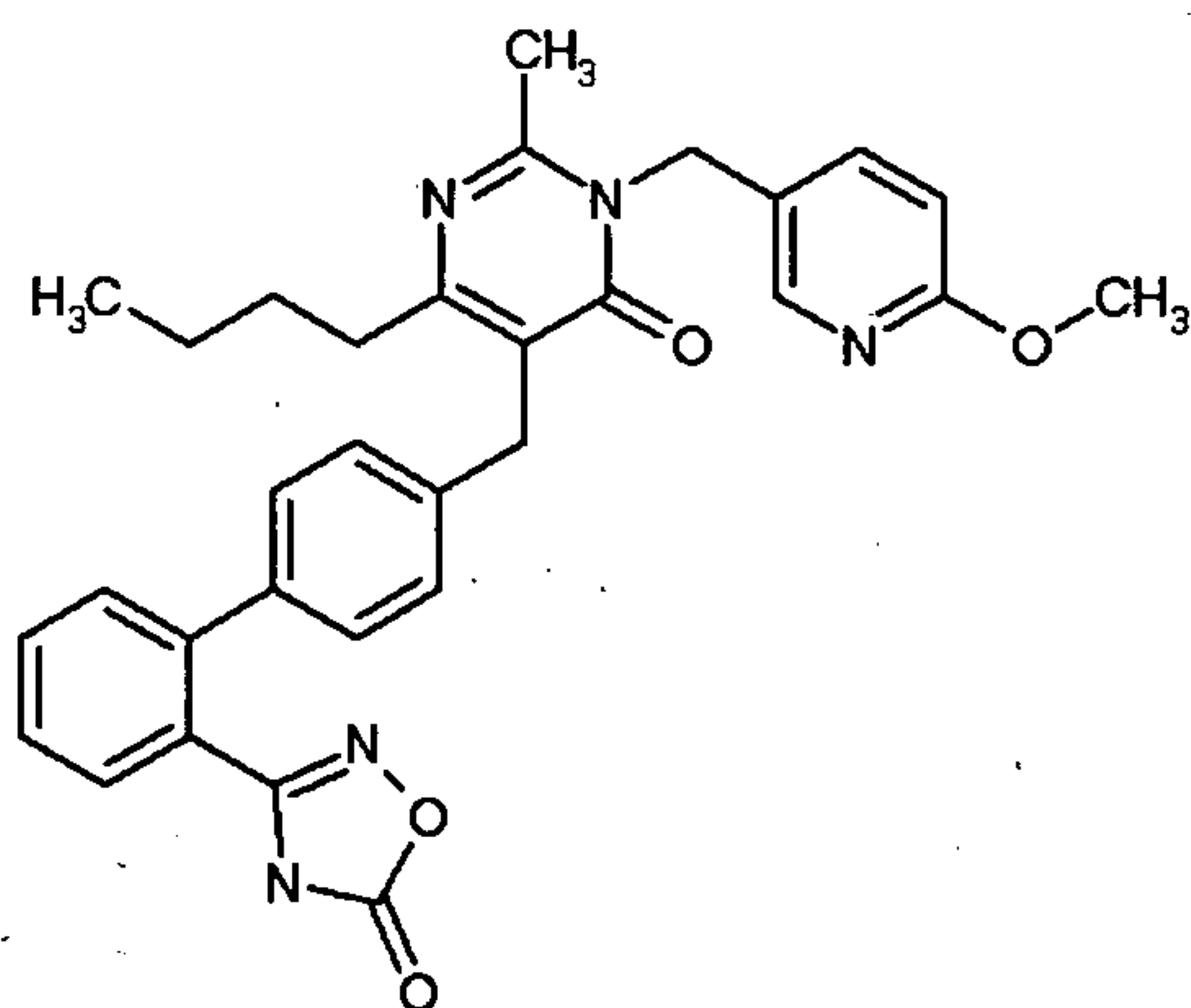


71a) 4'-({4-butyl-1-[(6-methoxypyridin-3-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine (1.56 mL), (6-methoxypyridin-3-yl)methanol (0.58 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated

under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (1.09 g, 81%).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.2), 1.31-1.44 (2H, m), 1.49-1.63 (2H, m), 2.50 (3H, s), 2.55-2.65 (2H, m), 3.91 (3H, s), 3.99 (2H, s), 5.19 (2H, s), 6.68-6.78 (1H, m), 7.32-7.65 (8H, m), 7.74 (1H, d, J = 7.7), 8.08 (1H, s)



71b) 6-butyl-3-[(6-methoxypyridin-3-yl)methyl]-2-methyl-5-yl)methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (2.37 g), sodium hydrogen carbonate (3.83 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-1-[(6-methoxypyridin-3-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile (1.09 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.44 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.38 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under

reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.38 g, 32%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.3), 1.19-1.33 (2H, m), 1.36-1.52 (2H, m), 2.42-2.47 (5H, m), 3.83 (3H, s), 3.89 (2H, s), 5.21 (2H, s), 6.82 (1H, d, J = 8.7), 7.17-7.30 (4H, m), 7.47-7.59 (3H, m), 7.62-7.74 (2H, m), 8.12 (1H, s), 12.39 (1H, s)

6-Butyl-3-[(6-methoxypyridin-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

6-butyl-3-[(6-methoxypyridin-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one sodium salt

6-butyl-3-[(6-methoxypyridin-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one potassium salt

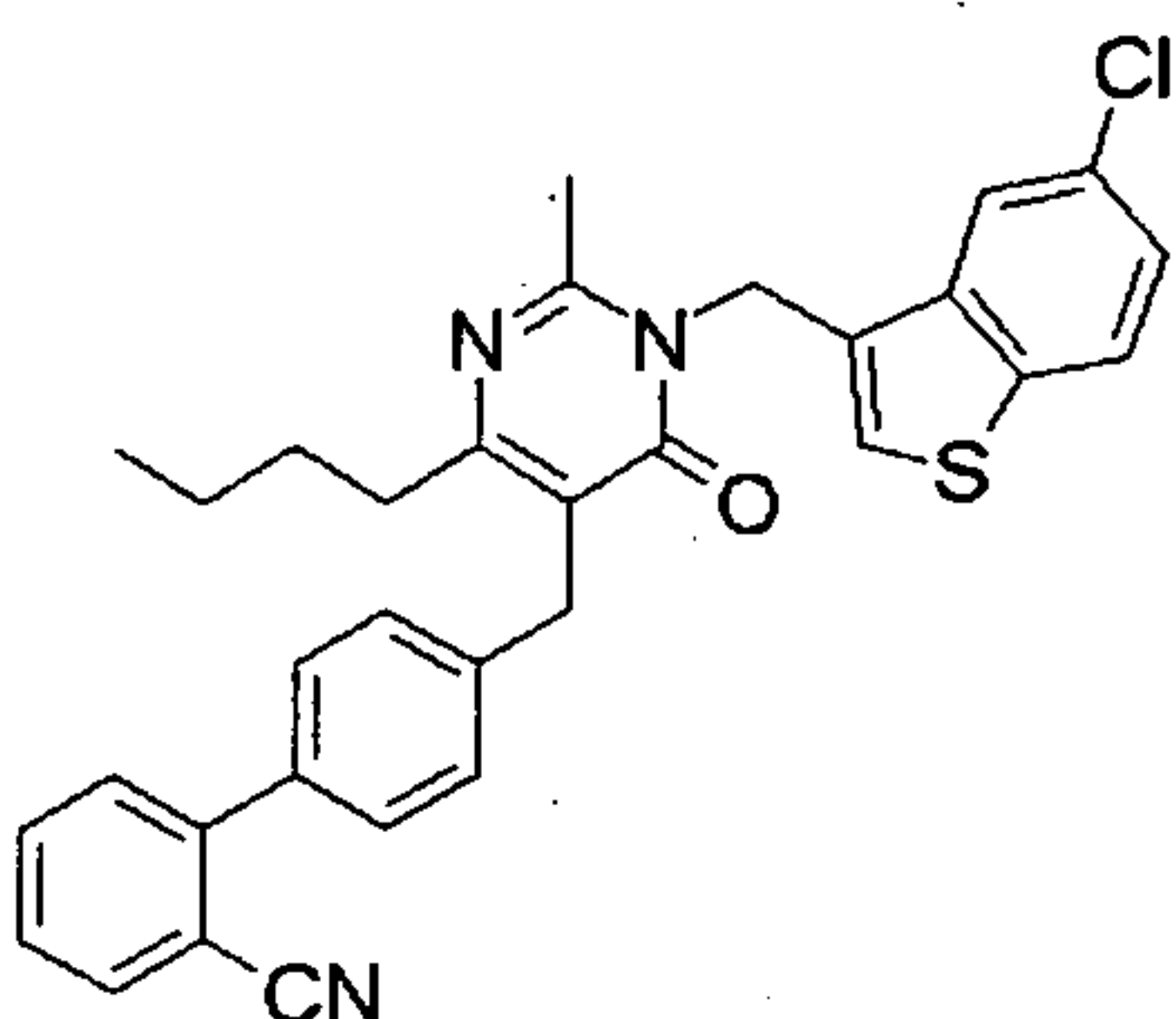
6-butyl-3-[(6-methoxypyridin-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one 0.5 calcium salt

6-butyl-3-[(6-methoxypyridin-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one hydrochloride

6-butyl-3-[(6-methoxypyridin-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one hydrobromide

Example 72

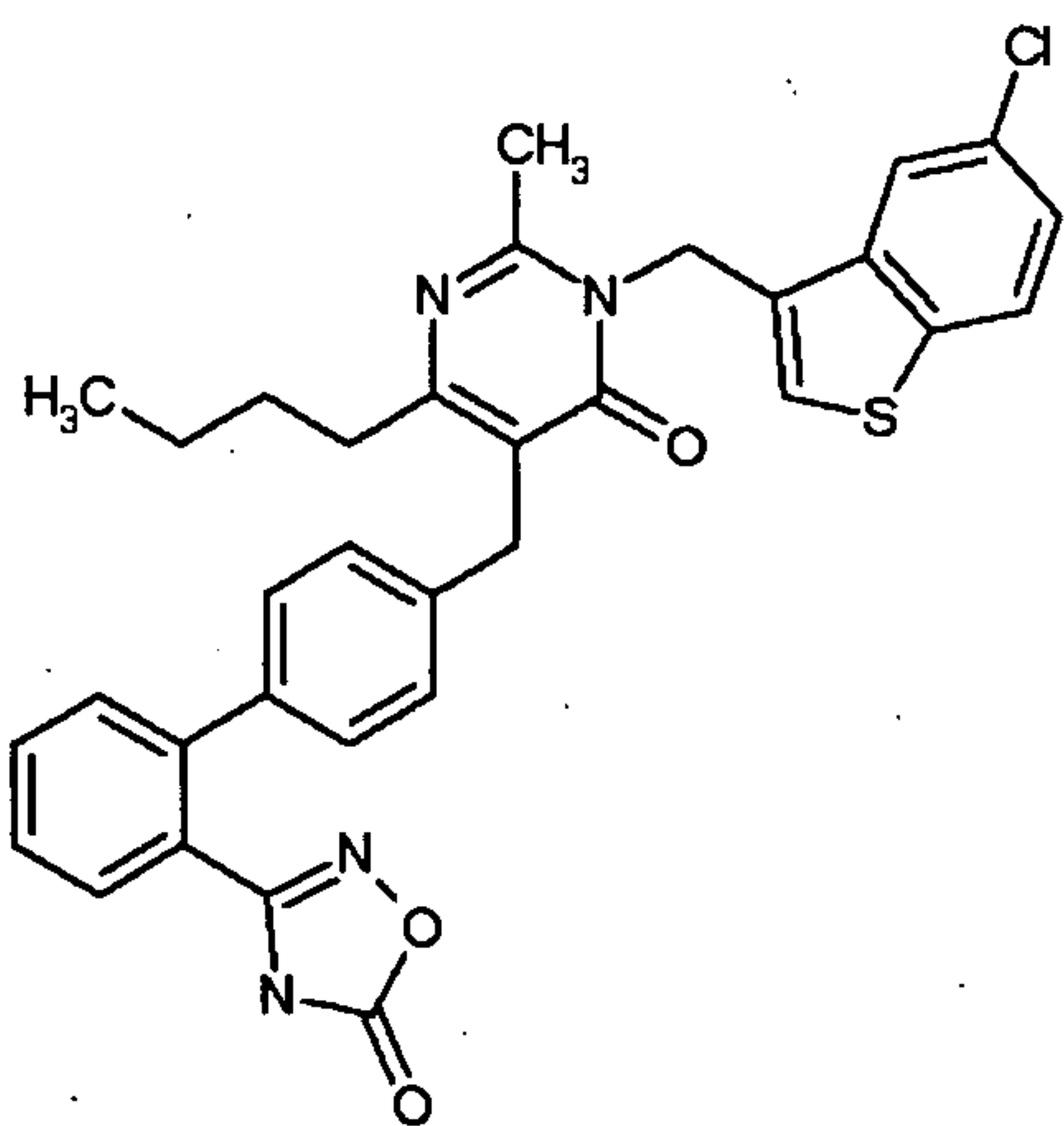
6-butyl-3-[(5-chloro-1-benzothien-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one



72a) 4'-[4-butyl-1-[(5-chloro-1-benzothien-3-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile

5 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine (1.56 mL), (5-chloro-1-benzothien-3-yl)methanol (0.83 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4
10 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M hydrochloric acid and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title
15 compound as a colorless solid (0.82 g, 55%).

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.4), 1.32-1.47 (2H, m), 1.52-1.67 (2H, m), 2.48 (3H, s), 2.60-2.68 (2H, m), 4.02 (2H, s), 5.45 (2H, s), 7.05 (1H, s), 7.32-7.51 (7H, m), 7.59-7.67 (1H, m), 7.72-7.84 (3H, m)



20

72b) 6-butyl-3-[(5-chloro-1-benzothien-3-yl)methyl]-2-methyl-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-

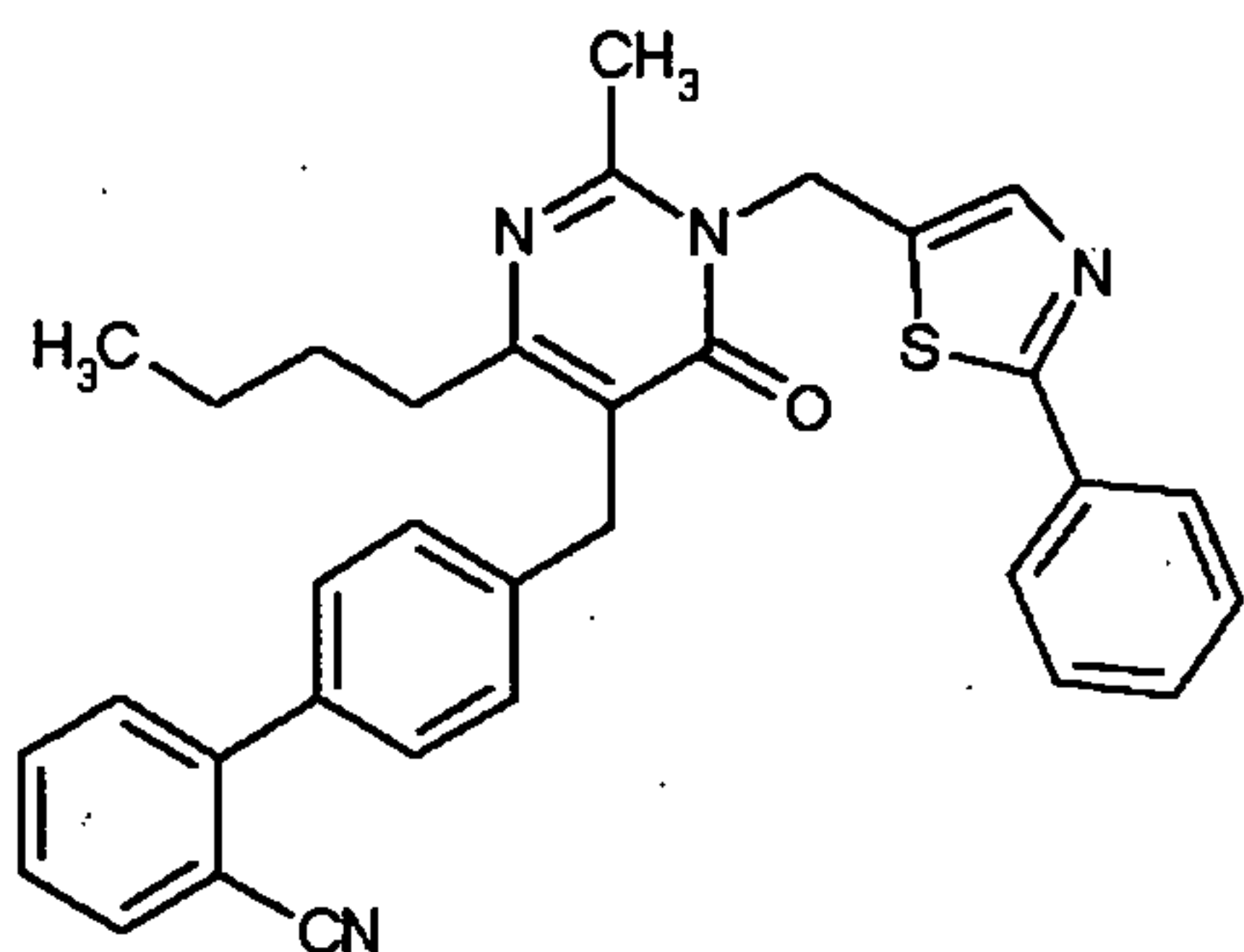
yl)methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.62 g), sodium hydrogen carbonate (2.6 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-1-[(5-chloro-1-benzothien-3-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-carbonitrile (0.82 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.30 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.26 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.58 g, 62%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.22-1.35 (2H, m), 1.41-1.52 (2H, m), 2.41-2.51 (5H, m), 3.92 (2H, s), 5.50 (2H, s), 7.25 (4H, q, J = 8.2), 7.42-7.60 (4H, m), 7.63-7.74 (2H, m), 8.03-8.15 (2H, m), 12.38 (1H, br)

25 Example 73

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]-3-[(2-phenyl-1,3-thiazol-5-yl)methyl]pyrimidin-4(3H)-one

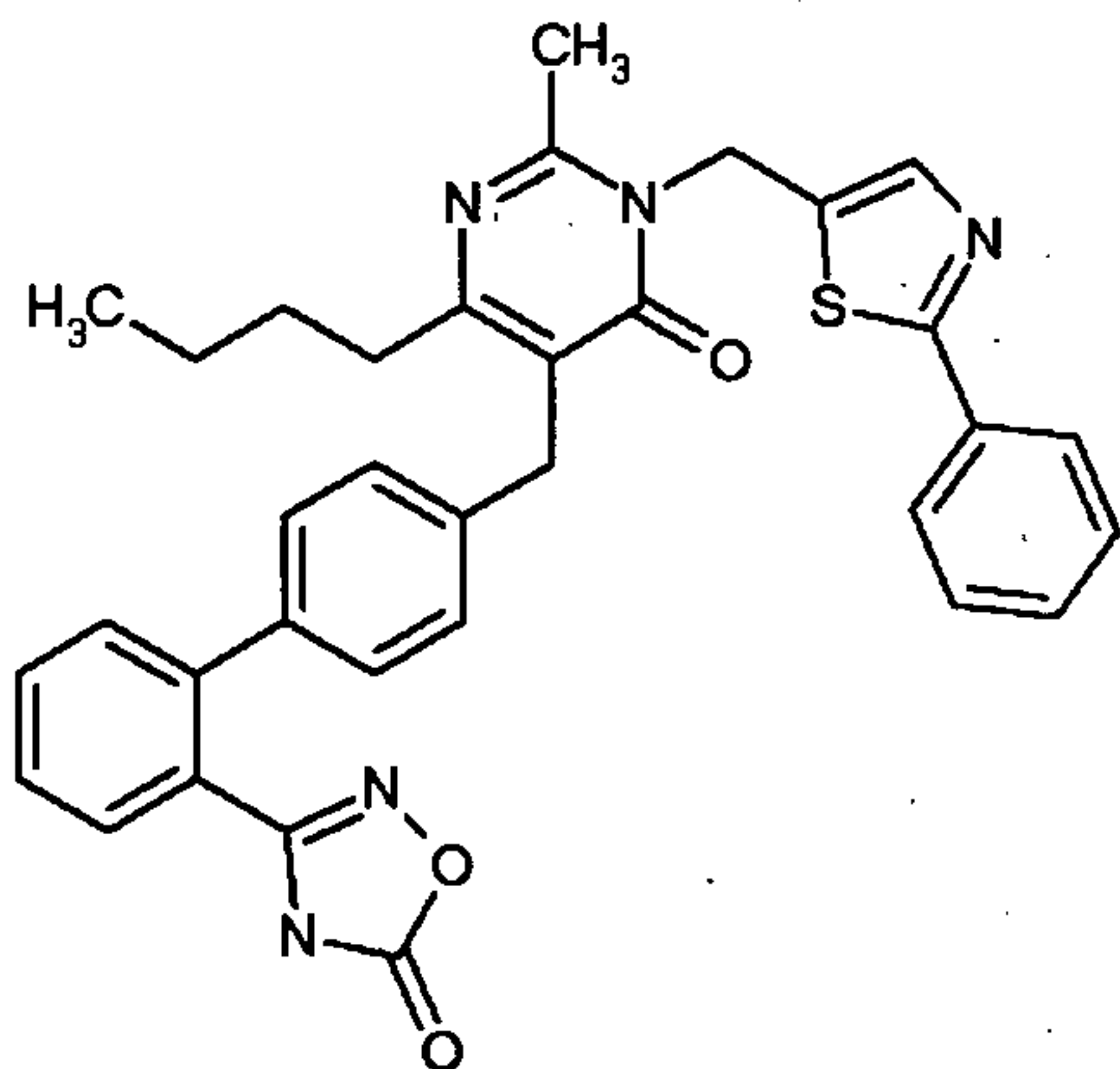


30 73a) 4'-({4-butyl-2-methyl-6-oxo-1-[(2-phenyl-1,3-thiazol-5-

yl)methyl]-1,6-dihydropyrimidin-5-yl)methyl)biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g),
 5 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine (1.56 mL), (2-phenyl-1,3-thiazol-5-yl)methanol (0.8 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried
 10 over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.93 g, 63%).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.3), 1.29-1.46 (2H, m), 1.50-1.62 (2H, m), 2.55-2.63 (2H, m), 2.82 (3H, s), 3.97 (2H, s), 5.37 (2H, s), 7.24-7.50 (10H, m), 7.57-7.65 (1H, m), 7.74 (1H, dd, J = 7.7, 0.9), 7.88-7.96 (2H, m)



73b) 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-[(2-phenyl-1,3-thiazol-5-yl)methyl]pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.83 g), sodium hydrogen carbonate (2.94 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (0.93 g) was added, and the
 25 mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then

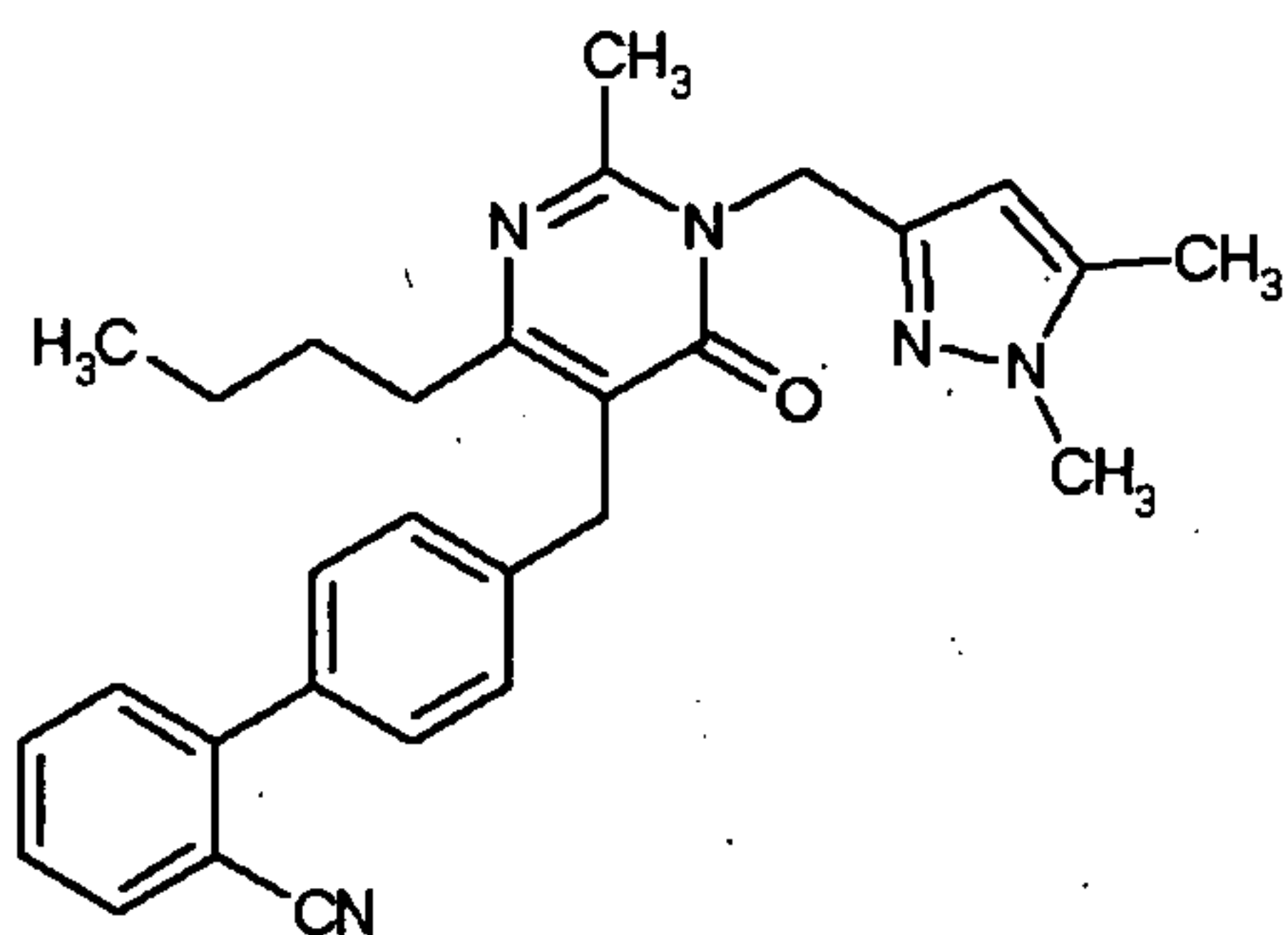
with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.34 g) and then 1,8-

5 diazabicyclo[5.4.0]undec-7-ene (0.29 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over
10 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.6 g, 58%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.20-1.35
15 (2H, m), 1.38-1.53 (2H, m), 2.44-2.49 (2H, m), 2.66 (3H, s), 3.86 (2H, s), 5.35 (2H, s), 7.14-7.25 (4H, m), 7.42-7.61 (6H, m), 7.59-7.69 (2H, m), 7.84-7.91 (2H, m), 12.36 (1H, s)

Example 74

6-butyl-3-[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]-2-methyl-5-
20 {[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
yl]methyl}pyrimidin-4(3H)-one

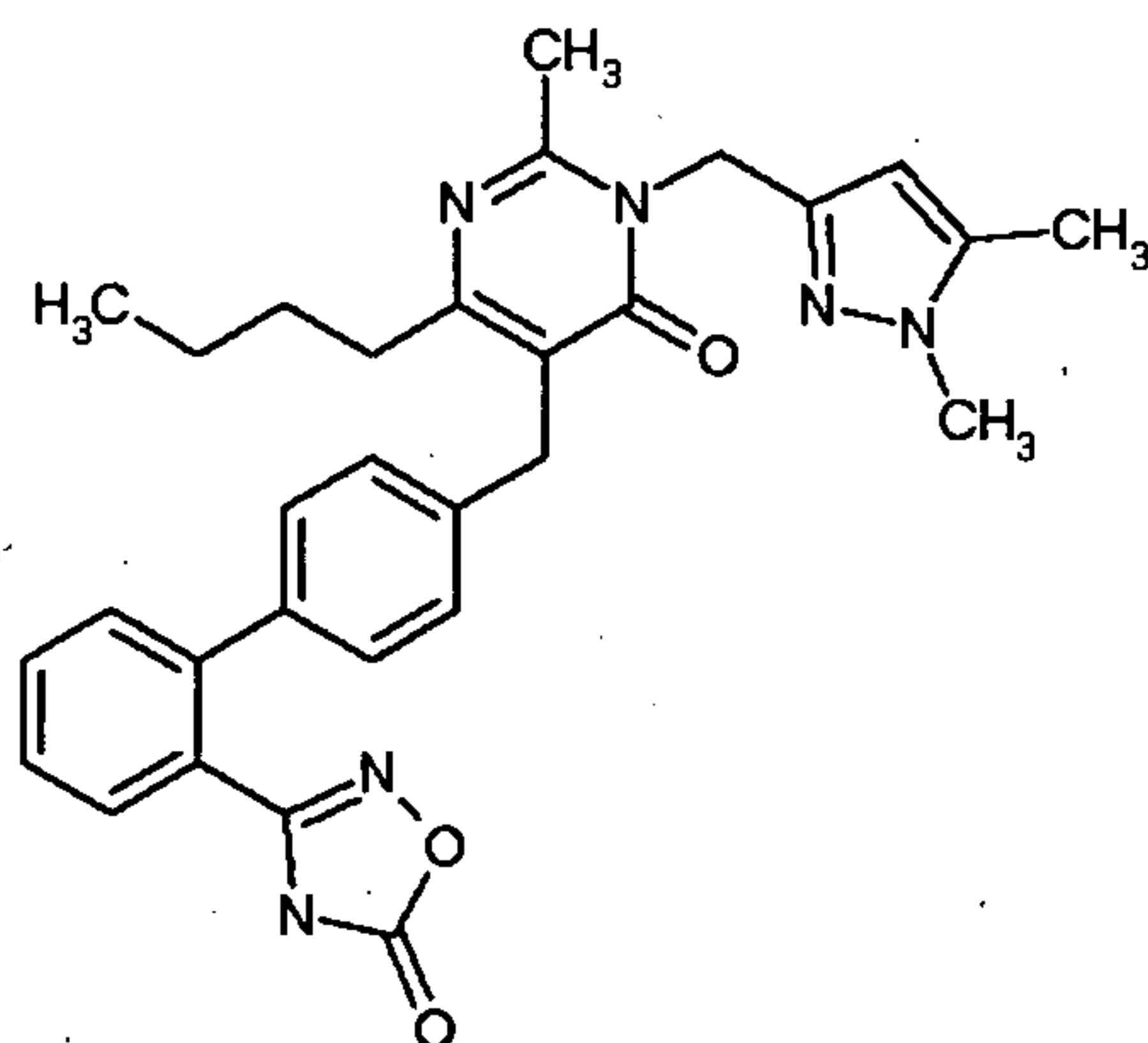


74a) 4'-({4-butyl-1-[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]-2-
methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl}biphenyl-2-
25 carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine (1.56 mL), (1,5-dimethyl-1H-pyrazol-3-yl)methanol (0.53 g) and
30 tetrahydrofuran (50 mL) was stirred at room temperature for 4

hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.80 g, 61%).

¹H NMR (300 MHz, CDCl₃) δ 0.87-0.95 (3H, m), 1.33-1.48 (4H, m), 2.19 (3H, s), 2.54 (3H, s), 2.56-2.66 (2H, m), 3.82 (3H, s), 3.97 (2H, s), 5.22 (2H, s), 5.74 (1H, s), 7.30-7.50 (6H, m), 7.56-7.66 (1H, m), 7.74 (1H, d, J = 7.7)



74b) 6-butyl-3-[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

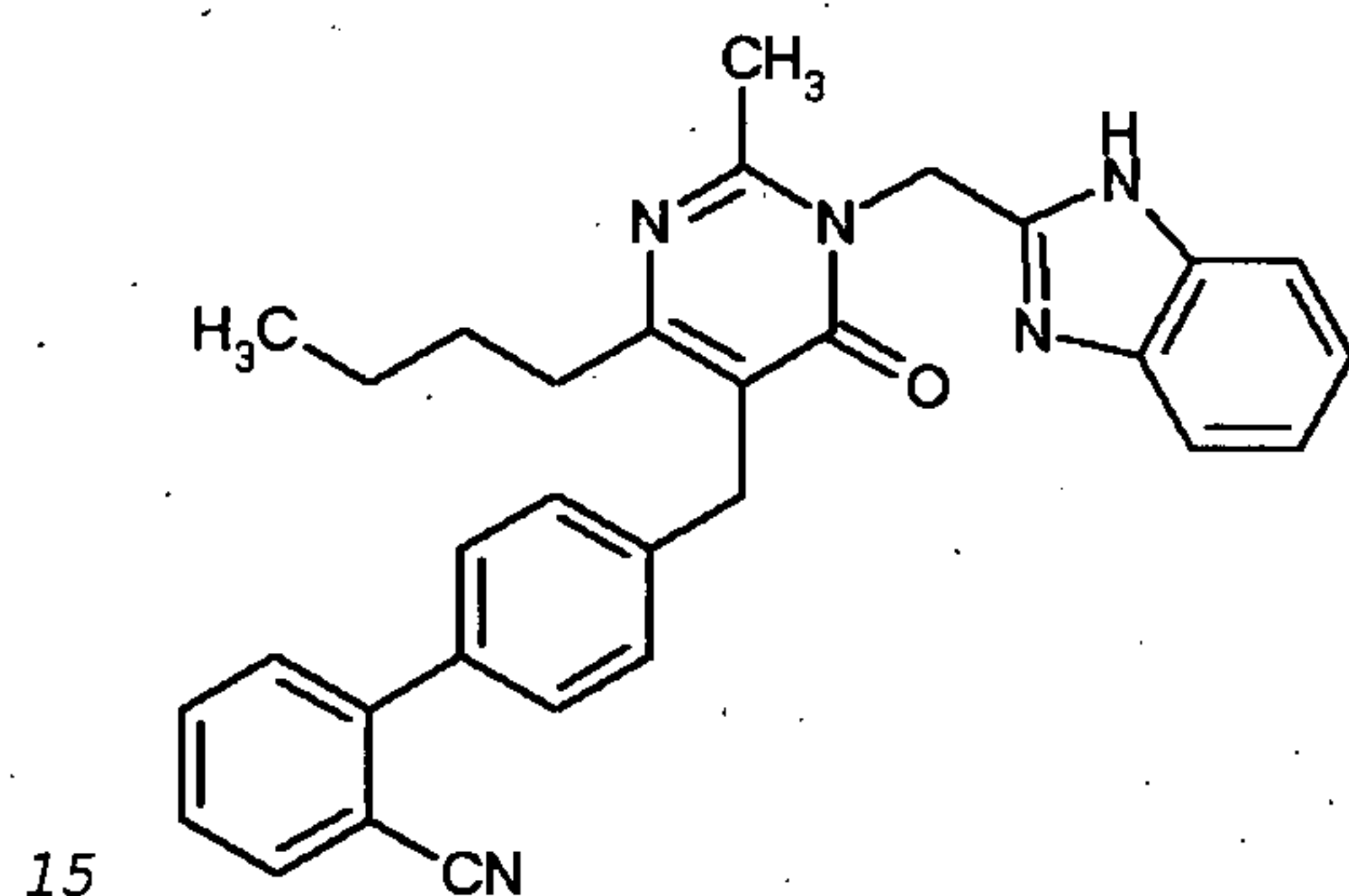
A mixture of hydroxylammonium chloride (1.79 g), sodium hydrogen carbonate (2.89 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-1-[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}methyl)biphenyl-2-carbonitrile (0.8 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.34 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.28 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric

acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.25 g, 27%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.2), 1.22-1.49 (4H, m), 2.05 (3H, s), 2.42-2.48 (5H, m), 3.77 (3H, s), 3.87 (2H, s), 5.23 (2H, s), 5.61 (1H, s), 7.19-7.25 (4H, m), 7.52 (2H, dd, J = 17.8, 7.2), 7.62-7.73 (2H, m), 12.43 (1H, br)

Example 75

6-butyl-2-methyl-3-[(1-methyl-1H-benzimidazol-2-yl)methyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

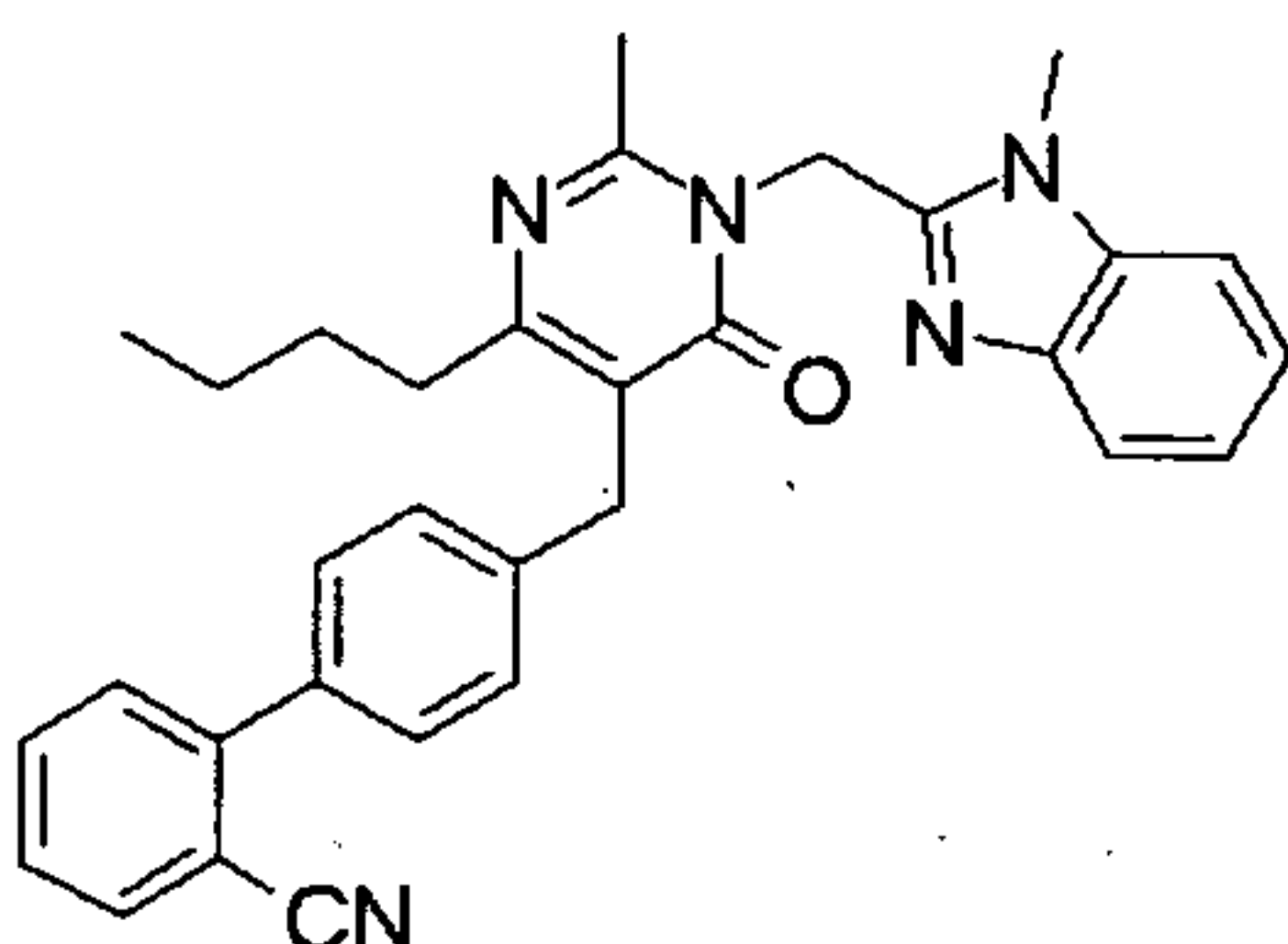


75a) 4'-{[1-(1H-benzimidazol-2-ylmethyl)-4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), cesium carbonate (1.82 g), tert-butyl 2-(chloromethyl)-1H-benzimidazole-1-carboxylate (1.12 g), potassium iodide (0.046 g) and N,N-dimethylacetamide (10 mL) was stirred at 130°C for 3 days. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.24 g, 18%).

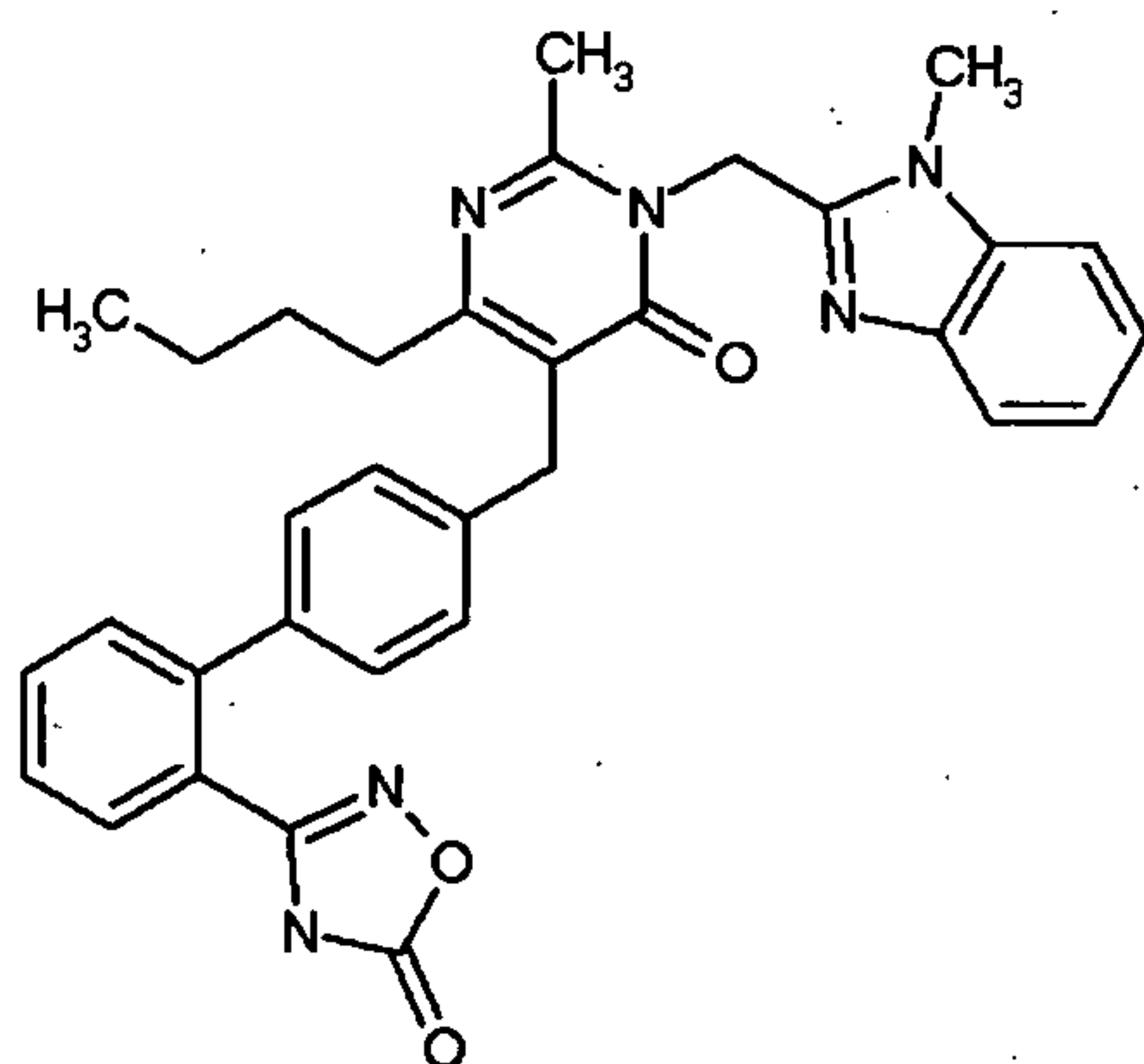
¹H NMR (300 MHz, CDCl₃) δ 0.88 (3H, t, J = 7.3), 1.26-1.41 (2H, m), 1.47-1.61 (2H, m), 2.52-2.64 (2H, m), 2.83 (3H, s), 4.02

(2H, s), 5.40 (2H, s), 7.20-7.30 (3H, m), 7.34 (1H, d, J = 8.3), 7.38-7.52 (5H, m), 7.57-7.68 (1H, m), 7.71-7.80 (2H, m)



75b) 4'-([4-butyl-2-methyl-1-[(1-methyl-1H-benzimidazol-2-yl)methyl]-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile

A mixture of 4'-{[1-(1H-benzimidazol-2-ylmethyl)-4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (0.24 g), iodomethane (0.036 mL), potassium carbonate (0.14 g) and N,N-dimethylformamide (5 mL) was stirred at room temperature for 3 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.25 g, 100%).
¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.3), 1.31-1.44 (2H, m), 1.51-1.65 (2H, m), 2.54-2.65 (2H, m), 2.85 (3H, s), 3.87 (3H, s), 3.95 (2H, s), 5.51 (2H, s), 7.20-7.49 (9H, m), 7.57-7.66 (1H, m), 7.68-7.76 (2H, m)

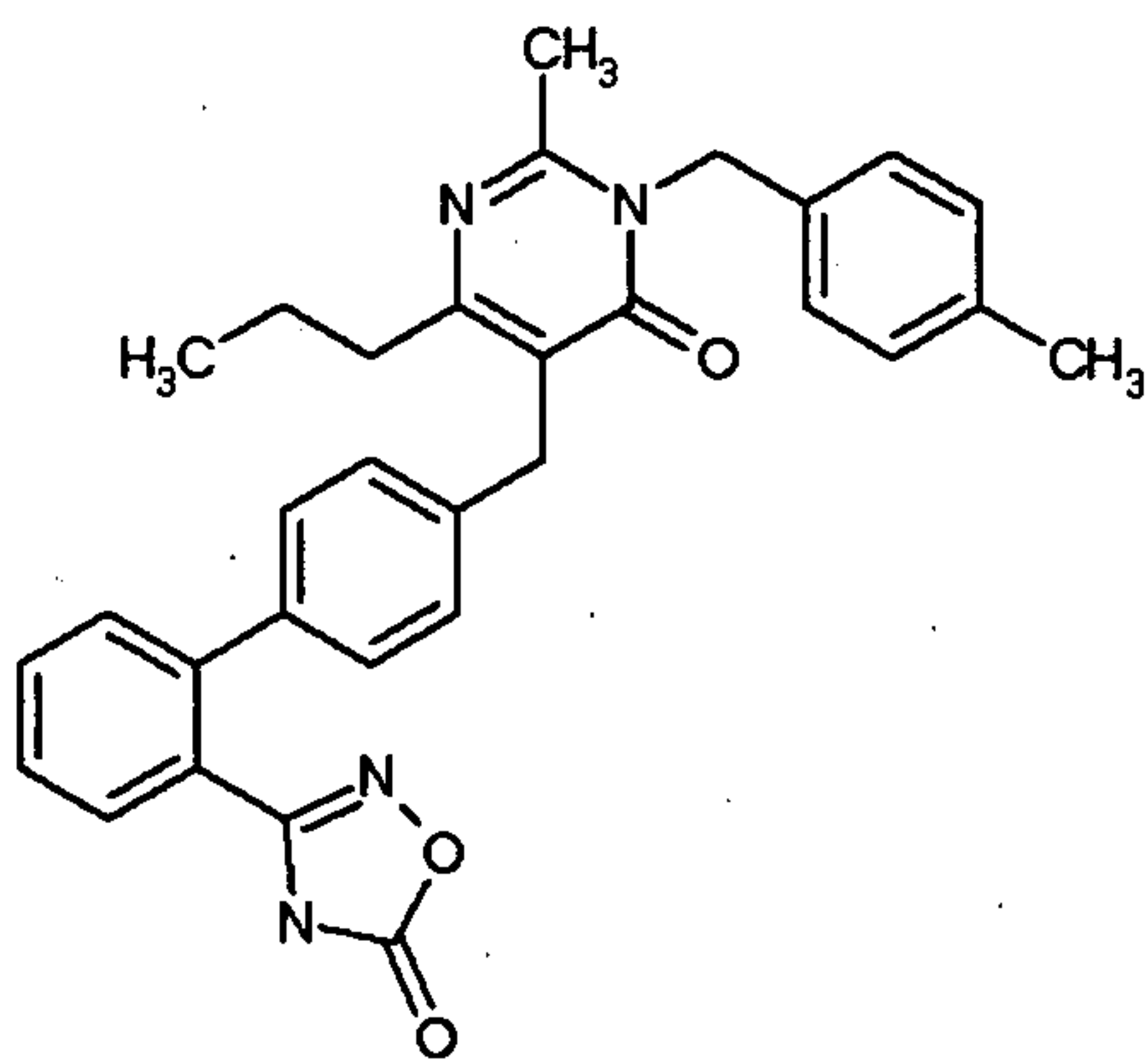


75c) 6-butyl-2-methyl-3-[(1-methyl-1H-benzimidazol-2-yl)methyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (0.51 g), sodium hydrogen carbonate (0.82 g) and dimethyl sulfoxide (10 mL) was stirred at 40°C for 30 min, 4'-({4-butyl-2-methyl-1-[(1-methyl-1H-benzimidazol-2-yl)methyl]-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)biphenyl-2-carbonitrile (0.25 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.096 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.08 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.18 g, 65%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.86 (3H, t, J = 7.2), 1.25-1.39 (2H, m), 1.41-1.56 (2H, m), 2.52-2.56 (2H, m), 2.59 (3H, s), 3.84 (2H, s), 3.90 (3H, s), 5.51 (2H, s), 7.12-7.29 (6H, m), 7.43-7.59 (4H, m), 7.61-7.71 (2H, m), 12.37 (1H, br)

Example 76



2-methyl-3-(4-methylbenzyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-

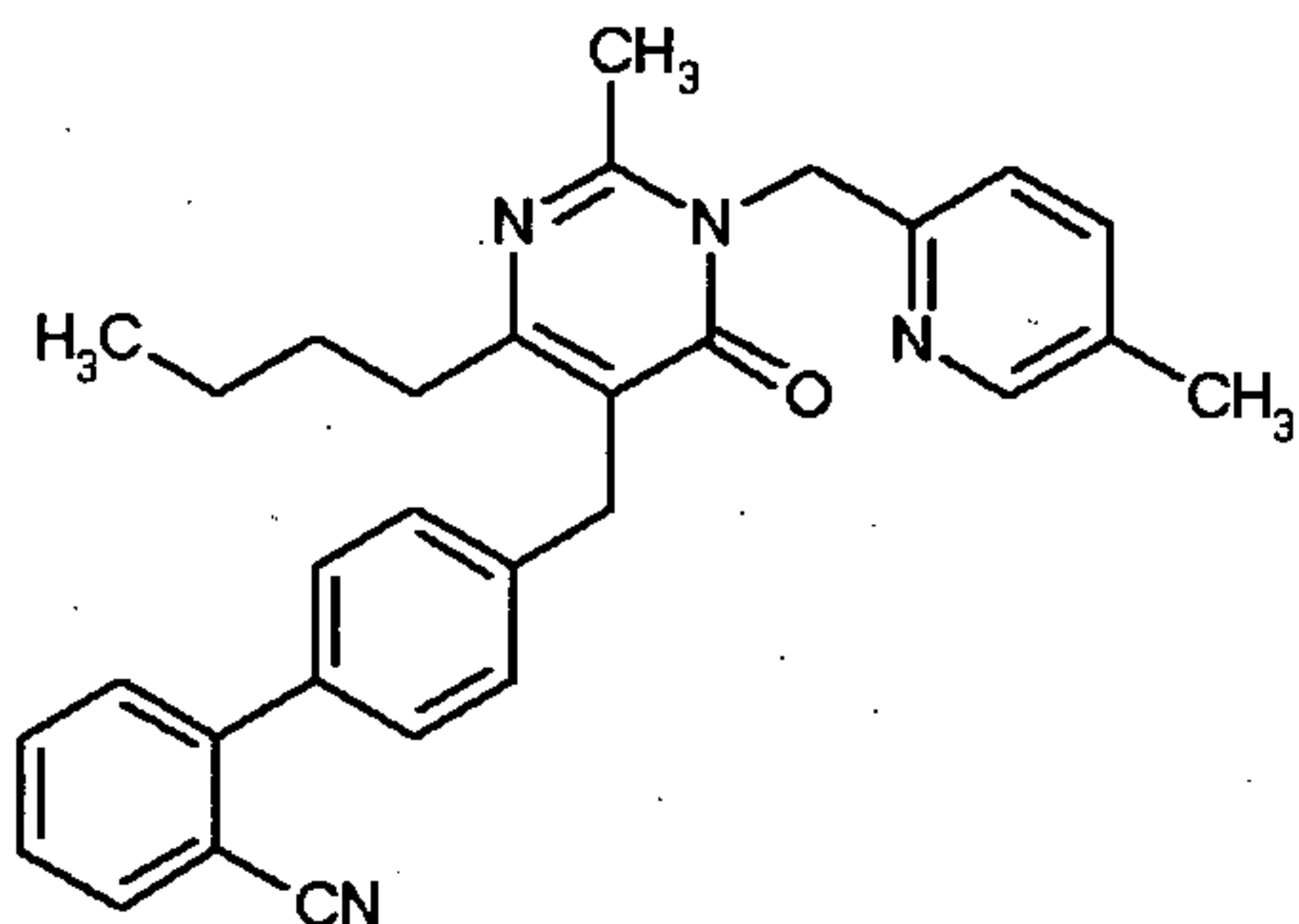
one

A mixture of 4'-[(2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (4 g), sodium hydride (0.7 g) and N,N-dimethylformamide (40 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)-4-methylbenzene (2.57 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (15 mL), and added to a mixture of hydroxylammonium chloride (7.78 g), sodium hydrogen carbonate (12.5 g) and dimethyl sulfoxide (30 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (40 mL), N,N'-carbonyldiimidazole (1.45 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.23 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (2.42 g, 64%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (3H, t, J = 7.4), 1.41-1.60 (2H, m), 2.27 (3H, s), 2.38 (3H, s), 2.44-2.48 (2H, m), 3.91 (2H, s), 5.24 (2H, s), 7.06 (2H, d, J = 8.1), 7.17 (2H, d, J = 7.9), 7.20-7.30 (4H, m), 7.53 (2H, dd, J = 13.4, 7.2), 7.59-7.75 (2H, m), 12.38 (1H, s)

Example 77

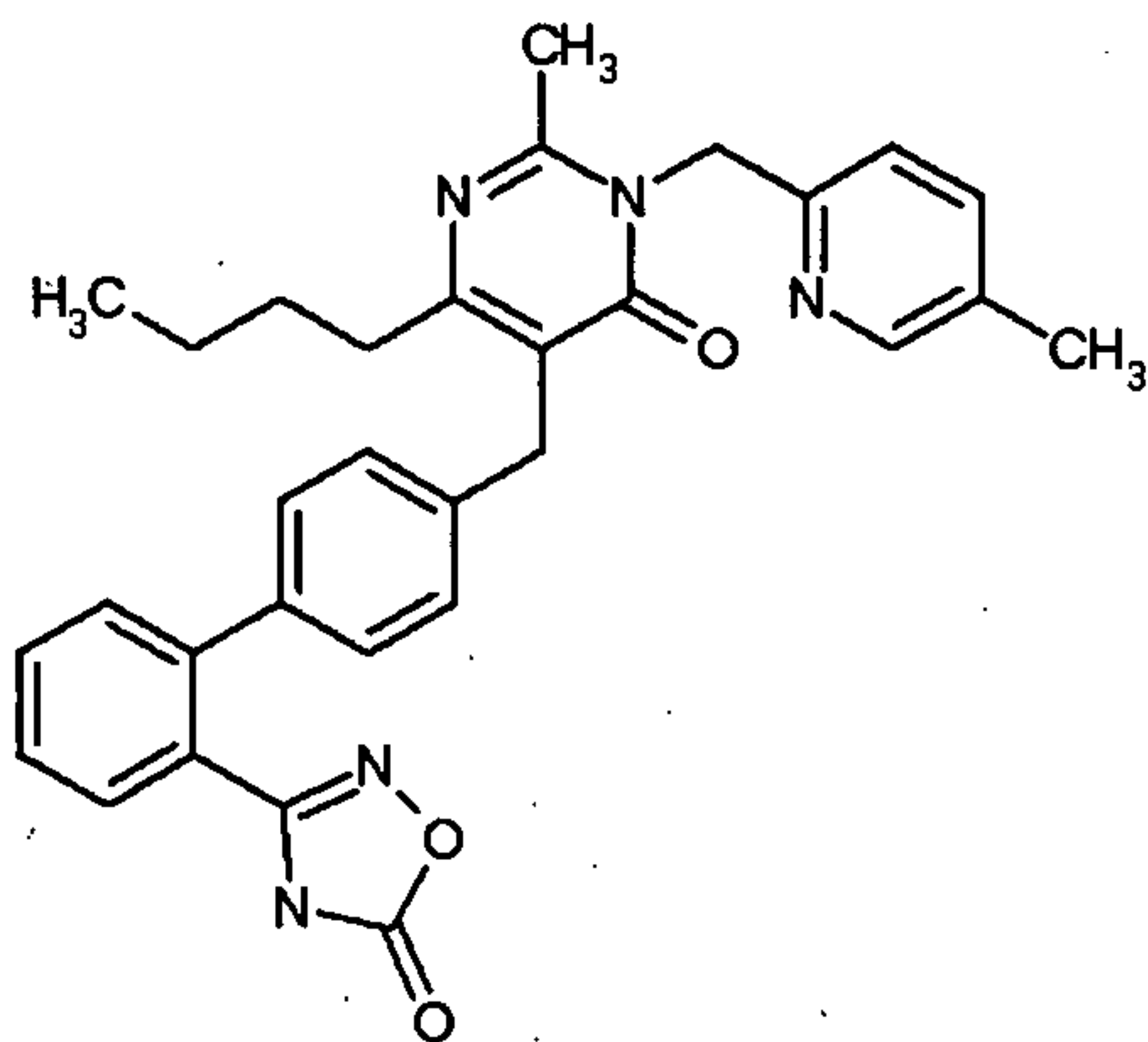
6-butyl-2-methyl-3-[(5-methylpyridin-2-yl)methyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one



5 77a) 4'-[(4-butyl-2-methyl-1-[(5-methylpyridin-2-yl)methyl]-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine
10 (1.56 mL), (5-methylpyridin-2-yl)methanol (0.5 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated
15 under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.59 g, 47%).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.4), 1.29-1.46 (2H, m), 1.49-1.64 (2H, m), 2.31 (3H, s), 2.55-2.68 (5H, m), 3.98
20 (2H, s), 5.33 (2H, s), 7.16 (1H, d, J = 8.0), 7.33-7.53 (7H, m), 7.57-7.67 (1H, m), 7.74 (1H, d, J = 8.0), 8.35 (1H, d, J = 1.9)



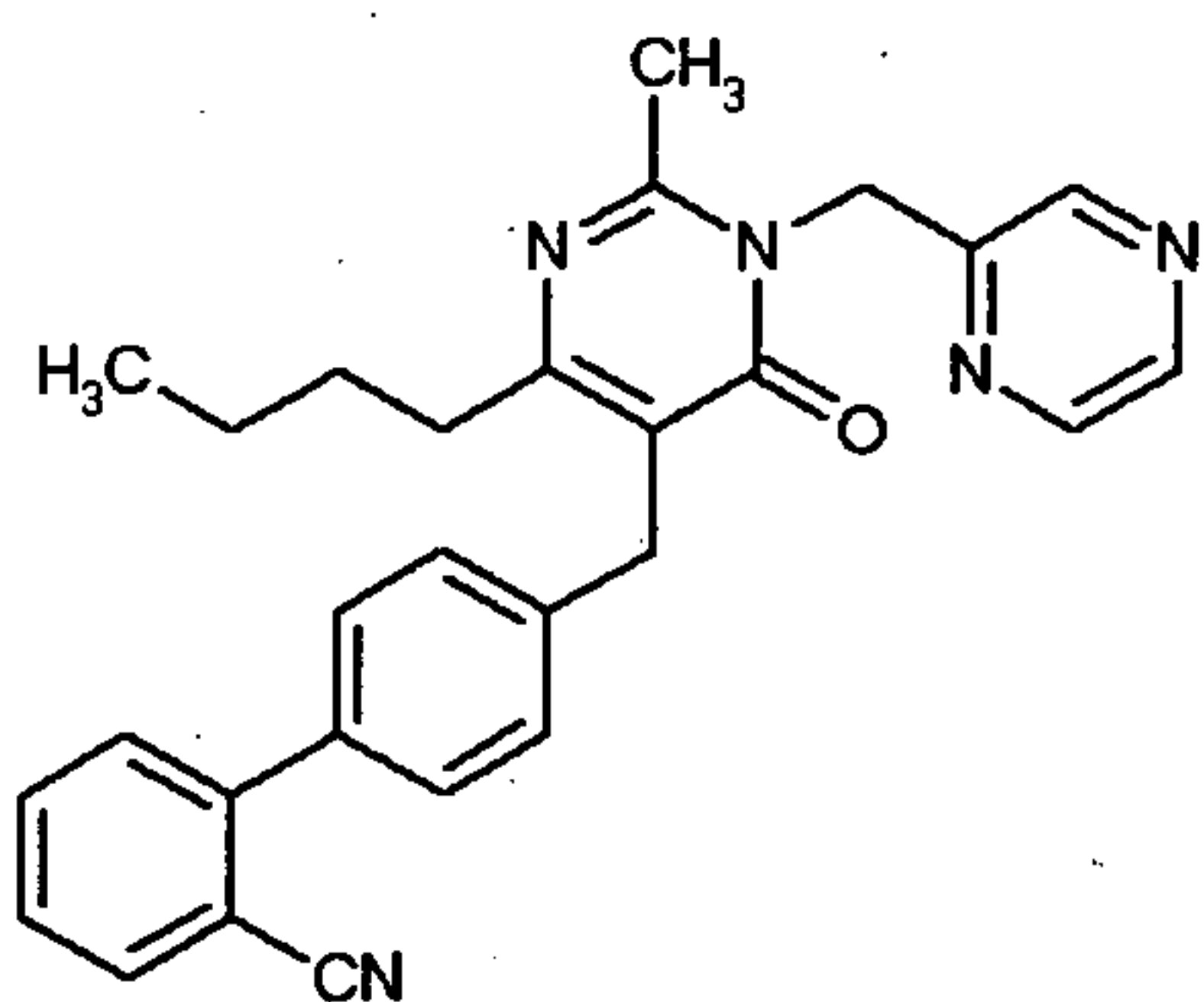
77b) 6-butyl-2-methyl-3-[(5-methylpyridin-2-yl)methyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.3 g), sodium
5 hydrogen carbonate (2.2 g) and dimethyl sulfoxide (10 mL) was
stirred at 40°C for 30 min, 4'-({4-butyl-2-methyl-1-[(5-
methylpyridin-2-yl)methyl]-6-oxo-1,6-dihydropyrimidin-5-
yl)methyl)biphenyl-2-carbonitrile (0.59 g) was added, and the
mixture was stirred at 90°C for 16 hr. The reaction mixture
10 was diluted with ethyl acetate, washed with water and then
with saturated brine, and dried over anhydrous magnesium
sulfate. The solvent was evaporated under reduced pressure.
The residue was dissolved in tetrahydrofuran (20 mL), N,N'-
carbonyldiimidazole (0.25 g) and then 1,8-
15 diazabicyclo[5.4.0]undec-7-ene (0.21 mL) were added, and the
mixture was stirred at room temperature for 2 hr. The reaction
mixture was adjusted to pH 5 with water and 1 M hydrochloric
acid, and extracted with ethyl acetate. The ethyl acetate
layer was washed with saturated brine, and dried over
20 anhydrous magnesium sulfate. The solvent was evaporated under
reduced pressure and the residue was purified by silica gel
column chromatography to give the title compound as colorless
crystals (0.42 g, 63%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (3H, t, J = 7.3), 1.23-1.37
25 (2H, m), 1.39-1.53 (2H, m), 2.27 (3H, s), 2.44-2.51 (5H, m),
3.84 (2H, s), 5.29 (2H, s), 7.15-7.26 (5H, m), 7.45-7.74 (5H,
m), 8.32 (1H, d, J = 0.8), 12.38 (1H, s)

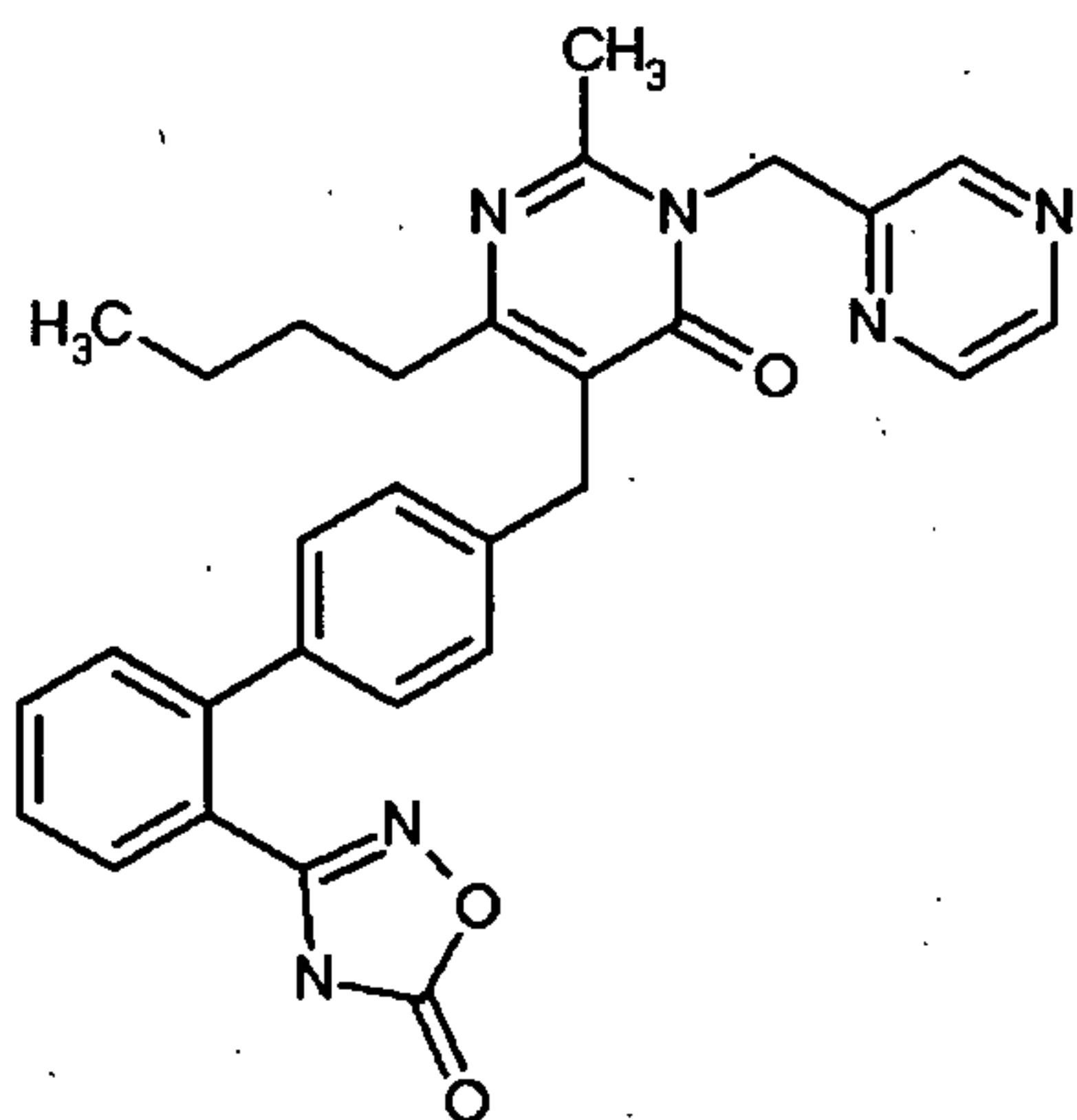
Example 78

6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(pyrazin-2-ylmethyl)pyrimidin-
30 4(3H)-one



78a) 4'-{[4-butyl-2-methyl-6-oxo-1-(pyrazin-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g),
 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine (1.56 mL), pyrazin-2-ylmethanol (0.46 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with water and
 10 then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.87 g, 69%).
¹H NMR (300 MHz, CDCl₃) δ 0.87-0.98 (3H, m), 1.35-1.50 (4H, m),
 15 2.55-2.68 (5H, m), 3.96 (2H, s), 5.37 (2H, s), 7.29-7.53 (6H, m), 7.56-7.65 (1H, m), 7.74 (1H, d, J = 7.6), 8.53 (2H, s), 8.71 (1H, s)



78b) 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(pyrazin-2-ylmethyl)pyrimidin-4(3H)-one

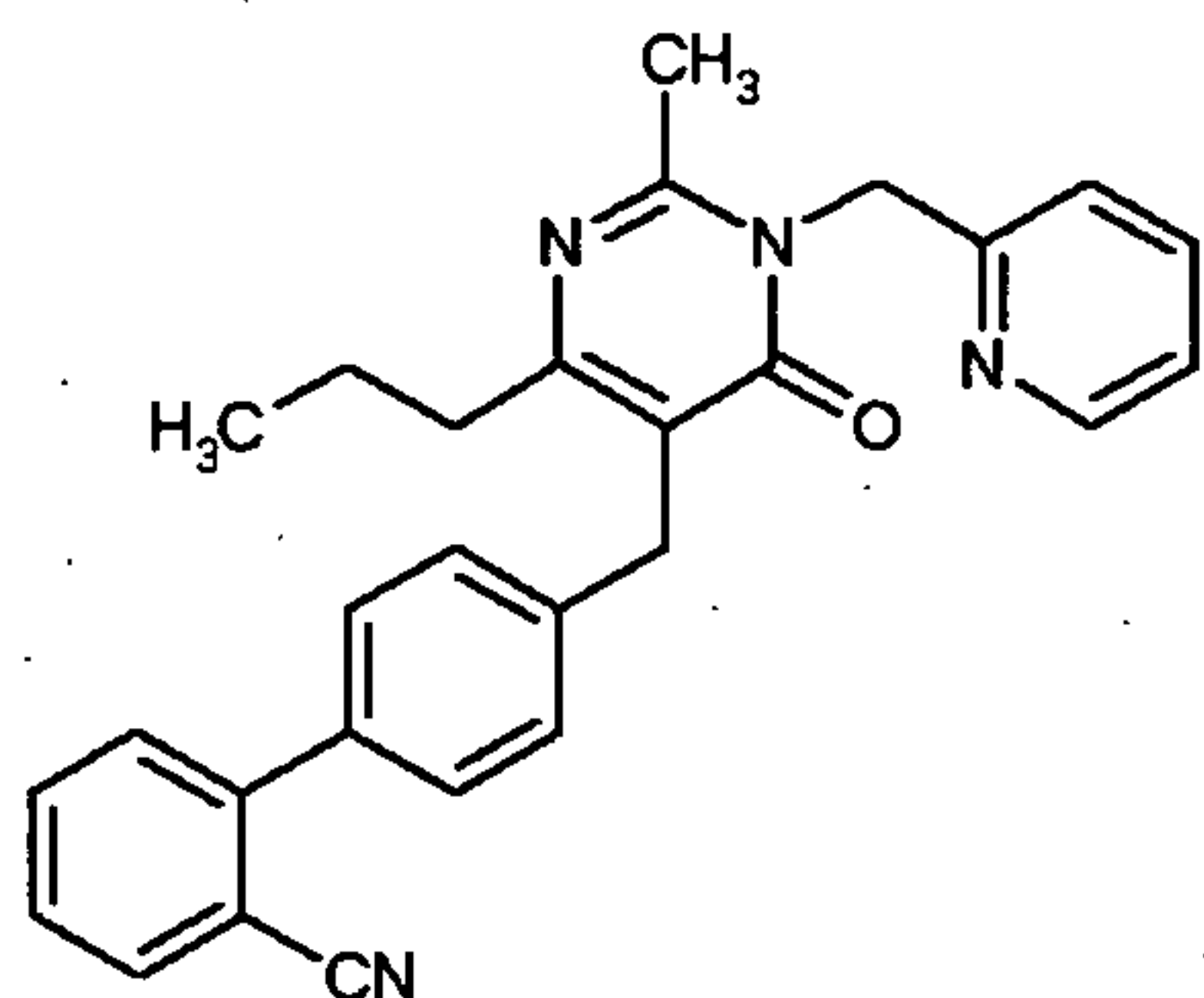
A mixture of hydroxylammonium chloride (2.1 g), sodium hydrogen carbonate (3.2 g) and dimethyl sulfoxide (15 mL) was

stirred at 40°C for 30 min, 4'-{[4-butyl-2-methyl-6-oxo-1-(pyrazin-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.87 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.38 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.32 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.4 g, 38%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (3H, t, J = 7.0), 1.22-1.36 (2H, m), 1.38-1.53 (2H, m), 2.42-2.58 (5H, m), 3.83 (2H, s), 5.40 (2H, s), 7.17-7.23 (4H, m), 7.43-7.59 (2H, m), 7.61-7.71 (2H, m), 8.56 (2H, s), 8.76 (1H, s), 12.02 (1H, br)

Example 79

2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one

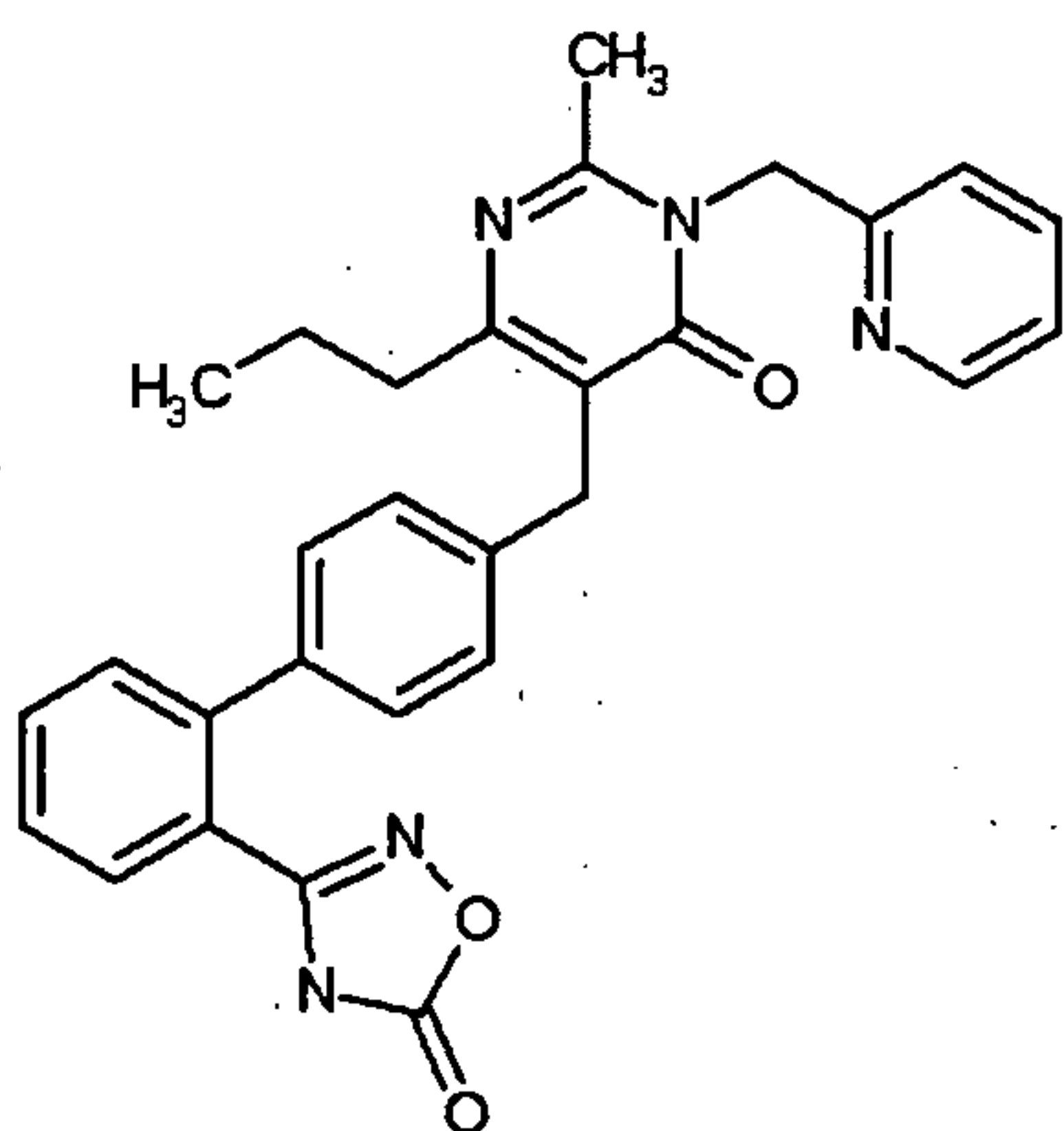


79a) 4'-{[2-methyl-6-oxo-4-propyl-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(2-methyl-6-oxo-4-propyl-1,6-

dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (7 g),
 1,1'-(azodicarbonyl)dipiperidine (9.9 g), tributylphosphine
 (12.2 mL), pyridin-2-ylmethanol (2.8 mL) and tetrahydrofuran
 (350 mL) was stirred at room temperature for 4 hr. The
 5 reaction mixture was concentrated, and the residue was diluted
 with ethyl acetate, washed with water and then with saturated
 brine, and dried over anhydrous magnesium sulfate. The solvent
 was evaporated under reduced pressure and the residue was
 purified by silica gel column chromatography to give the title
 10 compound as colorless crystals (2.6 g, 31%).

¹H NMR (300 MHz, CDCl₃) δ 0.96 (3H, t, J = 7.3), 1.56-1.72 (2H, m), 2.54-2.64 (5H, m), 3.99 (2H, s), 5.38 (2H, s), 7.12-7.27 (2H, m), 7.32-7.52 (6H, m), 7.56-7.71 (2H, m), 7.74 (1H, dd, J = 7.7, 1.3), 8.54 (1H, dd, J = 4.0, 0.9)



15

79b) 2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propyl-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one

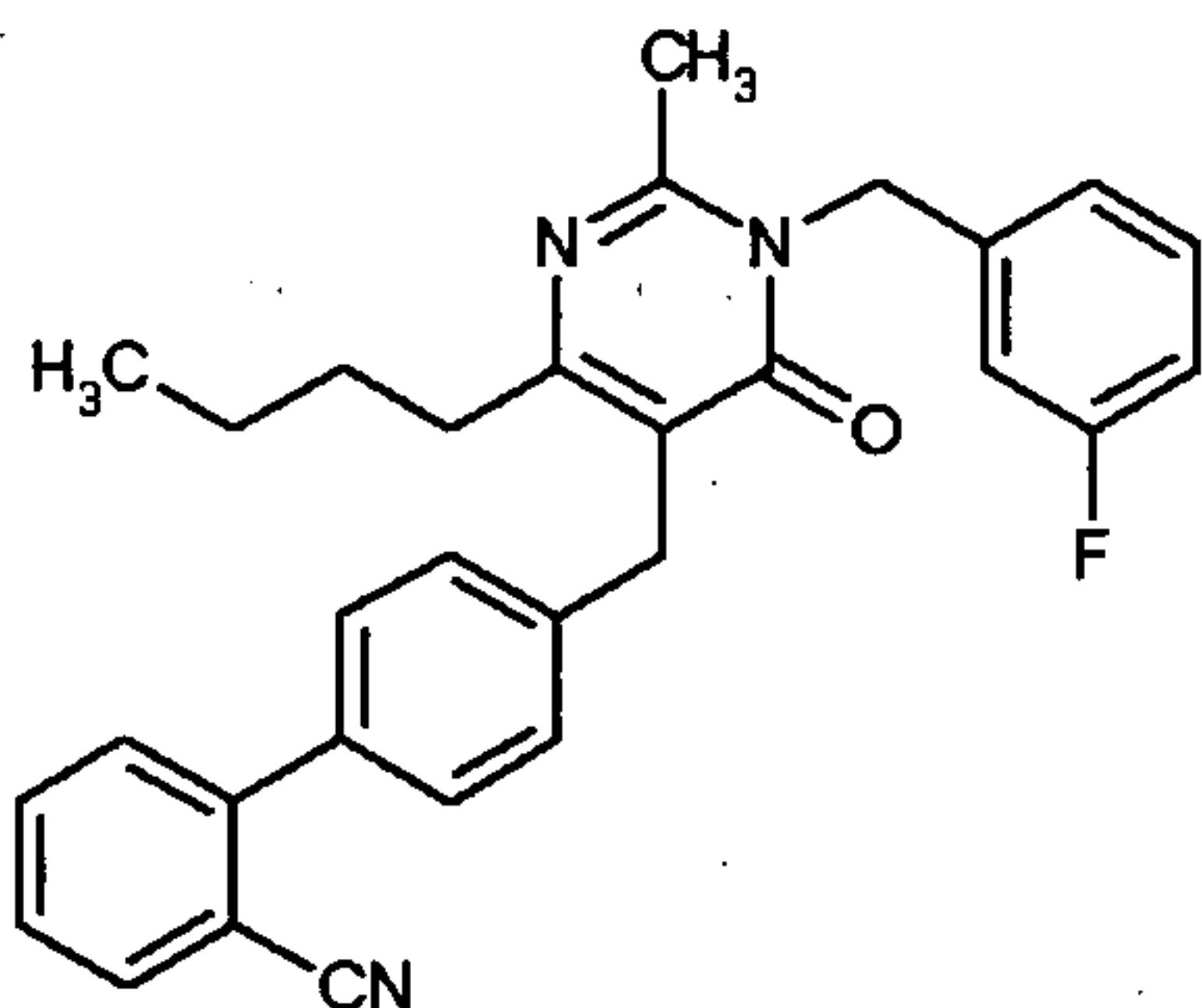
A mixture of hydroxylammonium chloride (6.23 g), sodium
 20 hydrogen carbonate (10.1 g) and dimethyl sulfoxide (30 mL) was
 stirred at 40°C for 30 min, 4'-{[2-methyl-6-oxo-4-propyl-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (2.6 g) was added, and the
 mixture was stirred at 90°C for 16 hr. The reaction mixture
 25 was diluted with ethyl acetate, washed with water and then
 with saturated brine, and dried over anhydrous magnesium
 sulfate. The solvent was evaporated under reduced pressure.
 The residue was dissolved in tetrahydrofuran (40 mL), N,N'-

carbonyldiimidazole (1.16 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.99 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (2.07 g, 70%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.86 (3H, t, J = 7.3), 1.42-1.60 (2H, m), 2.43-2.49 (5H, m), 3.85 (2H, s), 5.34 (2H, s), 7.16-7.25 (4H, m), 7.27-7.38 (2H, m), 7.46-7.57 (2H, m), 7.62-7.73 (2H, m), 7.76-7.85 (1H, m), 8.46-8.51 (1H, m), 12.37 (1H, s)

Example 80

6-butyl-3-(3-fluorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

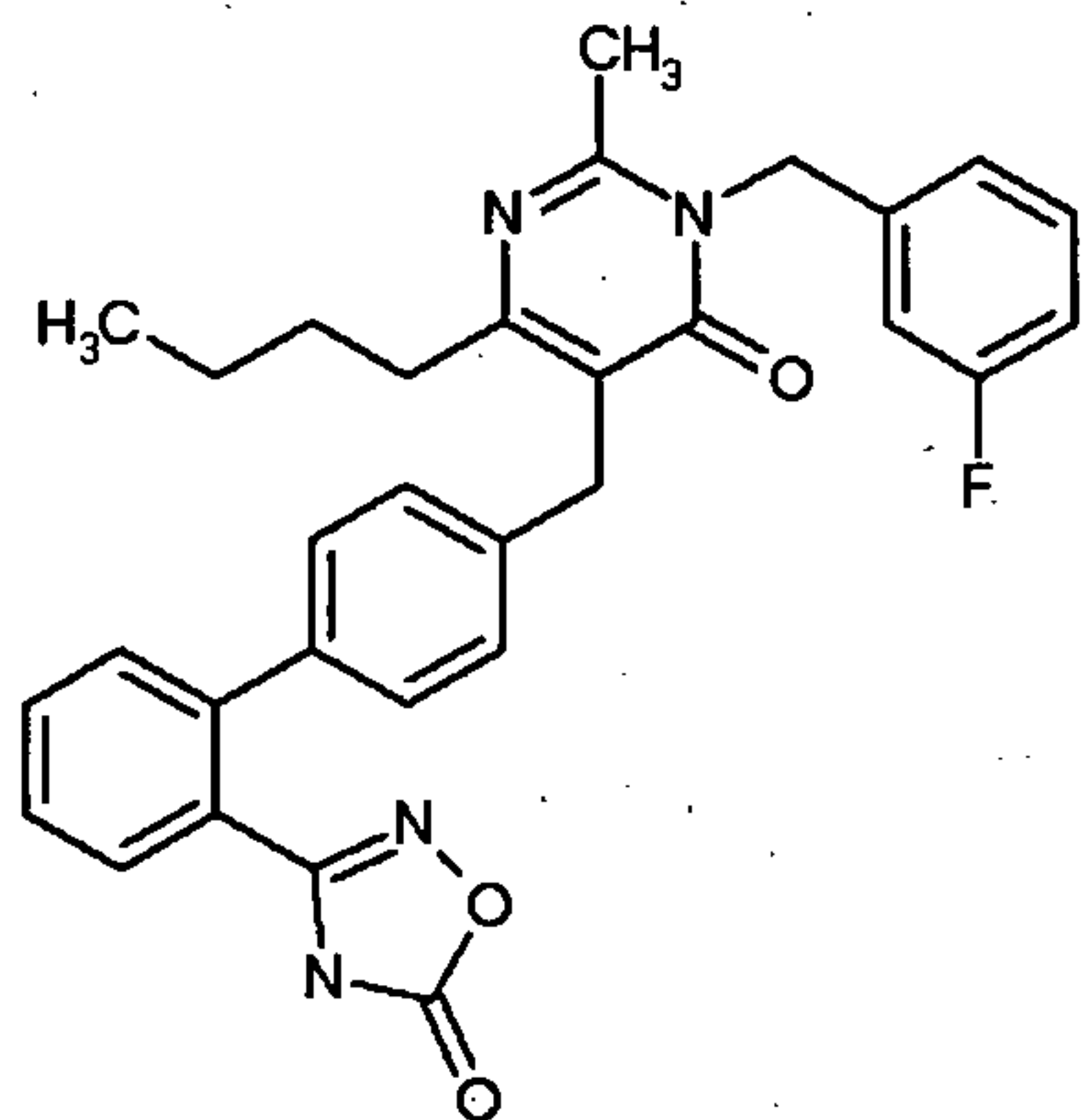


80a) 4'-{[4-butyl-1-(3-fluorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-{[4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)-3-fluorobenzene (0.41 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified

by silica gel column chromatography to give the title compound as a colorless solid (0.82 g, 63%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.2), 1.30-1.46 (2H, m), 1.52-1.66 (2H, m), 2.44 (3H, s), 2.54-2.67 (2H, m), 4.01 (2H, s), 5.28 (2H, s), 6.85-7.02 (3H, m), 7.24-7.51 (7H, m), 7.62 (1H, t, J = 7.8), 7.74 (1H, d, J = 8.0)



80b) 6-butyl-3-(3-fluorobenzyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)pyrimidin-
 10 4(3H)-one

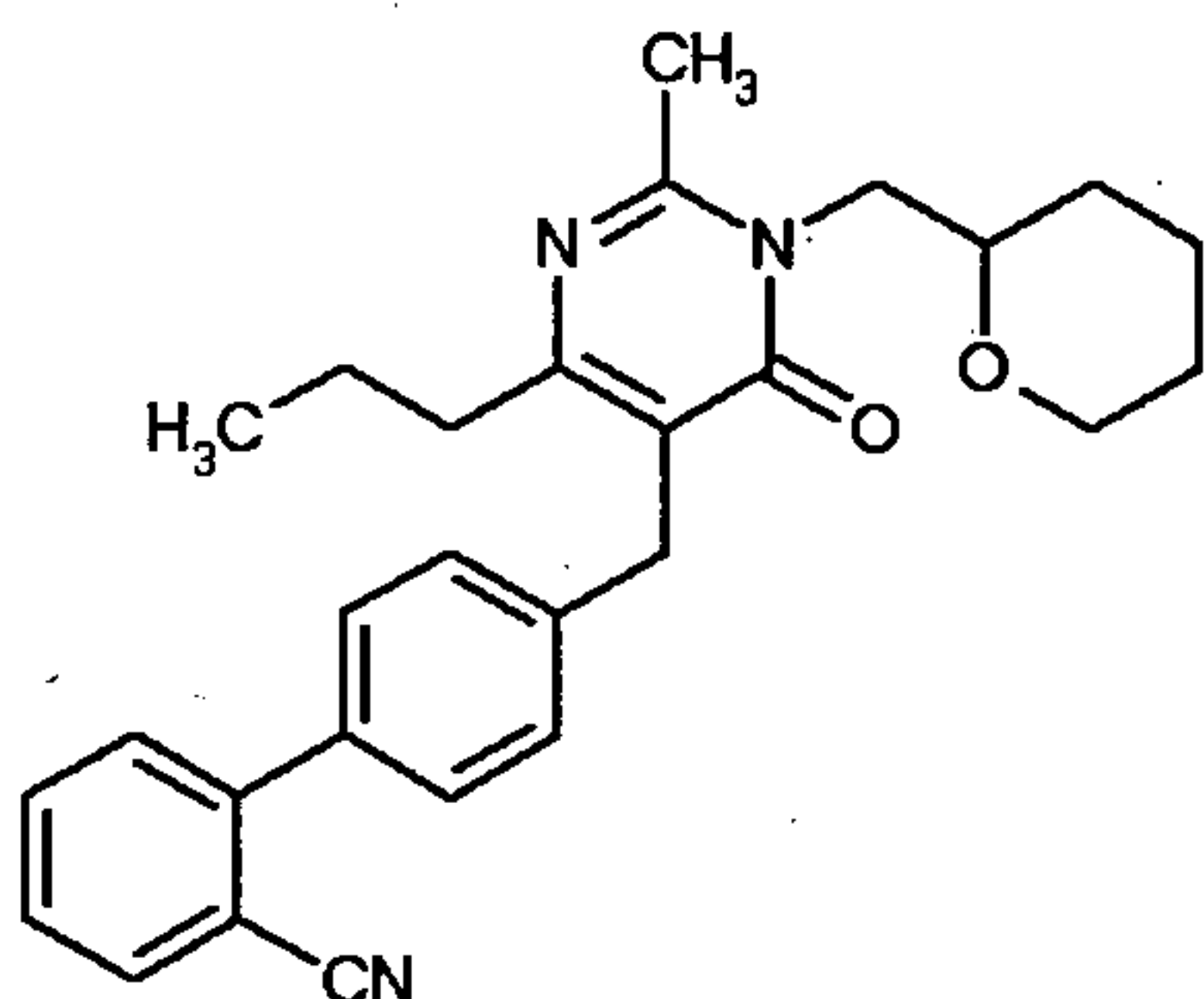
A mixture of hydroxylammonium chloride (1.83 g), sodium hydrogen carbonate (2.96 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-1-(3-fluorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.86 g) was added, and the mixture was stirred
 15 at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was
 20 dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.34 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.29 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate
 25 solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a

colorless solid (0.64 g, 69%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.3), 1.22-1.35 (2H, m), 1.38-1.53 (2H, m), 2.39 (3H, s), 2.46-2.53 (2H, m), 3.91 (2H, s), 5.29 (2H, s), 6.94-7.07 (2H, m), 7.08-7.18 (1H, m), 7.19-7.29 (4H, m), 7.36-7.46 (1H, m), 7.46-7.58 (2H, m), 7.62-7.72 (2H, m), 12.39 (1H, s)

Example 81

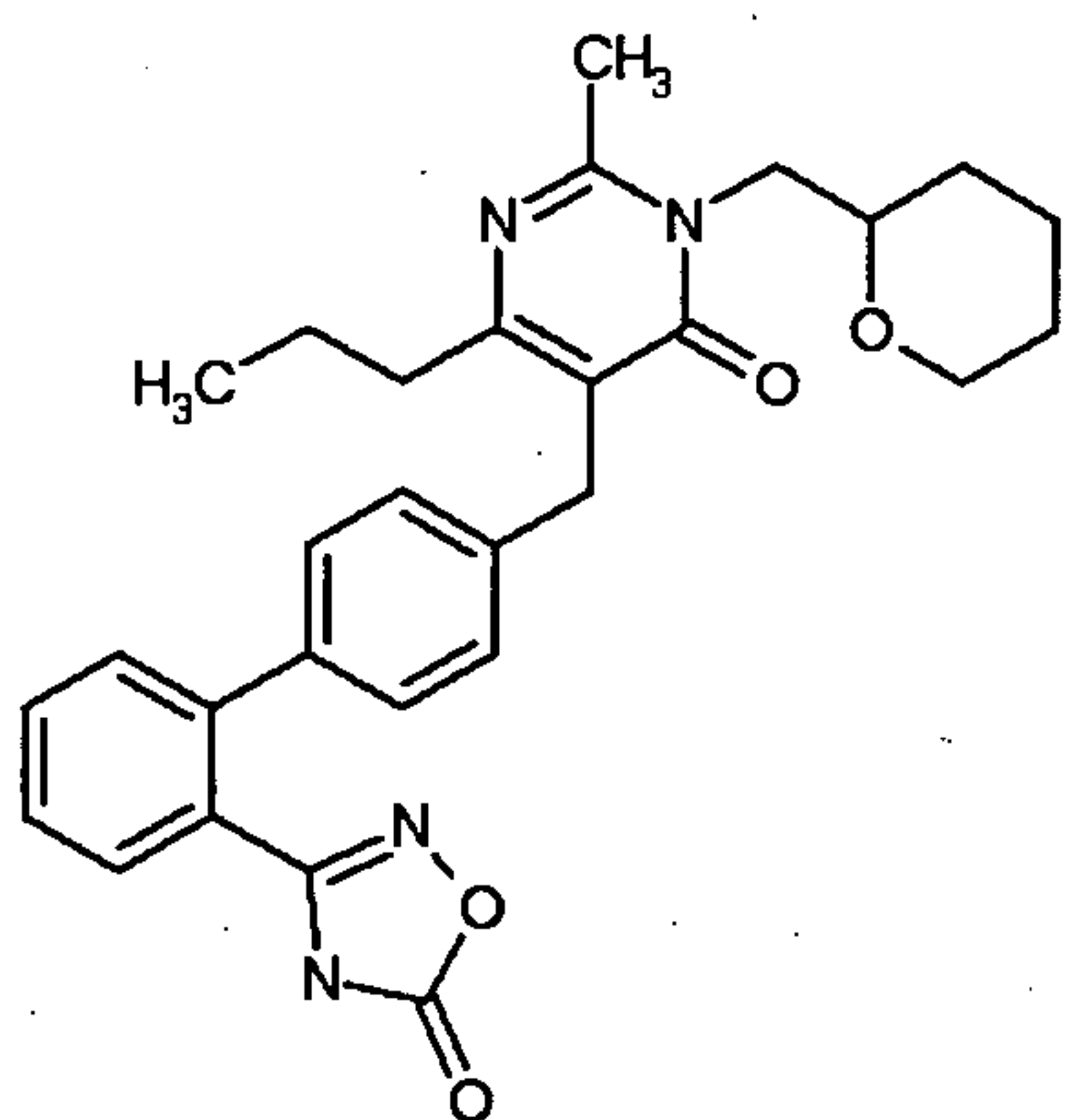
2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one



81a) 4'-([2-methyl-6-oxo-4-propyl-1-(tetrahydro-2H-pyran-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl)biphenyl-2-carbonitrile

A mixture of 4'-[(2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 2-(bromomethyl)tetrahydro-2H-pyran (0.45 mL), potassium carbonate (0.60 g) and N,N-dimethylformamide (10 mL) was stirred at 90°C for 3 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.64 g, 48%).

¹H NMR (300 MHz, CDCl₃) δ 0.96 (3H, t, J = 7.4), 1.27-1.37 (1H, m), 1.43-1.68 (5H, m), 1.69-1.79 (1H, m), 1.80-1.90 (1H, m), 2.53-2.64 (5H, m), 3.24-3.36 (1H, m), 3.62-3.75 (2H, m), 3.86-4.04 (3H, m), 4.19-4.31 (1H, m), 7.32-7.51 (6H, m), 7.57-7.65 (1H, m), 7.74 (1H, d, J = 7.6)



81b) 2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one

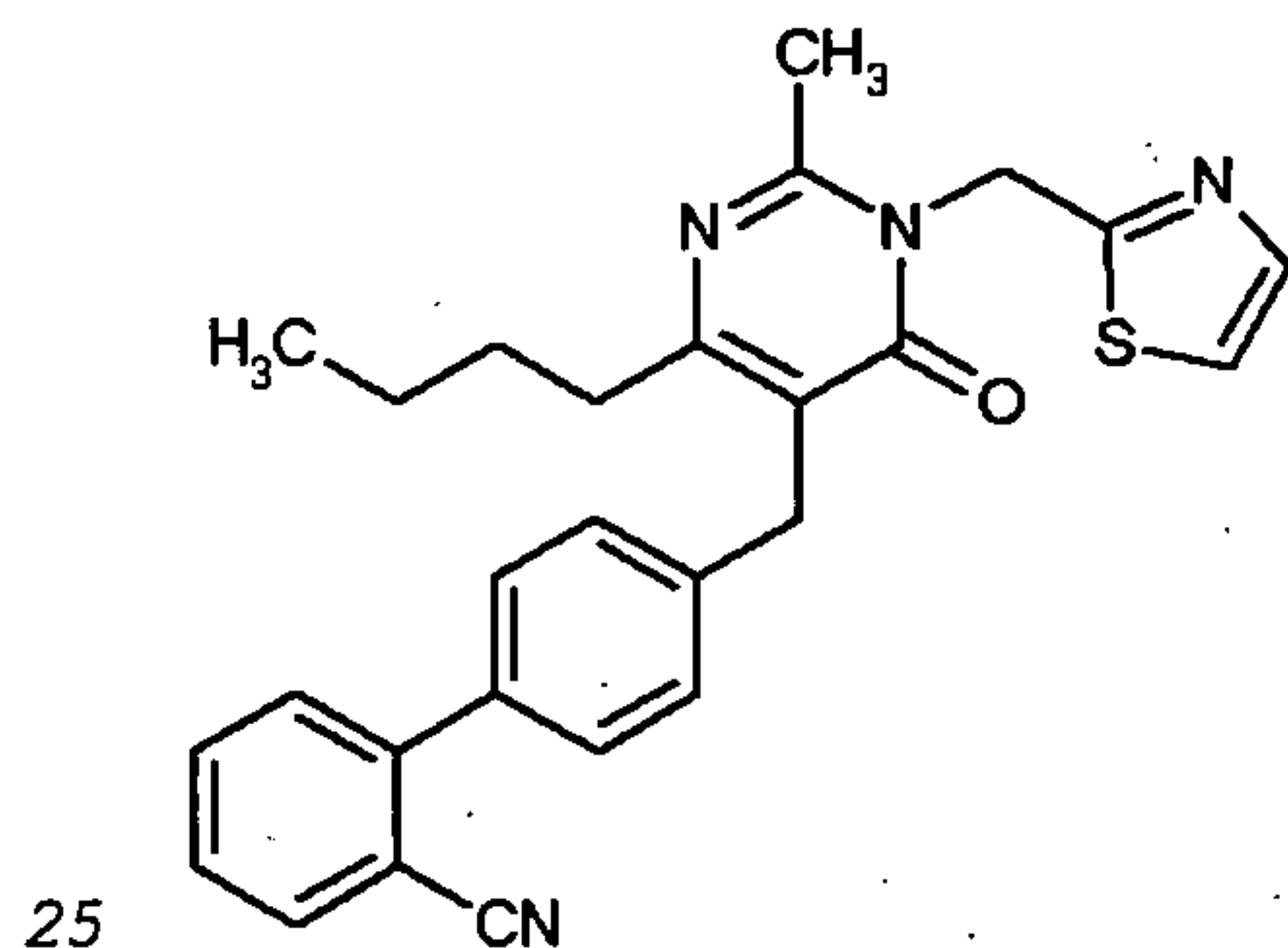
5 A mixture of hydroxylammonium chloride (1.47 g), sodium hydrogen carbonate (2.37 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[2-methyl-6-oxo-4-propyl-1-(tetrahydro-2H-pyran-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.64 g) was added, and the
 10 mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-
 15 carbonyldiimidazole (0.27 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.23 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with
 20 saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.48 g, 68%).
¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (3H, t, J = 7.3), 1.22-1.35 (1H, m), 1.37-1.55 (5H, m), 1.63 (1H, d, J = 13.9), 1.78 (1H, br), 2.40-2.55 (5H, m), 3.17-3.28 (1H, m), 3.56 (1H, t, J = 8.3), 3.74-3.92 (4H, m), 4.04-4.15 (1H, m), 7.16-7.28 (4H, m), 7.44-7.57 (2H, m), 7.61-7.73 (2H, m), 12.36 (1H, s)

2-Methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

- 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one sodium salt
- 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one potassium salt
- 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one 0.5 calcium salt
- 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one hydrochloride
- 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one hydrobromide

Example 82

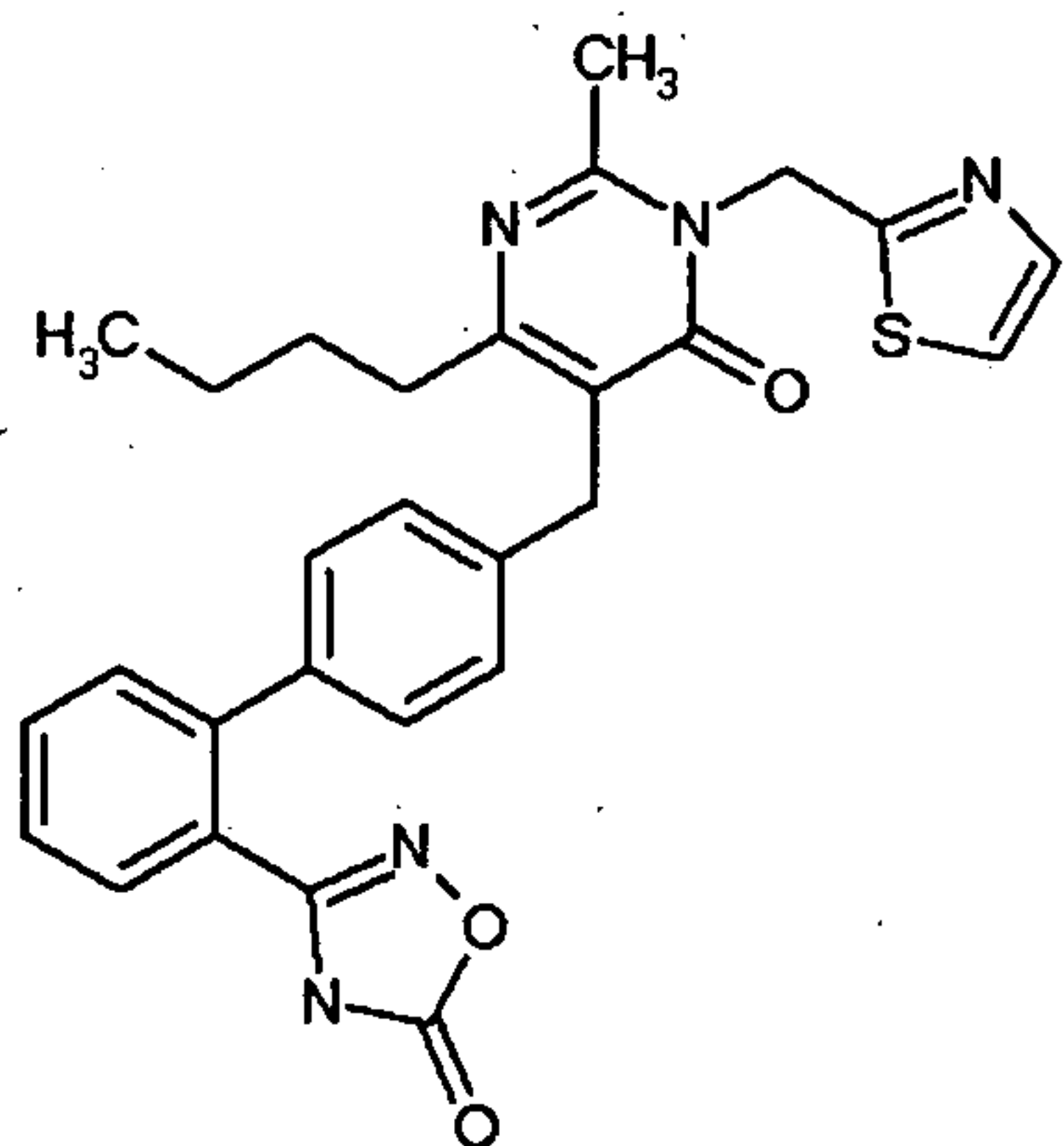
6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(1,3-thiazol-2-ylmethyl)pyrimidin-4(3H)-one



82a) 4'-{[4-butyl-2-methyl-6-oxo-1-(1,3-thiazol-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.41 g), tributylphosphine

(1.74 mL), 1,3-thiazol-2-ylmethanol (0.48 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was concentrated. The residue was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.96 g, 75%).
¹H NMR (300 MHz, CDCl₃) δ 0.89 (3H, t, J = 7.2), 1.32-1.48 (4H, m), 2.53-2.63 (2H, m), 2.70 (3H, s), 3.99 (2H, s), 5.52 (2H, s), 7.31-7.50 (7H, m), 7.57-7.67 (1H, m), 7.70-7.78 (2H, m)



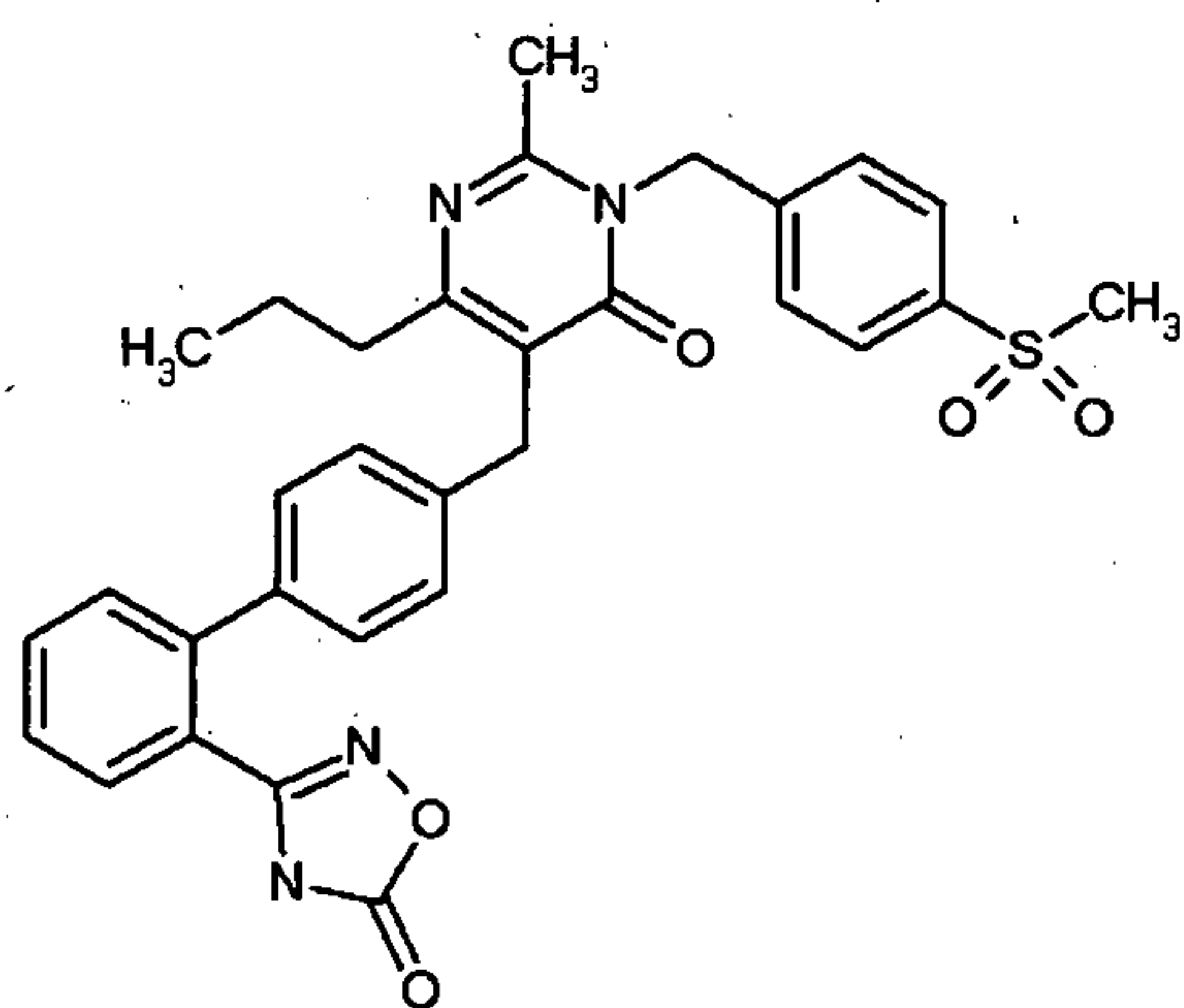
82b) 6-butyl-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-3-(1,3-thiazol-2-ylmethyl)pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (2.2 g), sodium hydrogen carbonate (3.5 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-{[4-butyl-2-methyl-6-oxo-1-(1,3-thiazol-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (0.96 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.41 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.35 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1

M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica
 5 gel column chromatography to give the title compound as colorless crystals (0.47 g, 44%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3H, t, J = 7.2), 1.21-1.35 (2H, m), 1.36-1.51 (2H, m), 2.43-2.49 (2H, m), 2.58 (3H, s), 3.87 (2H, s), 5.52 (2H, s), 7.16-7.28 (4H, m), 7.46-7.58 (2H,
 10 m), 7.61-7.73 (3H, m), 7.77 (1H, d, J = 3.2), 12.38 (1H, s)

Example 83



2-methyl-3-[4-(methylsulfonyl)benzyl]-5-{[2'-(5-oxo-4,5-
dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
 15 propylpyrimidin-4(3H)-one

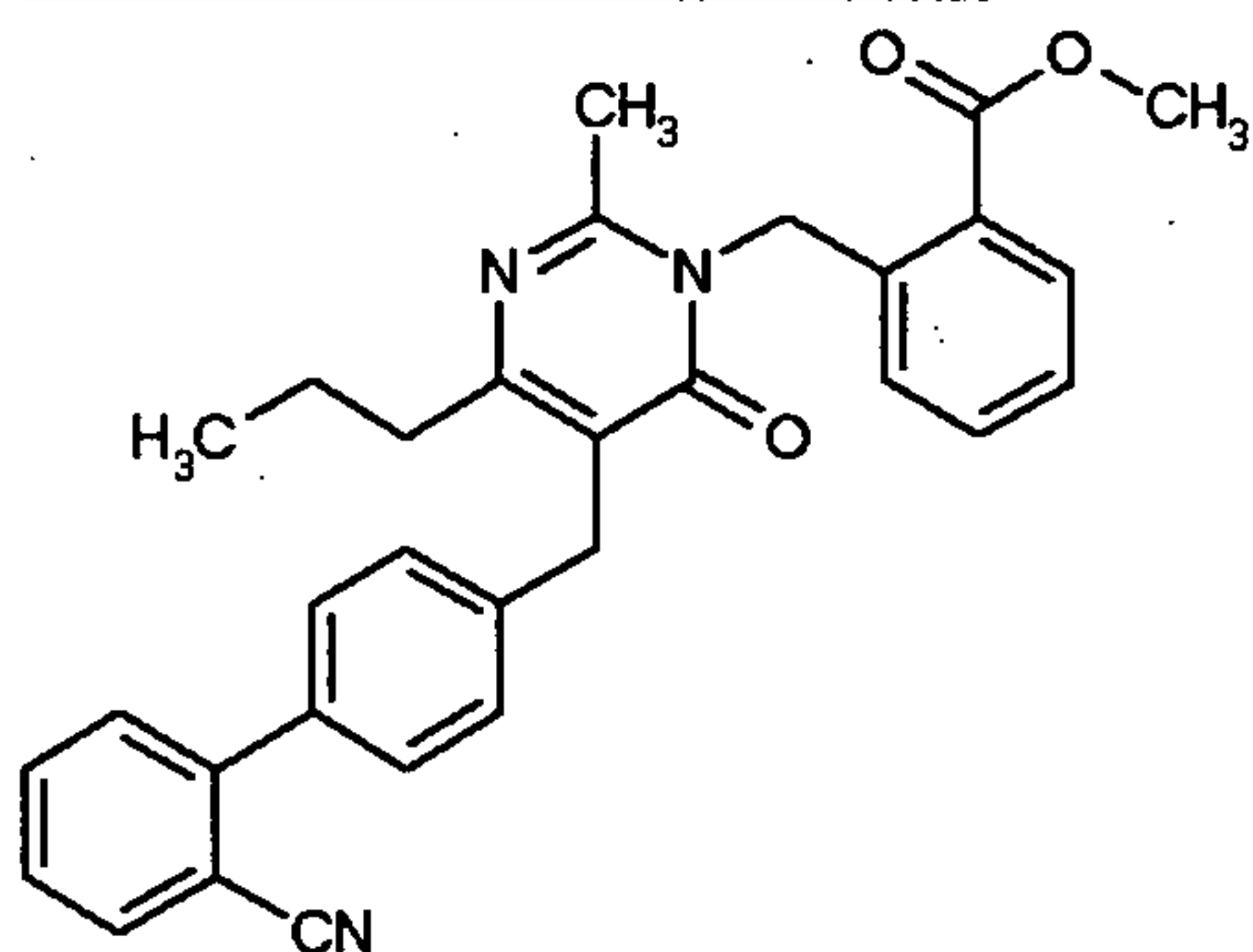
A mixture of 4'-[(2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.48 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(bromomethyl)-4-(
 20 (methylsulfonyl)benzene (0.87 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent
 25 was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.51 g), sodium hydrogen carbonate (0.82 g) and

dimethyl sulfoxide (10 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.096 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.081 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.19 g, 11%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.3), 1.46-1.61 (2H, m), 2.48 (3H, s), 2.59-2.69 (2H, m), 3.19 (3H, s), 4.03 (2H, s), 5.52 (2H, s), 7.13-7.26 (4H, m), 7.46-7.60 (4H, m), 7.62-7.72 (2H, m), 7.88 (2H, d, J = 8.5), 12.38 (1H, s)

20 Example 84

methyl 2-[(2-methyl-6-oxo-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-4-propylpyrimidin-1(6H)-yl)methyl]benzoate

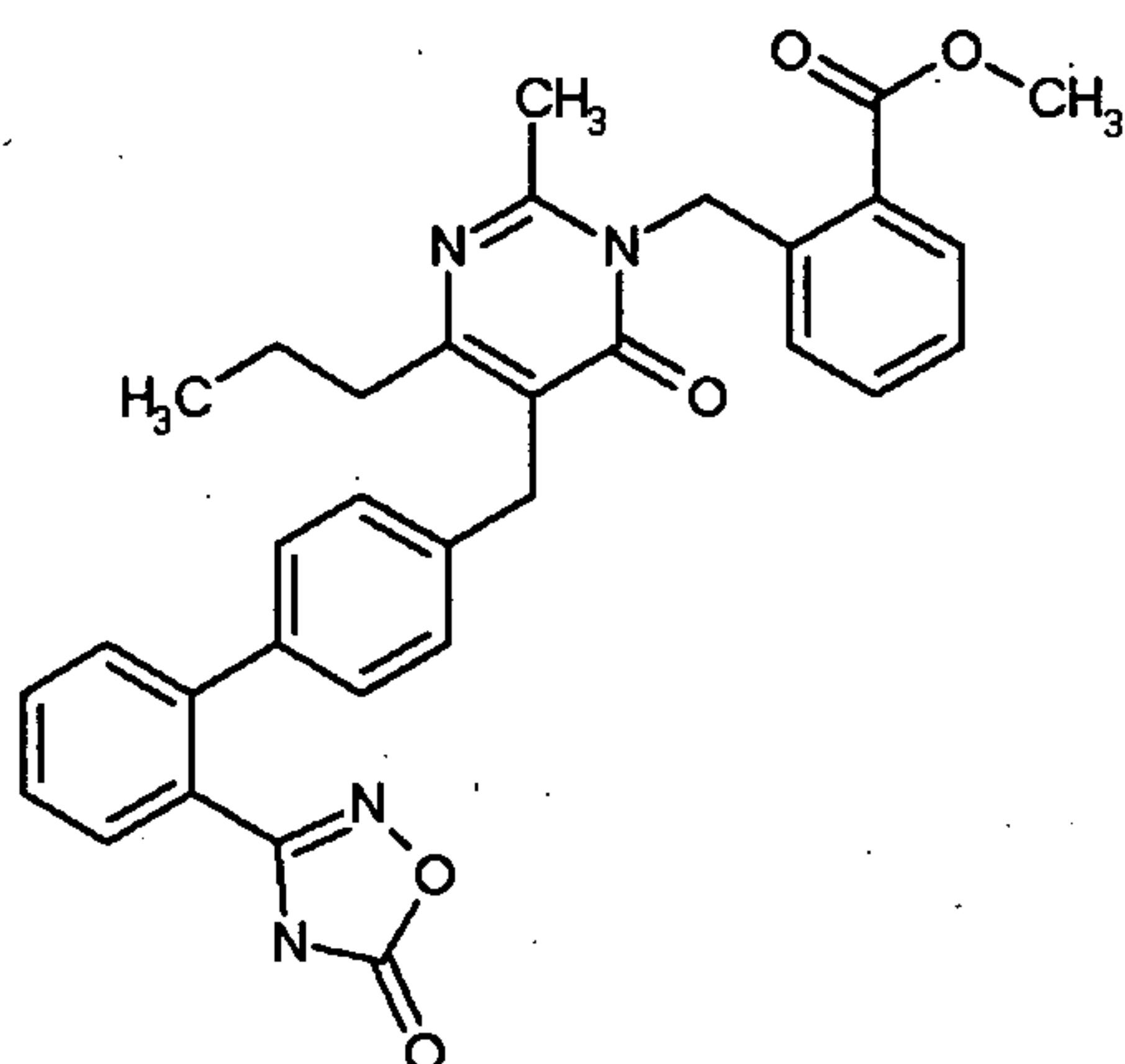


25 84a) methyl 2-[(5-{[2'-(2-cyanobiphenyl-4-yl)methyl]-2-methyl-6-oxo-4-propylpyrimidin-1(6H)-yl}methyl)benzoate

A mixture of 4'-[(2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (2 g), sodium hydride (0.28 g) and N,N-dimethylformamide (20 mL) was stirred at room temperature for 10 min, methyl 2-

(bromomethyl)benzoate (1.6 g) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (1.15 g, 40%).

¹H NMR (300 MHz, CDCl₃) δ 0.99 (3H, t, J = 7.3), 1.60-1.77 (2H, m), 2.39 (3H, s), 2.58-2.68 (2H, m), 3.93 (3H, s), 4.01 (2H, s), 5.76 (2H, s), 6.78 (1H, d, J = 7.7), 7.30-7.51 (8H, m), 7.57-7.67 (1H, m), 7.74 (1H, dd, J = 7.7, 0.9), 8.07 (1H, dd, J = 7.8, 1.4)



84b) methyl 2-[(2-methyl-6-oxo-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-4-propylpyrimidin-1(6H)-yl)methyl]benzoate

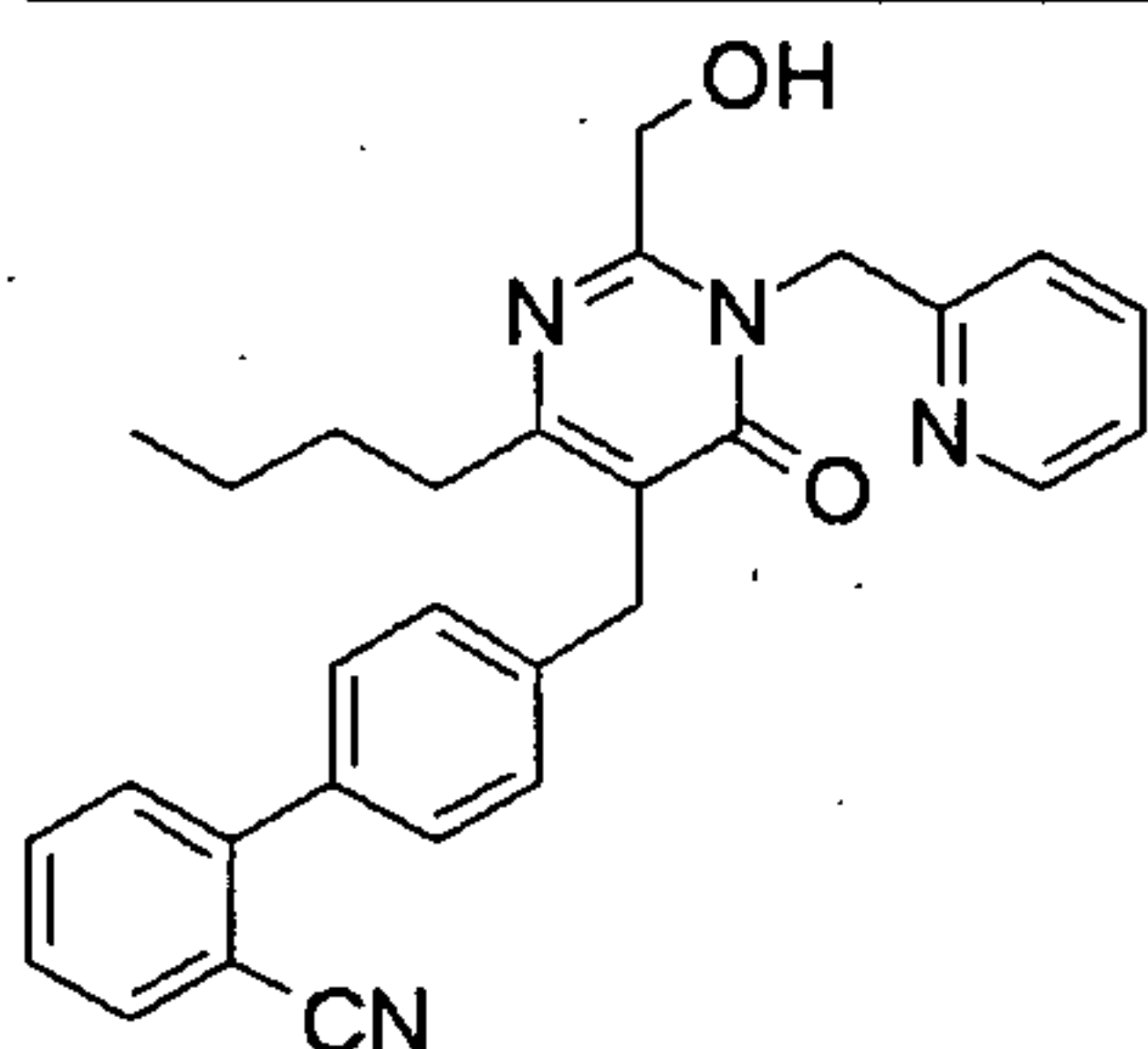
A mixture of hydroxylammonium chloride (2.44 g), sodium hydrogen carbonate (3.93 g) and dimethyl sulfoxide (30 mL) was stirred at 40°C for 30 min, methyl 2-[(5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-methyl-6-oxo-4-propylpyrimidin-1(6H)-yl)methyl]benzoate (1.15 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (40 mL), N,N'-carbonyldiimidazole (0.45 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.39 mL)

were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over
 5 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as colorless crystals (0.48 g, 37%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.87 (3H, t, J = 7.4), 1.46-1.61
 10 (2H, m), 2.32 (3H, s), 2.51-2.56 (2H, m), 3.90 (5H, s), 5.59 (2H, s), 6.70 (1H, d, J = 7.3), 7.19-7.28 (4H, m), 7.39-7.72 (6H, m), 8.00 (1H, dd, J = 7.7, 1.3), 12.38 (1H, s)

Example 85

6-butyl-2-(hydroxymethyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one
 15

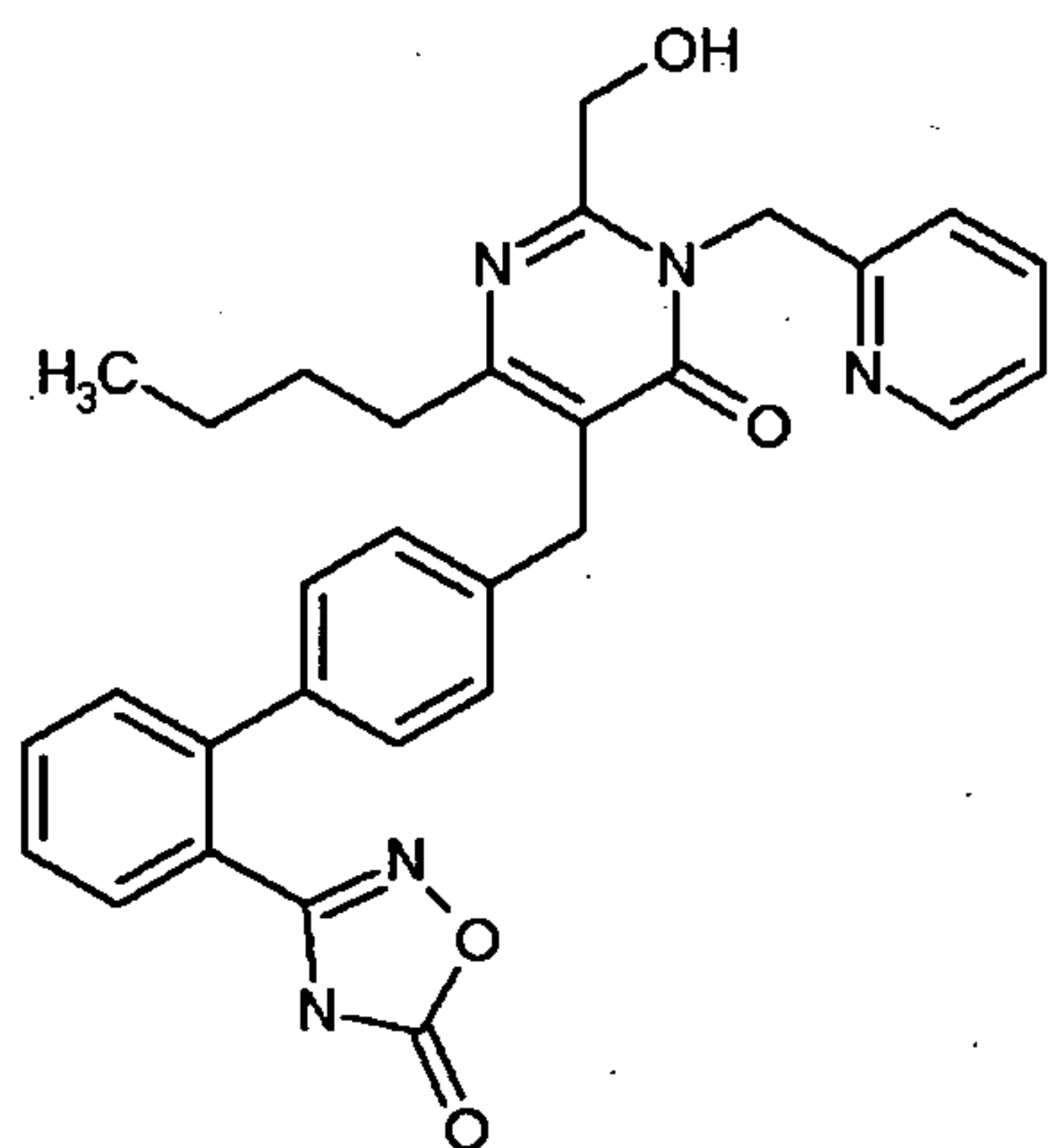


85a) 4'-{[4-butyl-2-(hydroxymethyl)-6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile
 20

A mixture of 4'-{[4-butyl-2-(hydroxymethyl)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1 g), cesium carbonate (2.1 g), 2-(bromomethyl)pyridine hydrobromide (0.81 g) and N,N-dimethylformamide (10 mL) was stirred at 50°C
 25 for 4 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a
 30 colorless solid (0.62 g, 50%).

¹H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.3), 1.30-1.45 (2H,

m), 1.55-1.67 (2H, m), 2.61-2.71 (2H, m), 3.98 (2H, s), 4.75 (2H, s), 5.09 (1H, br.), 5.21 (2H, s), 7.18-7.25 (1H, m), 7.30-7.35 (2H, m), 7.37-7.50 (5H, m), 7.57-7.78 (3H, m), 8.49-8.53 (1H, m)



5

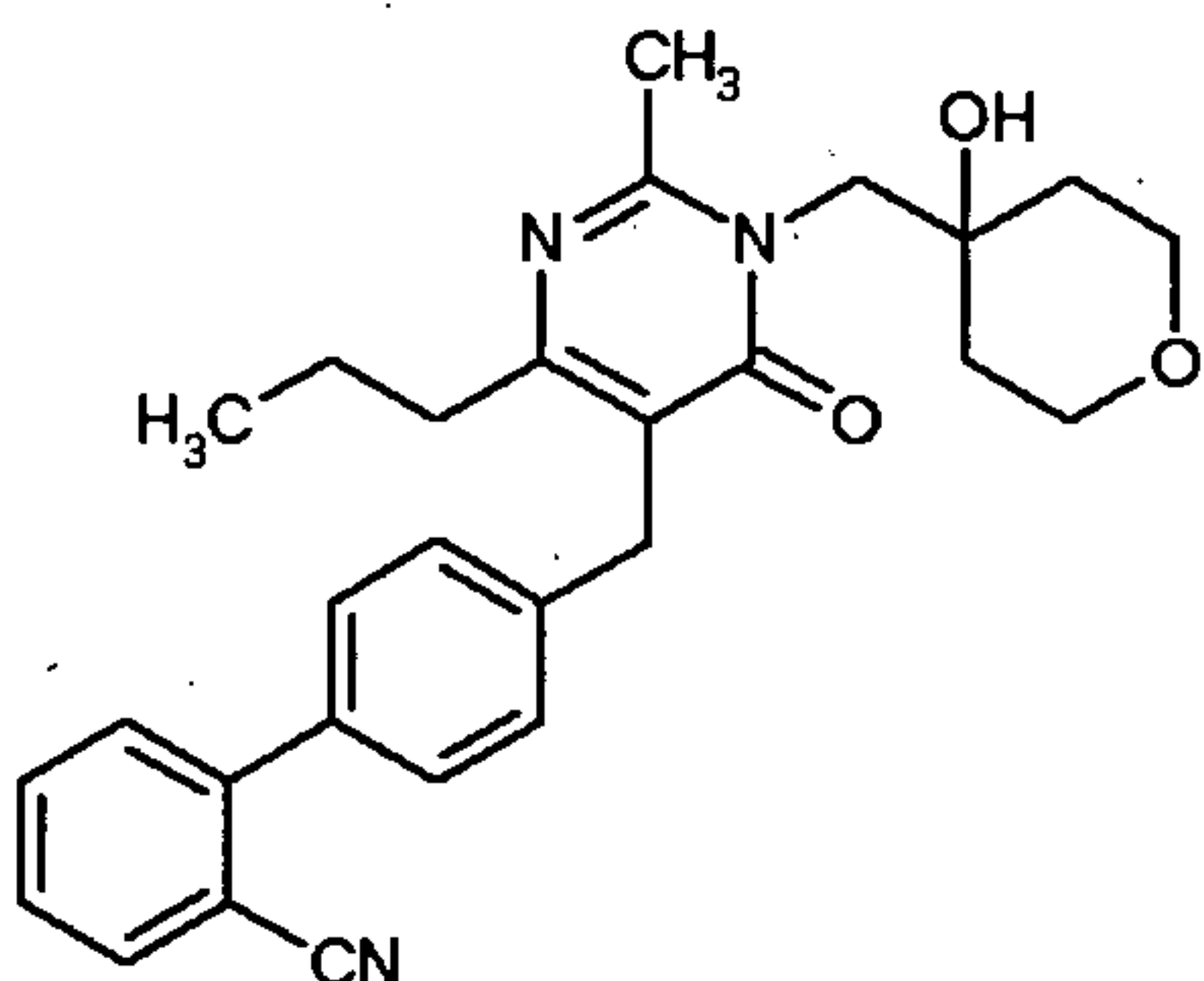
85b) 6-butyl-2-(hydroxymethyl)-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one

A mixture of hydroxylammonium chloride (1.39 g), sodium
 10 hydrogen carbonate (2.2 g) and dimethyl sulfoxide (15 mL) was
 stirred at 40°C for 30 min, 4'-([4-butyl-2-(hydroxymethyl)-6-
 oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-5-
 yl]methyl)biphenyl-2-carbonitrile (0.62 g) was added, and the
 mixture was stirred at 90°C for 16 hr. The reaction mixture
 15 was diluted with ethyl acetate, washed with water and then
 with saturated brine, and dried over anhydrous magnesium
 sulfate. The solvent was evaporated under reduced pressure and
 the residue was dissolved in tetrahydrofuran (20 mL), N,N'-
 carbonyldiimidazole (0.26 g) and then 1,8-
 20 diazabicyclo[5.4.0]undec-7-ene (0.22 mL) were added, and the
 mixture was stirred at room temperature for 2 hr. The reaction
 mixture was adjusted to pH 5 with water and 1 M hydrochloric
 acid, and extracted with ethyl acetate. The ethyl acetate
 layer was washed with saturated brine, and dried over
 25 anhydrous magnesium sulfate. The solvent was evaporated under
 reduced pressure and the residue was purified by silica gel
 column chromatography to give the title compound as colorless
 crystals (0.18 g, 26%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.3), 1.21-1.39 (2H, m), 1.41-1.59 (2H, m), 2.51-2.61 (2H, m), 3.86 (2H, s), 4.48 (2H, d, J = 5.7), 5.41 (2H, s), 5.63 (1H, t, J = 5.7), 7.21 (4H, s), 7.24-7.41 (2H, m), 7.52 (2H, dd, J = 18.2, 7.6), 7.64 (2H, d, J = 7.0), 7.74-7.85 (1H, m), 8.46 (1H, s), 12.38 (1H, s)

Example 86

3-[(4-hydroxytetrahydro-2H-pyran-4-yl)methyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-
6-propylpyrimidin-4(3H)-one

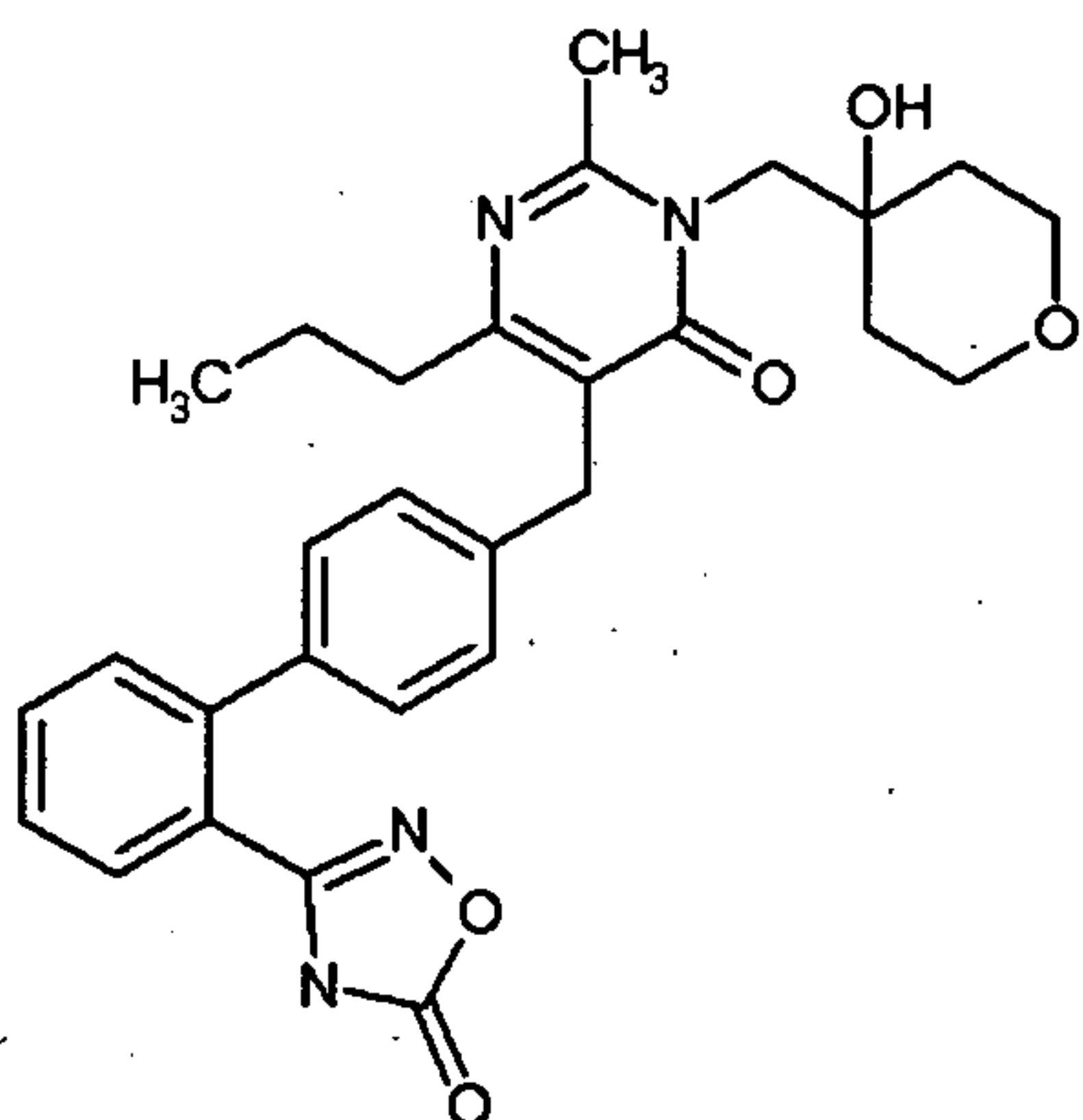


86a) 4'-([1-[(4-hydroxytetrahydro-2H-pyran-4-yl)methyl]-2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl]methyl)biphenyl-2-carbonitrile

To a mixture of tetrahydro-4H-pyran-4-one (0.73 g), diiodomethane (0.7 mL) and tetrahydrofuran (20 mL) was added methyllithium (2.1 M diethyl ether solution, 6.95 mL) at 0°C. The reaction mixture was stirred at room temperature for 4 hr, and extracted with saturated aqueous ammonium chloride solution and diethyl ether. The diethyl ether layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained oil was dissolved in N,N-dimethylformamide (15 mL), 4'-[(2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g) and potassium carbonate (0.8 g) were added, and the mixture was stirred at 90°C for 24 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under

reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.7 g, 53%).

¹H NMR (300 MHz, CDCl₃) δ 0.95 (3H, t, J = 7.4), 1.48-1.81 (6H, m), 2.55-2.63 (5H, m), 3.80 (4H, d, J = 7.7), 3.97 (2H, s), 4.16 (2H, s), 4.71 (1H, s), 7.25-7.50 (5H, m), 7.62 (1H, t, J = 7.6), 7.74 (1H, d, J = 7.5), 8.02 (1H, s)



86b) 3-[(4-hydroxytetrahydro-2H-pyran-4-yl)methyl]-2-methyl-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-6-propylpyrimidin-4(3H)-one

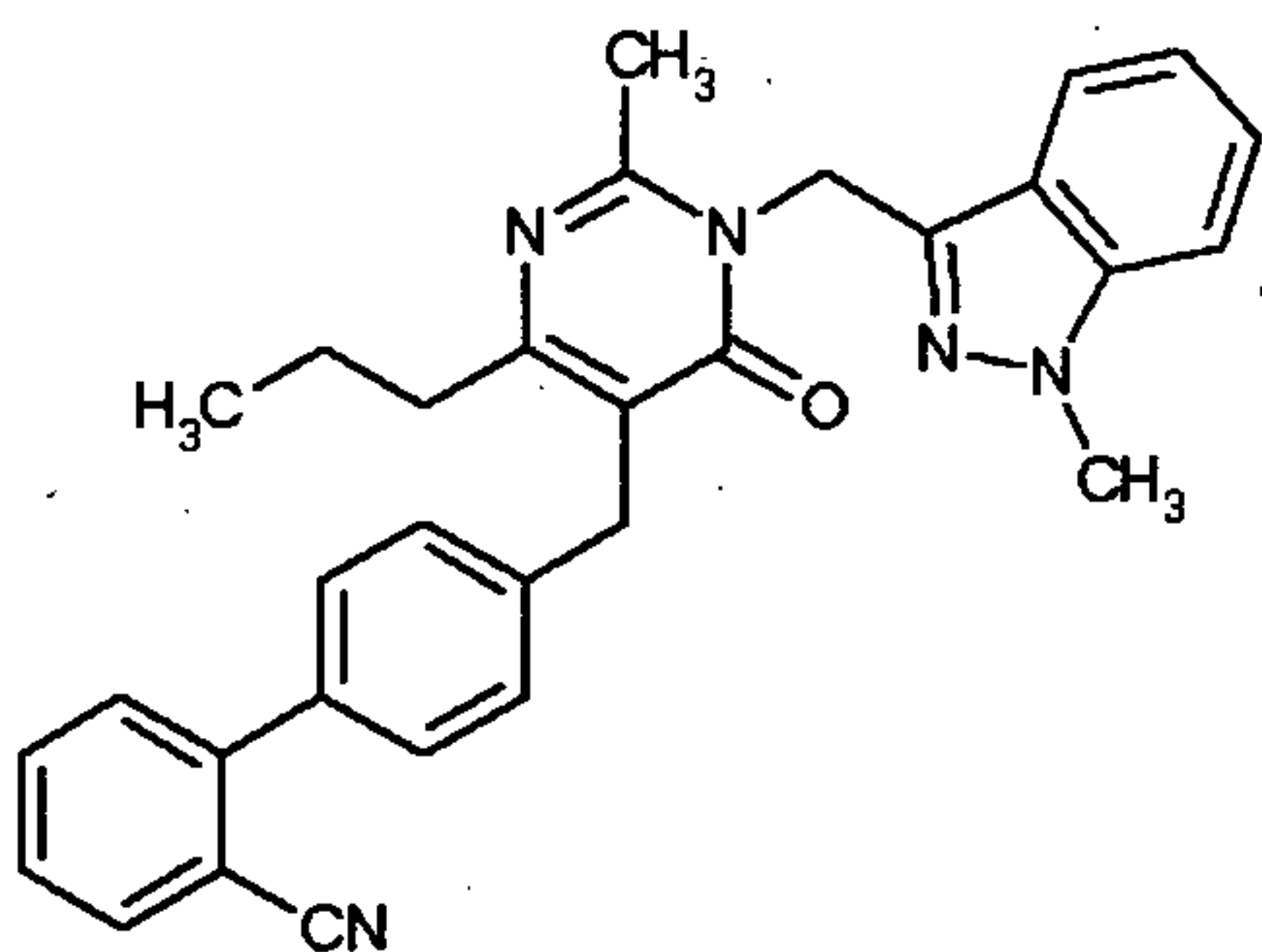
A mixture of hydroxylammonium chloride (1.6 g), sodium hydrogen carbonate (2.57 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({1-[(4-hydroxytetrahydro-2H-pyran-4-yl)methyl]-2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl)biphenyl-2-carbonitrile (0.7 g) was added, and the mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.26 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.22 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the

residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.14 g, 18%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.85 (3H, t, J = 7.2), 1.13-1.73 (6H, m), 2.43 (2H, t, J = 7.6), 2.61 (3H, s), 3.49-3.67 (4H, m), 3.85 (2H, s), 3.97-4.11 (2H, m), 4.96 (1H, s), 7.14-7.29 (4H, m), 7.52 (2H, dd, J = 18.1, 7.5), 7.60-7.72 (2H, m), 12.37 (1H, s)

Example 87

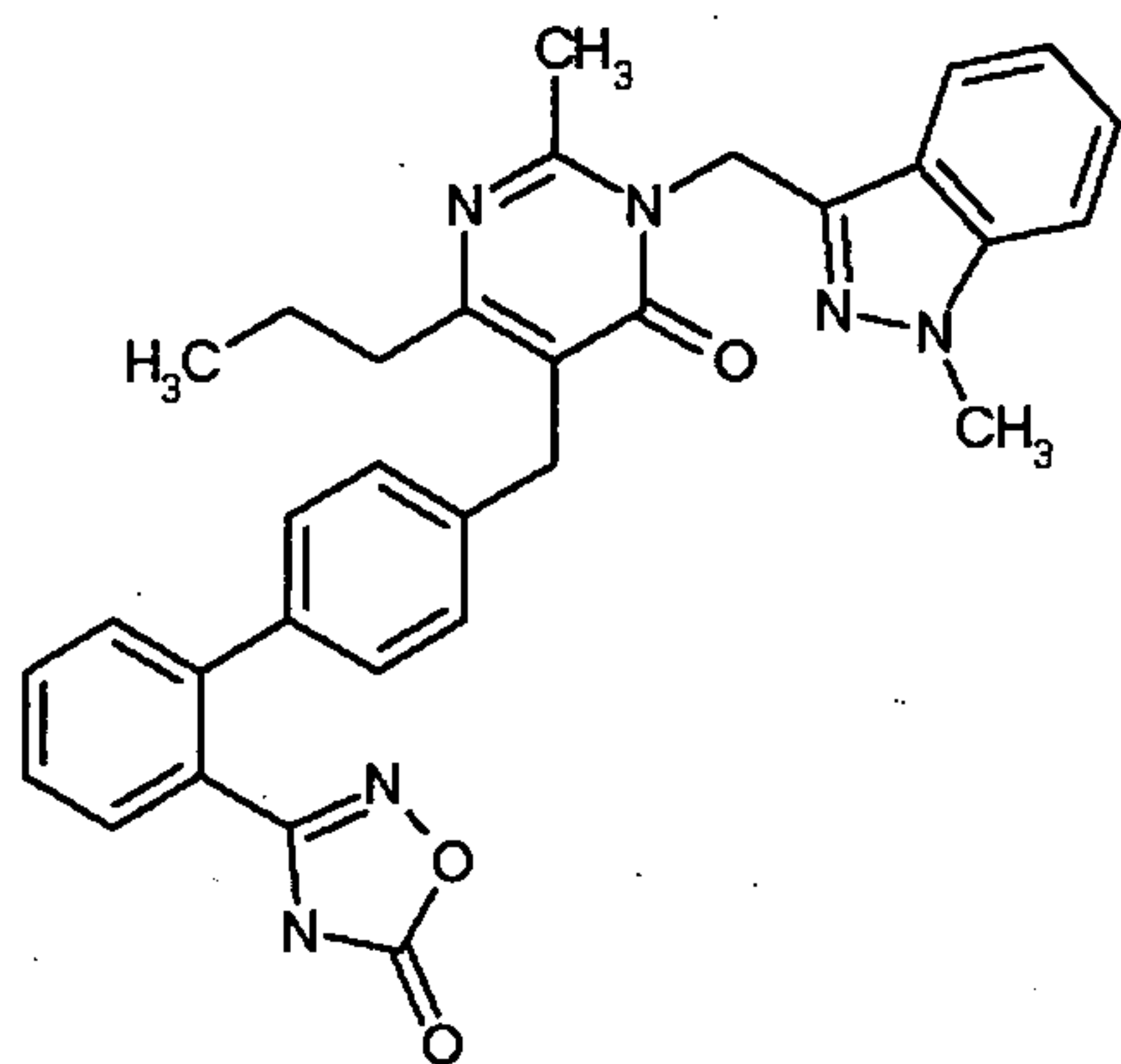
2-methyl-3-[(1-methyl-1H-indazol-3-yl)methyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one



87a) 4'-({2-methyl-1-[(1-methyl-1H-indazol-3-yl)methyl]-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl}methyl)biphenyl-2-carbonitrile

A mixture of 4'-[(2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), 1,1'-(azodicarbonyl)dipiperidine (1.47 g), tributylphosphine (1.81 mL), (1-methyl-1H-indazol-3-yl)methanol (0.51 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 4 hr. The reaction mixture was concentrated. The residue was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.67 g, 47%).

¹H NMR (300 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.4), 1.52-1.65 (2H, m), 2.48-2.58 (2H, m), 2.72 (3H, s), 4.03 (5H, s), 5.64 (2H, s), 7.01-7.12 (1H, m), 7.30-7.53 (8H, m), 7.58-7.67 (1H, m), 7.75 (1H, d, J = 8.0), 7.86 (1H, d, J = 8.0)



87b) 2-methyl-3-[(1-methyl-1H-indazol-3-yl)methyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one

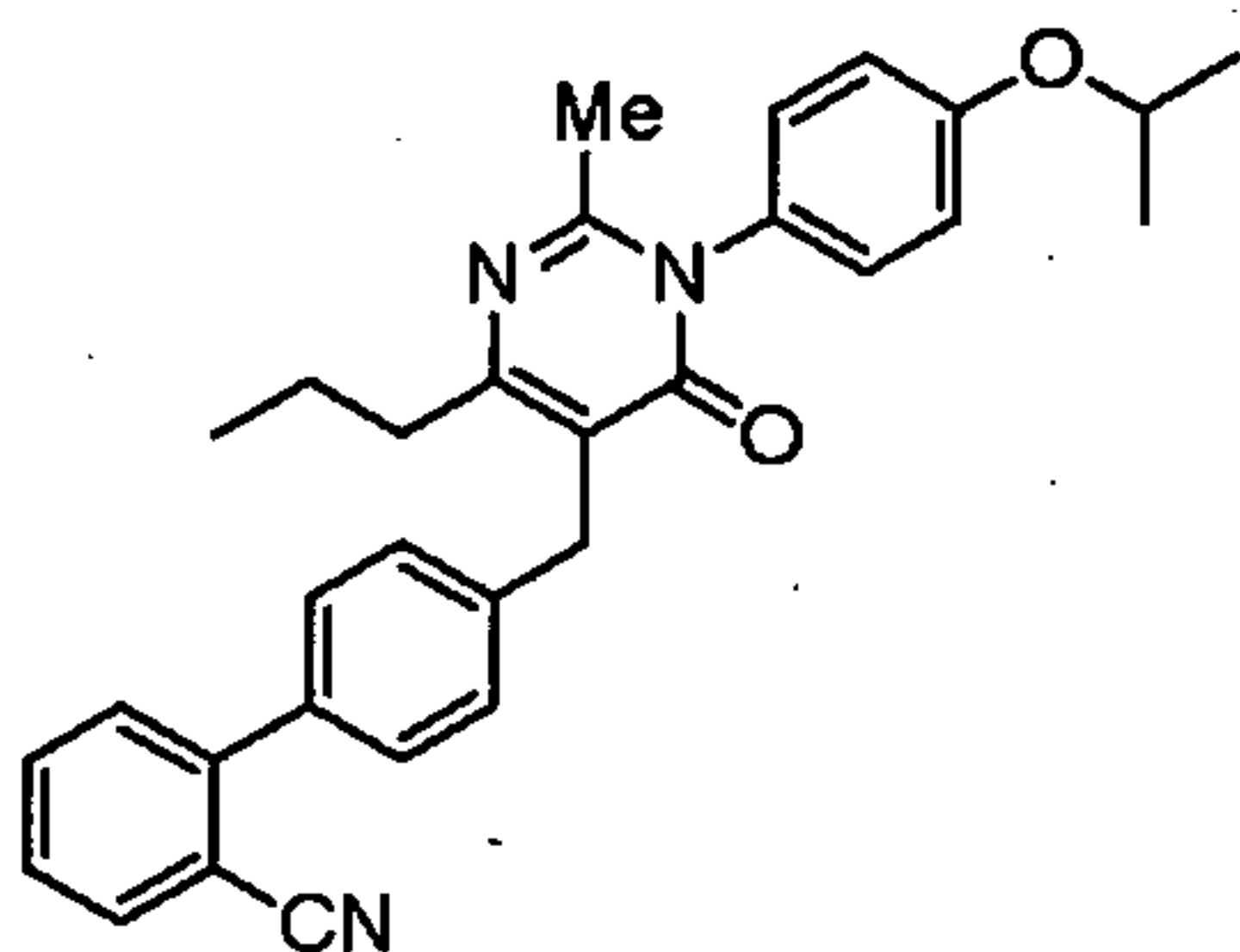
5 A mixture of hydroxylammonium chloride (1.43 g), sodium hydrogen carbonate (2.3 g) and dimethyl sulfoxide (15 mL) was stirred at 40°C for 30 min, 4'-({2-methyl-1-[(1-methyl-1H-indazol-3-yl)methyl]-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl)methyl)biphenyl-2-carbonitrile (0.67 g) was added, and the
10 mixture was stirred at 90°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL), N,N'-
15 carbonyldiimidazole (0.27 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.23 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was adjusted to pH 5 with water and 1 M hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate
20 layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.38 g, 51%).

25 ¹H NMR (300 MHz, DMSO-d₆) δ 0.83 (3H, t, J = 7.4), 1.40-1.56 (2H, m), 2.40-2.48 (2H, m), 2.62 (3H, s), 3.89 (2H, s), 4.00 (3H, s), 5.58 (2H, s), 7.10 (1H, t, J = 7.4), 7.22 (4H, q, J = 8.2), 7.40 (1H, t, J = 8.0), 7.47-7.72 (5H, m), 7.79 (1H, d, J

= 8.3), 11.96 (1H, br)

Example 88

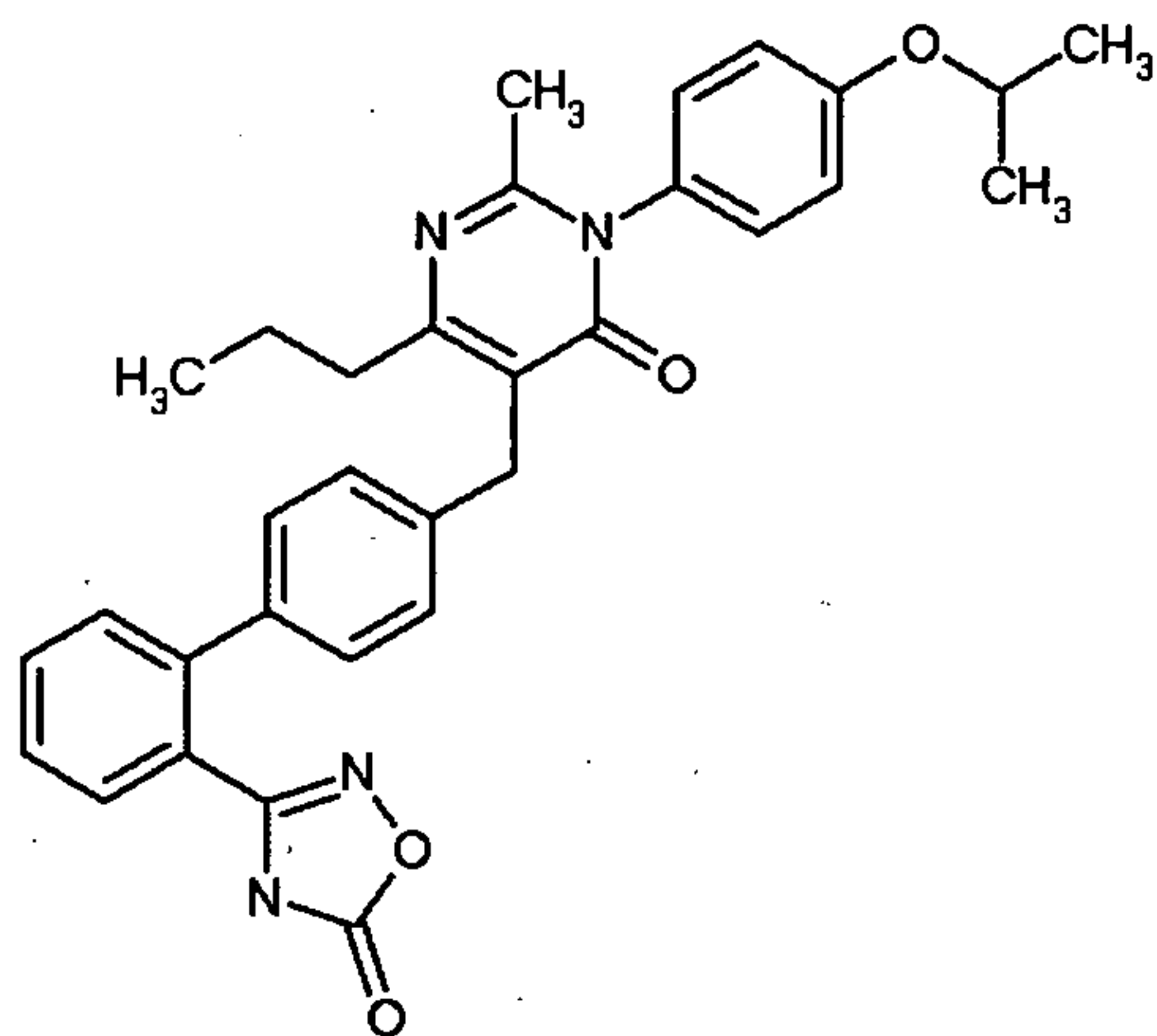
3-(4-isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-
1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-
5 4 (3H)-one



88a) 4'-{[1-(4-isopropoxyphenyl)-2-methyl-6-oxo-4-propyl-1,6-
dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile

To a suspension of 4'-[(2-methyl-6-oxo-4-propyl-1,6-
10 dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (2.0 g),
(4-isopropoxyphenyl)boronic acid (2.0 g), triethylamine (4.0
mL), pyridine (2.0 mL) and molecular sieves 4A (4.0 g) in
methylene chloride (30 mL) was added copper(II) acetate (2.0
g), and the mixture was stirred at room temperature for 2 days.
15 The reaction mixture was diluted with ethyl acetate. The
insoluble material was filtered off through celite, and the
filtrate was concentrated. The residue was purified by silica
gel column chromatography to give the title compound as a
pale-yellow viscous substance (1.88 g, 68%).

20 ¹H NMR (300 MHz, CDCl₃) δ 1.01 (t, J = 7.4, 3 H), 1.36 (d, J =
6.1, 6 H), 1.54 - 1.82 (m, 2 H), 2.18 (s, 3 H), 2.47 - 2.79 (m,
2 H), 3.97 (s, 2 H), 4.41 - 4.81 (m, 1 H), 6.72 - 7.81 (m, 12
H)



88b) 3-(4-isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one

5 A mixture of hydroxylammonium chloride (3.5 g), sodium hydrogen carbonate (5.0 g) and dimethyl sulfoxide (25 mL) was stirred at 40°C for 30 min, 4'-{[1-(4-isopropoxyphenyl)-2-methyl-6-oxo-4-propyl-1,6-dihydropyrimidin-5-yl]methyl}biphenyl-2-carbonitrile (1.88 g) was added, and the
10 mixture was stirred at 90°C for 15 hr. The reaction mixture was allowed to cool to room temperature, ethyl acetate and water were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was
15 evaporated. The residue was dissolved in tetrahydrofuran (25 mL), N,N'-carbonyldiimidazole (0.97 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.90 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 M
20 hydrochloric acid and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (1.54 g, 73%).

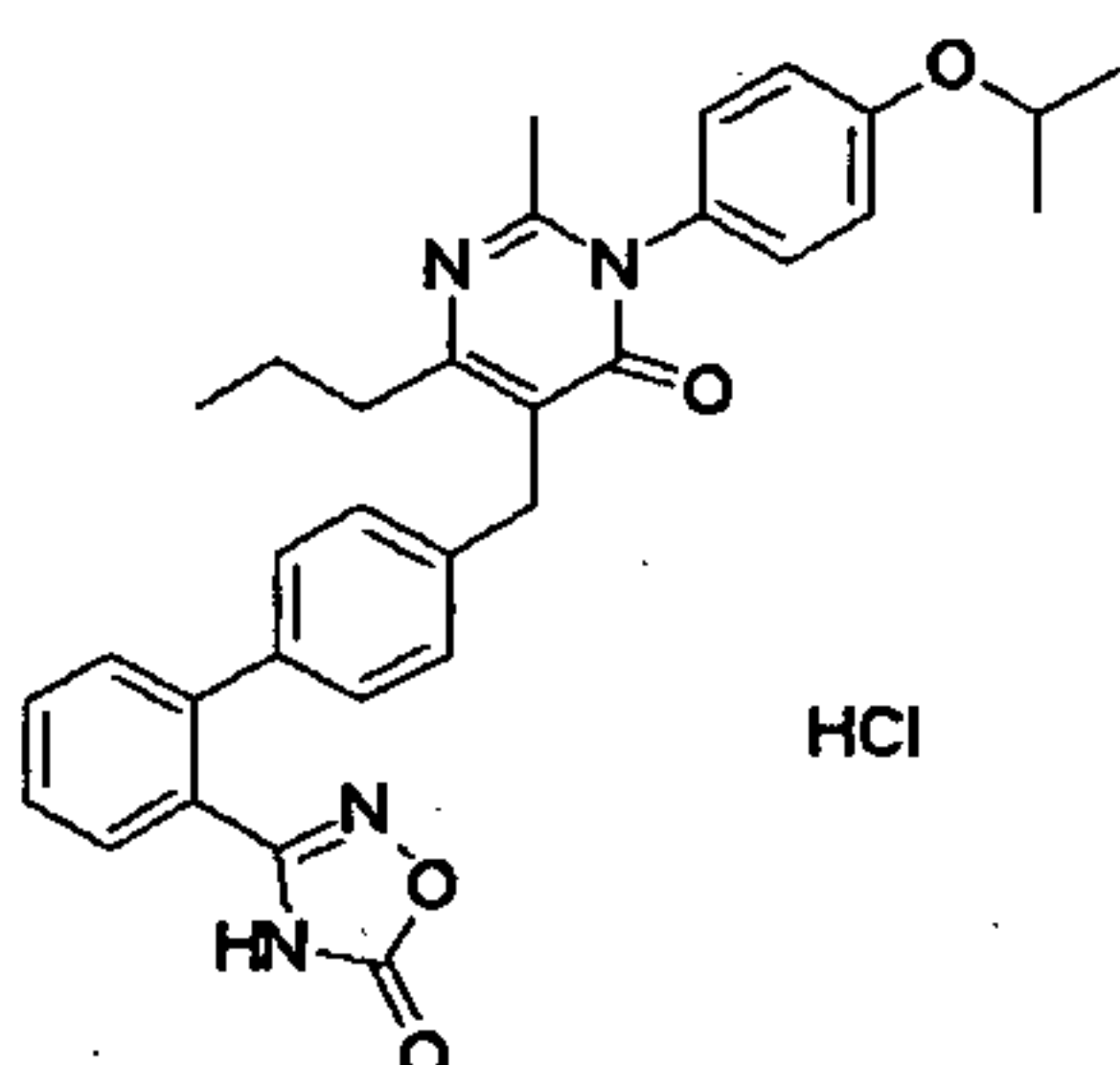
25 ¹H NMR (300 MHz, DMSO-d₆) δ 0.89 (t, J = 7.2, 3 H), 1.30 (d, J = 6.1, 6 H), 1.42 - 1.66 (m, 2 H), 2.07 (s, 3 H), 2.45 - 2.56 (m, 2 H), 3.86 (s, 2 H), 4.55 - 4.78 (m, 1 H), 6.98 - 7.73 (m,

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PCT/JP2007/073004

12 H), 12.39 (s, 1 H)

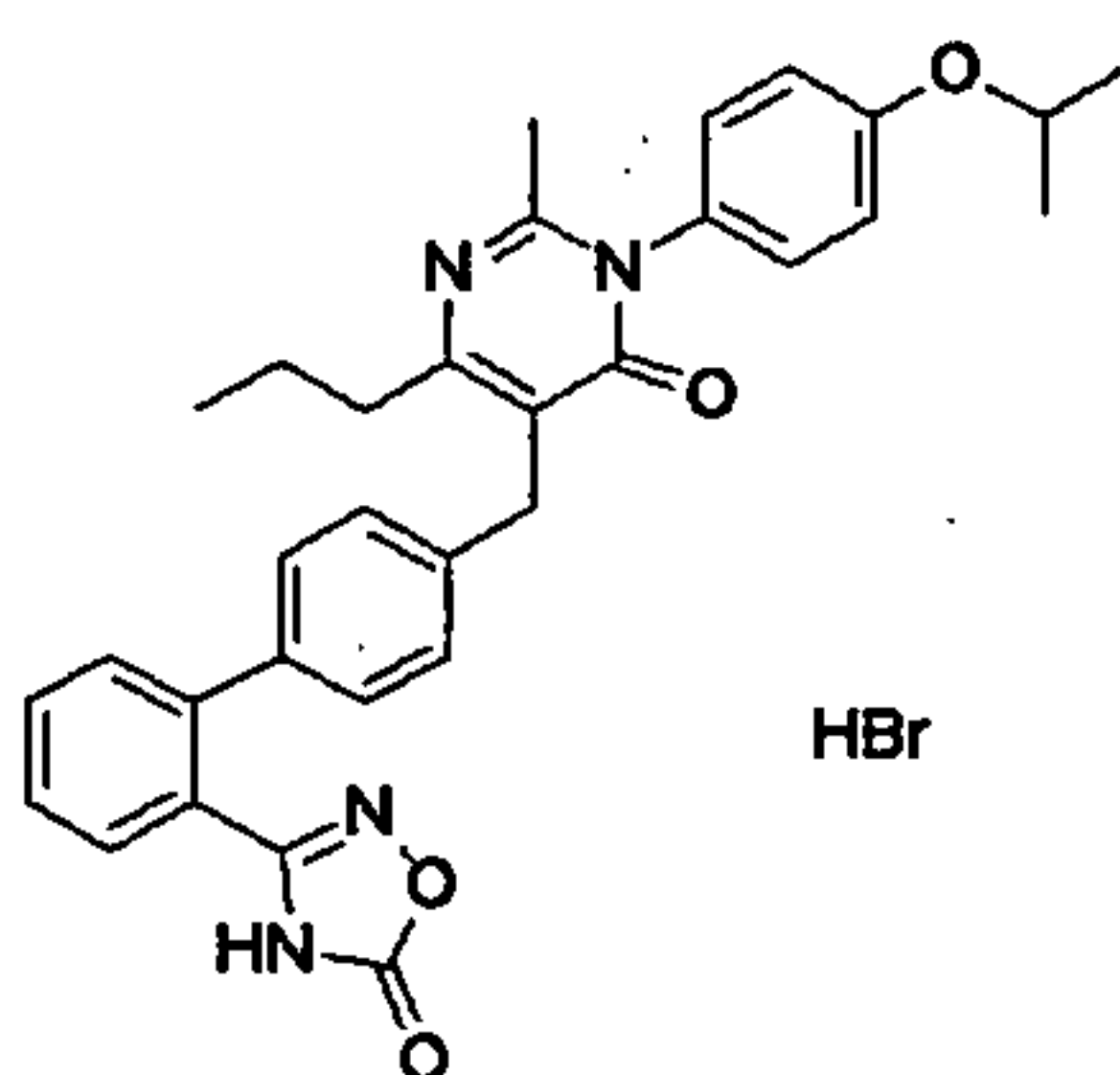
Example 89



3-(4-isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-
 5 1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-
 4(3H)-one hydrochloride

3-(4-Isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-
 dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
 propylpyrimidin-4(3H)-one (0.50 g) was dissolved in ethyl
 10 acetate (3 mL), and 4 M hydrochloric acid-ethyl acetate
 solution (0.28 mL) was added. Diisopropyl ether was further
 added and the precipitated solid was collected by filtration
 to give the title compound (0.40 g, 75%) as a colorless solid.
¹H NMR (300 MHz, DMSO-d₆) δ 0.93 (3 H, t, J = 7.2), 1.30 (6 H,
 15 d, J = 6.0), 1.49 - 1.65 (2 H, m), 2.27 (3 H, s), 2.65 (2 H, t,
 J = 7.7), 3.91 (2 H, s), 4.63 - 4.74 (1 H, m), 7.04 - 7.11 (2
 H, m), 7.20 - 7.37 (6 H, m), 7.48 - 7.59 (2 H, m), 7.63 - 7.73
 (2 H, m), 12.43 (1 H, s)

Example 90



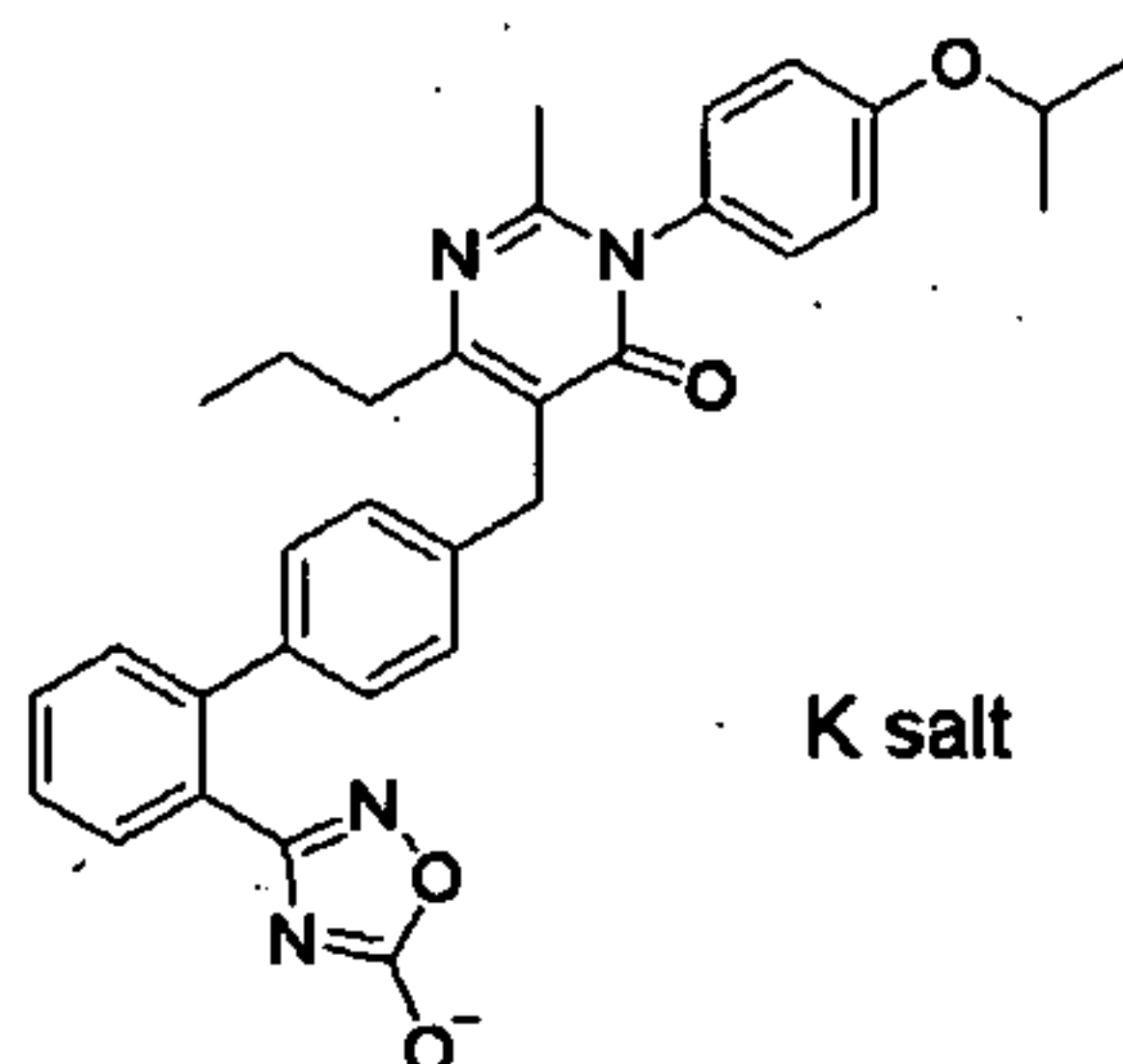
20 3-(4-isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-
 1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-
 4(3H)-one hydrobromide

3-(4-Isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-
 25 dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
 propylpyrimidin-4(3H)-one (0.50 g) was dissolved in ethyl
 acetate (10 mL), and 10% hydrogen bromide-ethanol solution

(0.75 mL) was added. After allowing to stand overnight at room temperature, the precipitated solid was collected by filtration to give the title compound (0.41 g, 71%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.93 (3 H, t, J = 7.1), 1.30 (6 H, d, J = 6.0), 1.47 - 1.62 (2 H, m), 2.22 (3 H, s), 2.62 (2 H, t, J = 7.5), 3.91 (2 H, s), 4.59 - 4.75 (1 H, m), 7.07 (2 H, d, J = 9.0), 7.20 - 7.36 (6 H, m), 7.46 - 7.60 (2 H, m), 7.62 - 7.74 (2 H, m), 12.41 (1 H, s)

Example 91

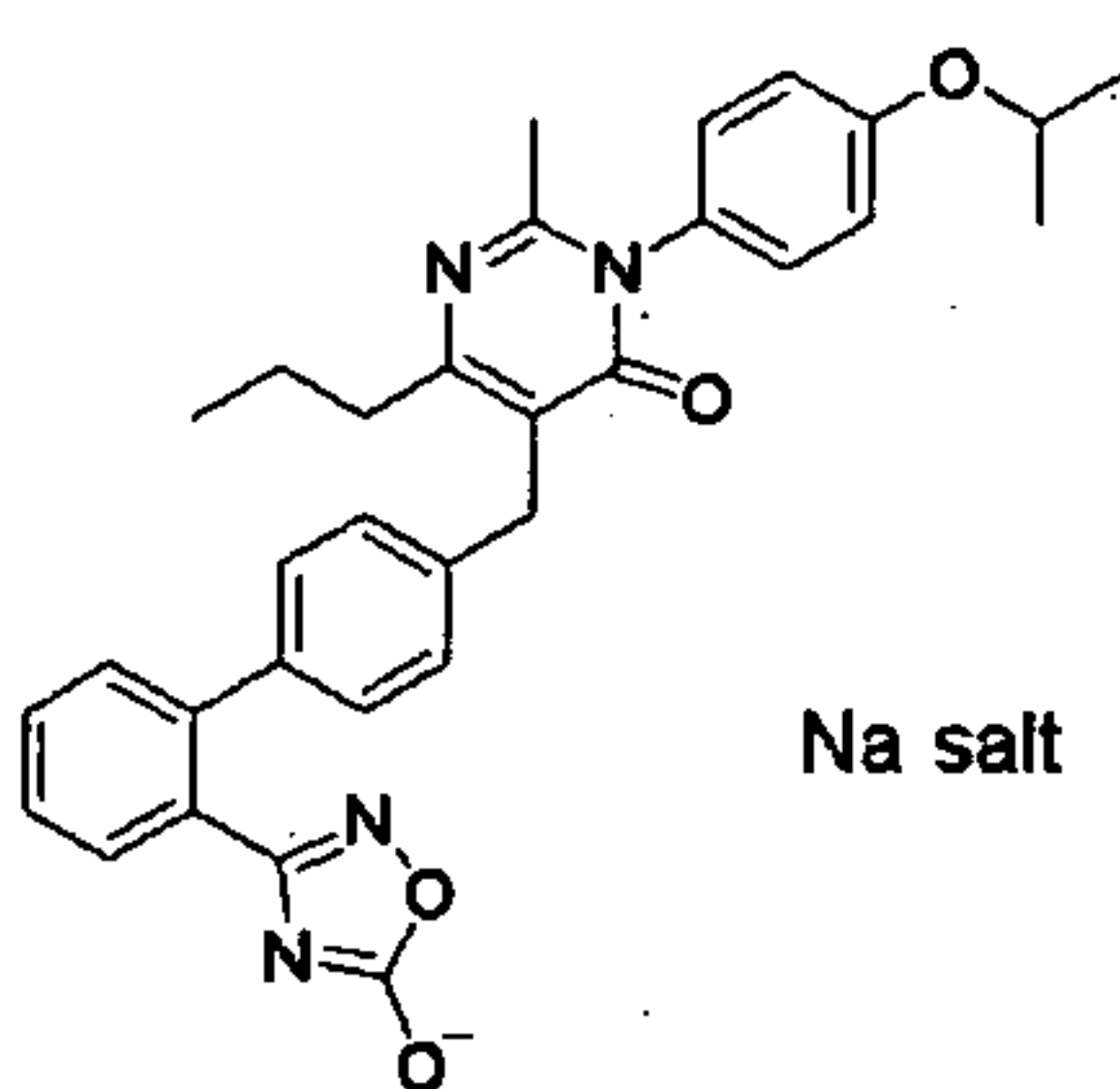


3-(4-isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one potassium salt

To a solution of 3-(4-isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one (1.42 g) in ethanol (10.0 mL) was added 8 M aqueous potassium hydroxide solution (0.33 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with diisopropyl ether to give the title compound (1.45 g, 95%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.93 (t, J = 7.4, 3 H), 1.30 (d, J = 6.1, 6 H), 1.51 - 1.66 (m, 2 H), 2.05 (s, 3 H), 2.51 - 2.57 (m, 2 H), 3.81 (s, 2 H), 4.59 - 4.75 (m, 1 H), 6.97 - 7.49 (m, 12 H)

Example 92

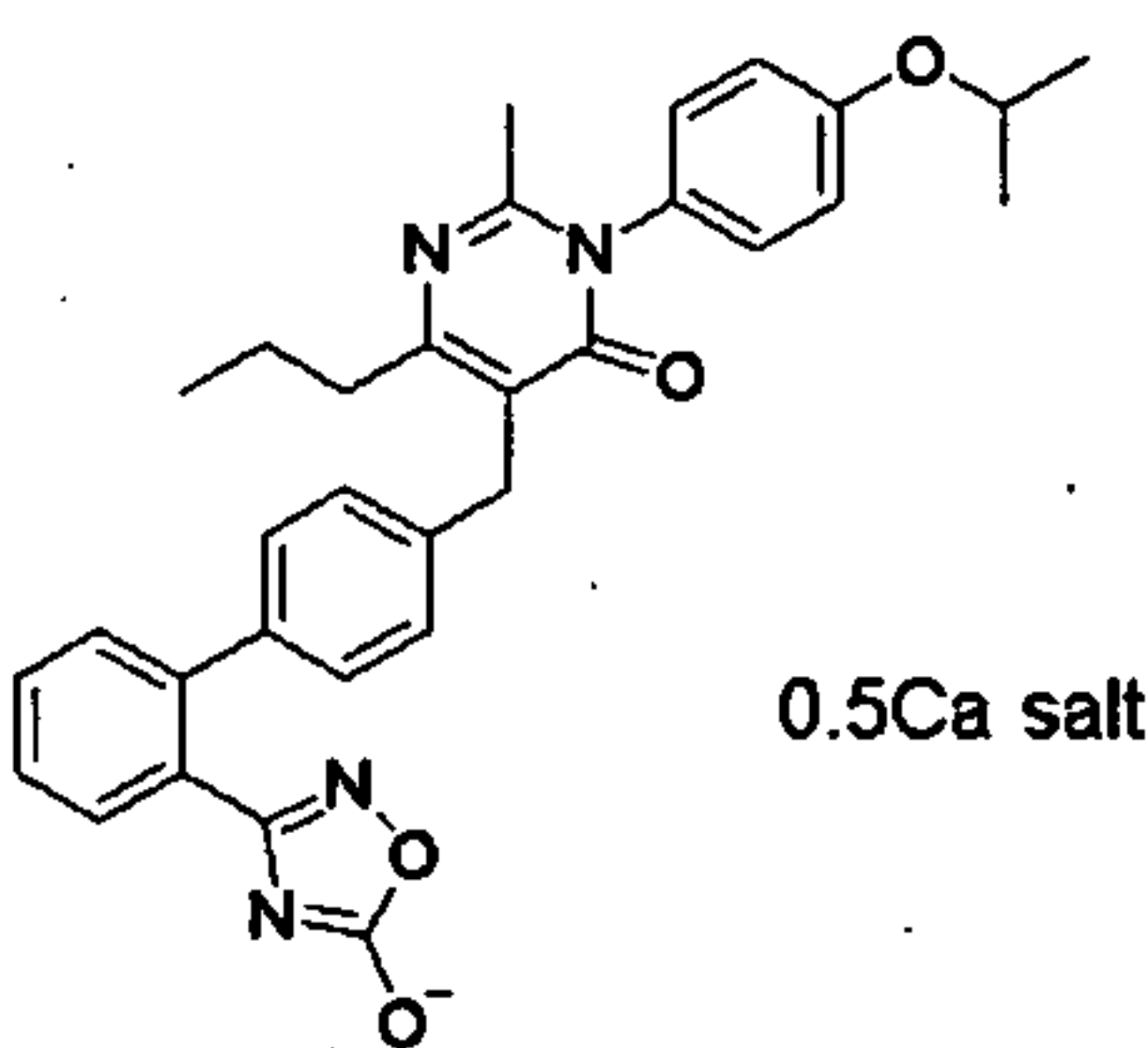


3-(4-isopropoxyphenyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one sodium salt

5 To a solution of 3-(4-isopropoxyphenyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one (1.07 g) in ethanol (1.0 mL) was added 8 M aqueous sodium hydroxide solution (0.25 mL), and the mixture was stirred at room temperature for 1 hr. The reaction
10 mixture was concentrated under reduced pressure, and the residue was triturated with diisopropyl ether to give the title compound (1.13 g, 100%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.93 (t, J = 7.4, 3 H), 1.29 (s, 3 H), 1.31 (s, 3 H), 1.49 - 1.68 (m, 2 H), 2.05 (s, 3 H), 2.51 -
15 2.57 (m, 2 H), 3.81 (s, 2 H), 4.58 - 4.74 (m, 1 H), 6.95 - 7.52 (m, 12 H)

Example 93



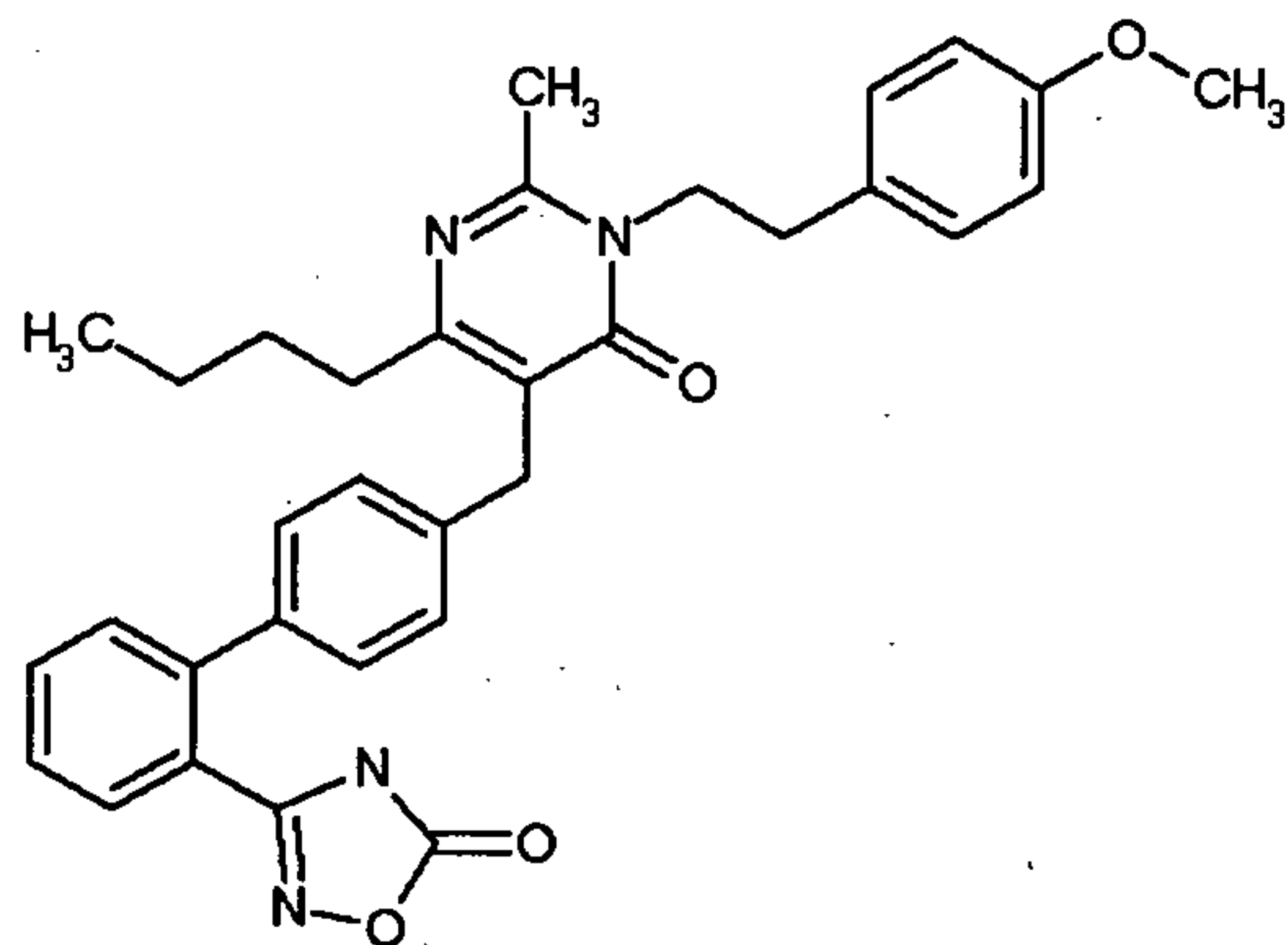
3-(4-isopropoxyphenyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one 0.5 calcium salt

To a solution of 3-(4-isopropoxyphenyl)-2-methyl-5-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-6-propylpyrimidin-4(3H)-one sodium salt (0.56 g) in water (2.0
25 mL) was added calcium chloride (0.056 g), and the mixture was stirred at room temperature for 1 hr. The resulting solid was collected by filtration to give the title compound (0.40 g,

71%) as a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 0.92 (t, J = 7.2, 3 H), 1.29 (s, 3 H), 1.31 (s, 3 H), 1.47 - 1.68 (m, 2 H), 2.06 (s, 3 H), 2.51 - 2.61 (m, 2 H), 3.82 (s, 2 H), 4.60 - 4.75 (m, 1 H), 6.96 - 7.56 (m, 12 H)

Example 94



6-butyl-3-[2-(4-methoxyphenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(2-bromoethyl)-4-methoxybenzene (0.95 g) was added, and the mixture was stirred at 150°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.41 g), sodium hydrogen carbonate (0.59 g) and dimethyl sulfoxide (20 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, diluted with ethyl acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved

in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.11 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.1 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.24 g, 17%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3 H, t, -J = 7.3), 1.25 (2 H, tt, J = 14.5, 7.2), 1.36 - 1.47 (2 H, m), 2.37 (3 H, s), 2.82 - 2.92 (2 H, m), 3.27 - 3.45 (2 H, m), 3.67 - 3.75 (3 H, m), 3.88 (2 H, s), 4.04 - 4.14 (2 H, m), 6.84 - 6.89 (2 H, m), 7.11 - 7.17 (2 H, m), 7.20 - 7.26 (4 H, m), 7.48 - 7.57 (2 H, m), 7.63 - 7.71 (2 H, m), 11.72 - 12.92 (1 H, br)

6-Butyl-3-[2-(4-methoxyphenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one obtained above is subjected to a conventional method of salt formation to give the following salts.

6-butyl-3-[2-(4-methoxyphenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one sodium salt

6-butyl-3-[2-(4-methoxyphenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one potassium salt

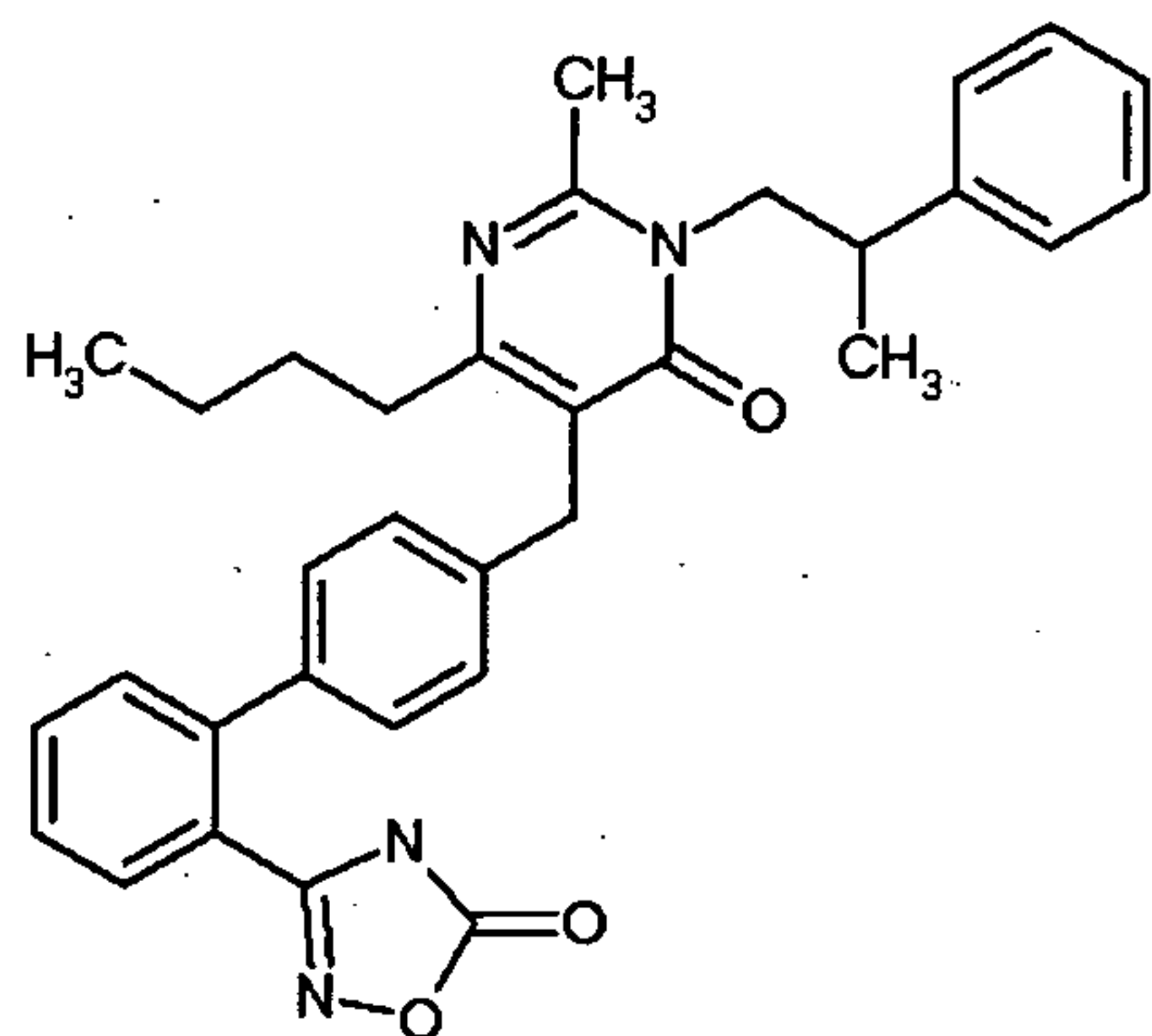
6-butyl-3-[2-(4-methoxyphenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one 0.5 calcium salt

6-butyl-3-[2-(4-methoxyphenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one hydrochloride

6-butyl-3-[2-(4-methoxyphenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-

yl)methyl}pyrimidin-4(3H)-one hydrobromide

Example 95



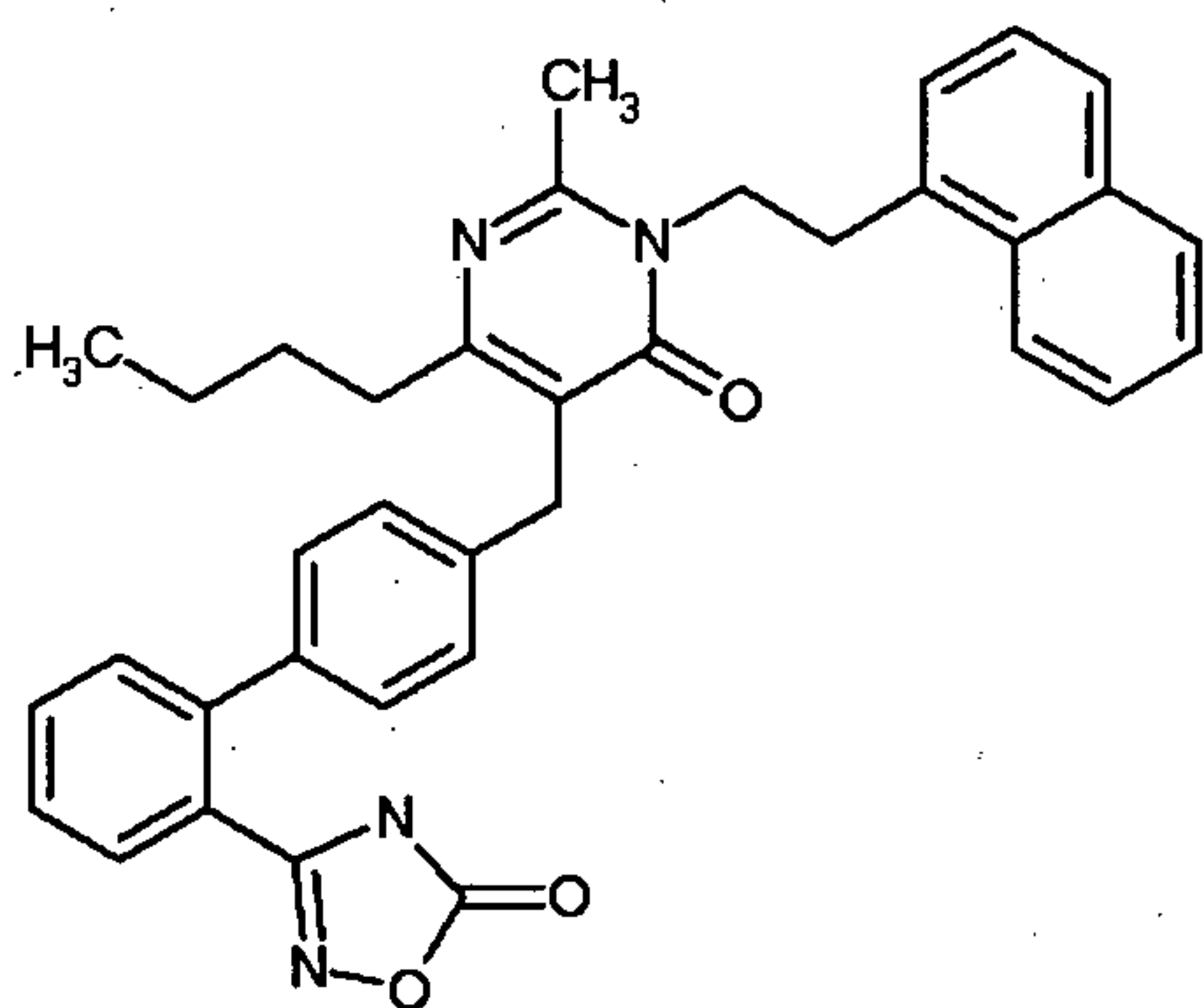
6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-phenylpropyl)pyrimidin-4(3H)-one

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, (2-bromo-1-methylethyl)benzene (1.1 g) was added, and the mixture was stirred at 150°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.28 g), sodium hydrogen carbonate (0.40 g) and dimethyl sulfoxide (20 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.078 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.066 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated

aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.12 g, 9%).

^1H NMR (300 MHz, DMSO- d_6) δ 0.82 (3 H, t, $J = 7.2$), 1.20 - 1.30 (5 H, m), 1.33 - 1.45 (2 H, m), 2.16 (3 H, s), 2.36 - 2.48 (2 H, m), 3.83 - 3.91 (4 H, m), 4.22 (1 H, dd, $J = 13.5, 6.9$), 7.16 - 7.30 (9 H, m), 7.46 - 7.58 (2 H, m), 7.62 - 7.72 (2 H, m), 11.98 - 12.74 (1 H, m)

Example 96



6-butyl-2-methyl-3-[2-(1-naphthyl)ethyl]-5-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]pyrimidin-
4(3H)-one

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(2-bromoethyl)naphthalene (1.0 g) was added, and the mixture was stirred at 150°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.64 g), sodium hydrogen carbonate (0.92 g) and dimethyl sulfoxide (20

mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate.

5 The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.18 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction

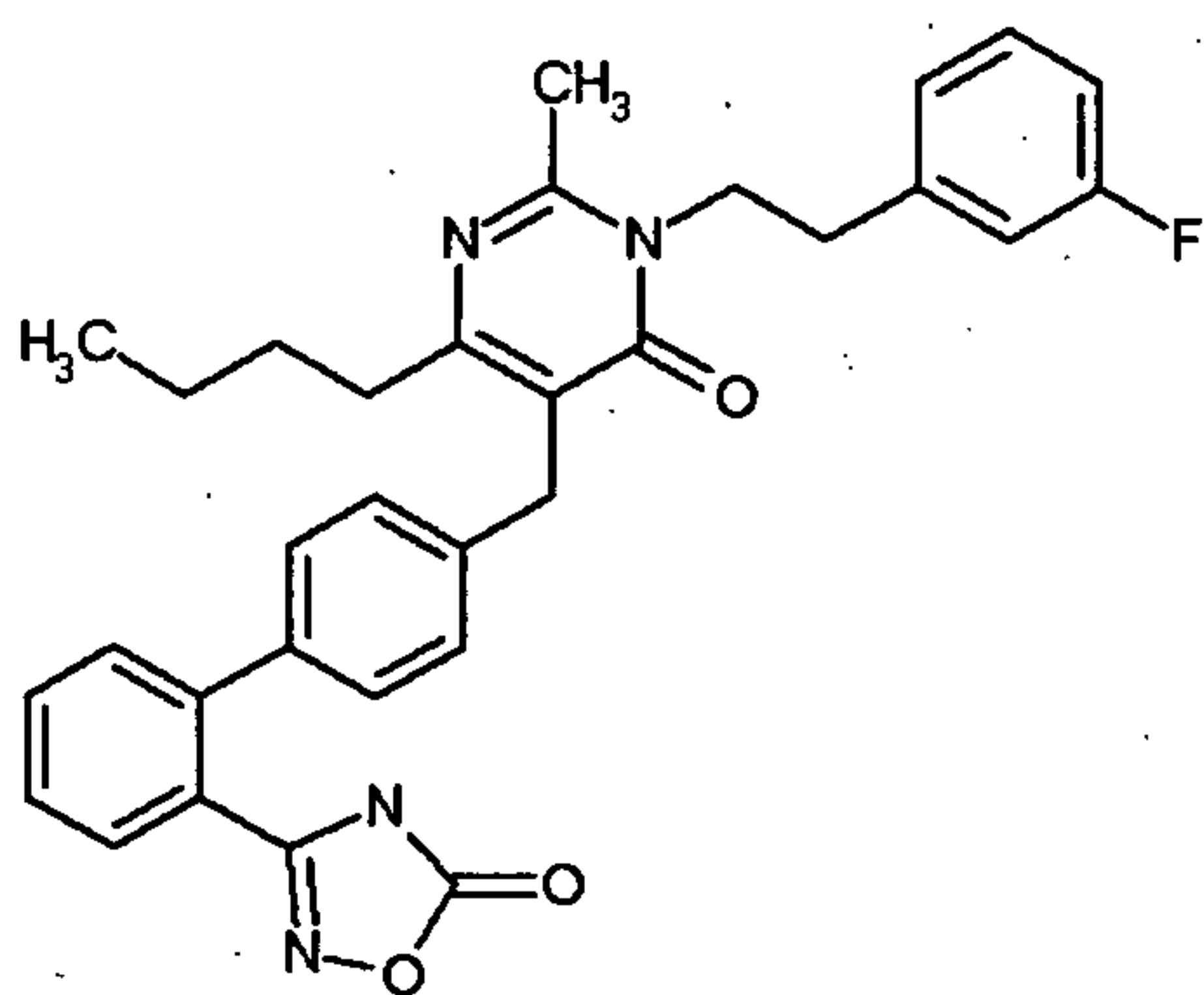
10 mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to

15 give the title compound as a colorless solid (0.33 g, 22%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.79 - 0.86 (3 H, m), 1.17 - 1.31 (2 H, m), 1.35 - 1.46 (2 H, m), 2.34 (3 H, s), 2.40 - 2.48 (2 H, m), 3.38 - 3.50 (2 H, m), 3.88 - 3.95 (2 H, m), 4.18 - 4.29 (2 H, m), 7.21 - 7.30 (4 H, m), 7.42 - 7.46 (2 H, m), 7.48 -

20 7.58 (4 H, m), 7.63 - 7.71 (2 H, m), 7.82 - 7.96 (2 H, m), 8.27 - 8.33 (1 H, m), 12.39 (1 H, d, J = 2.8)

Example 97



6-butyl-3-[2-(3-fluorophenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-

25 4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-

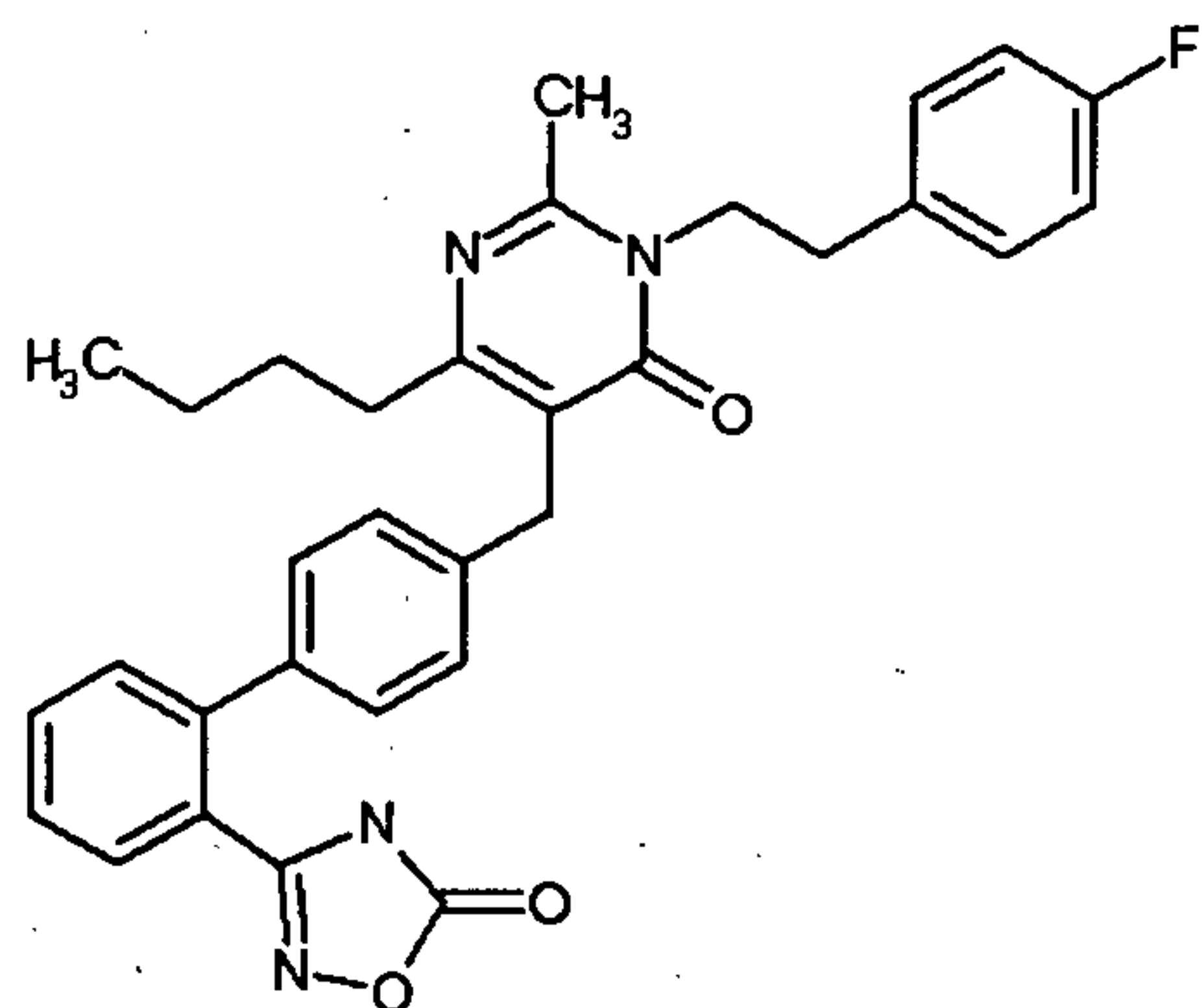
yl]methyl}pyrimidin-4(3H)-one

A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g),

sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(2-bromoethyl)-3-fluorobenzene (0.9 g) was added, and the mixture was stirred at 150°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.64 g), sodium hydrogen carbonate (0.92 g) and dimethyl sulfoxide (20 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, and diluted with ethyl acetate. The mixture was washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.18 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound as a colorless solid (0.14 g, 10%).

¹H NMR (300 MHz, DMSO-d₆) δ 0.82 (3 H, t, J = 7.3), 1.20 - 1.32 (2 H, m), 1.36 - 1.48 (2 H, m), 2.41 (3 H, s), 2.91 - 3.04 (2 H, m), 3.26 - 3.42 (2 H, m), 3.87 (2 H, s), 4.10 - 4.22 (2 H, m), 7.03 - 7.14 (3 H, m), 7.20 - 7.27 (4 H, m), 7.29 - 7.40 (1 H, m), 7.47 - 7.58 (2 H, m), 7.62 - 7.72 (2 H, m), 11.86 - 12.78 (1 H, m)

Example 98



6-butyl-3-[2-(4-fluorophenyl)ethyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one

5 A mixture of 4'-[(4-butyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]biphenyl-2-carbonitrile (1 g), sodium hydride (0.17 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 10 min, 1-(2-bromoethyl)-4-fluorobenzene (0.9 g) was added, and the mixture was stirred
10 at 150°C for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 5% aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue obtained by silica gel column
15 chromatography was dissolved in dimethyl sulfoxide (5 mL), and added to a mixture of hydroxylammonium chloride (0.9 g), sodium hydrogen carbonate (1.3 g) and dimethyl sulfoxide (20 mL) previously stirred at 40°C for 30 min. The reaction mixture was stirred at 90°C for 16 hr, diluted with ethyl
20 acetate, washed with water and then with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), N,N'-carbonyldiimidazole (0.25 g) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.21 mL) were
25 added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium hydrogen sulfate solution and then with saturated brine, and dried over

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 372

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

THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 372

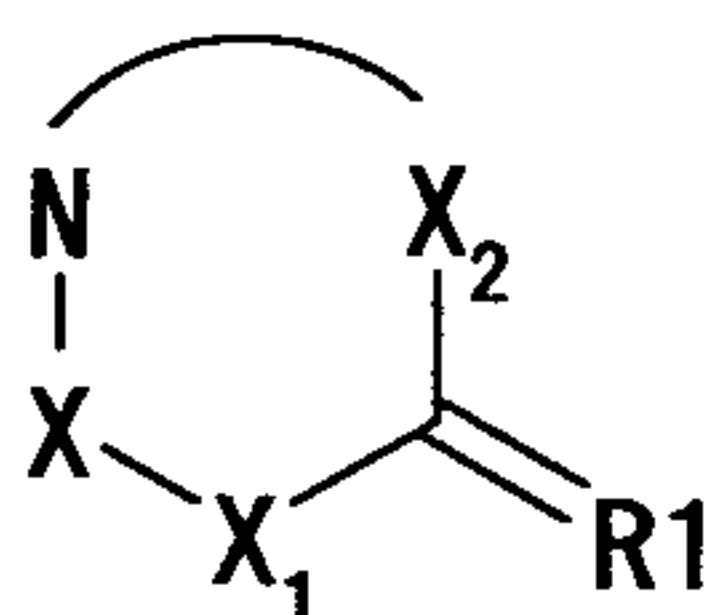
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NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

1. A compound represented by the following formula (I):



(I)

wherein

5 R1 is

- (1) an oxo group;
- (2) a thioxo group;
- (3) a group represented by the formula: =N-R

wherein

10 R is

- (i) an optionally substituted C1-C6 alkyl group;
- (ii) an optionally substituted C3-C6 cycloalkyl group;
- (iii) a group represented by the formula: -O-Ra

wherein Ra is hydrogen, an optionally substituted C1-C6
15 alkyl group or an optionally substituted C3-C6 cycloalkyl
group; or

- (iv) a group represented by the formula: -N(Rb)-Rc
wherein Rb and Rc are each independently hydrogen, an
optionally substituted C1-C6 alkyl group or an optionally
20 substituted C3-C6 cycloalkyl group, or Rb and Rc are bonded
to each other to form, together with the nitrogen atom
bonded thereto, an optionally substituted nitrogen-
containing heterocyclic group;

- (4) a group represented by the formula: =N-CO-R'

25 wherein R' is an optionally substituted C1-C6 alkyl group or
an optionally substituted cyclic group;

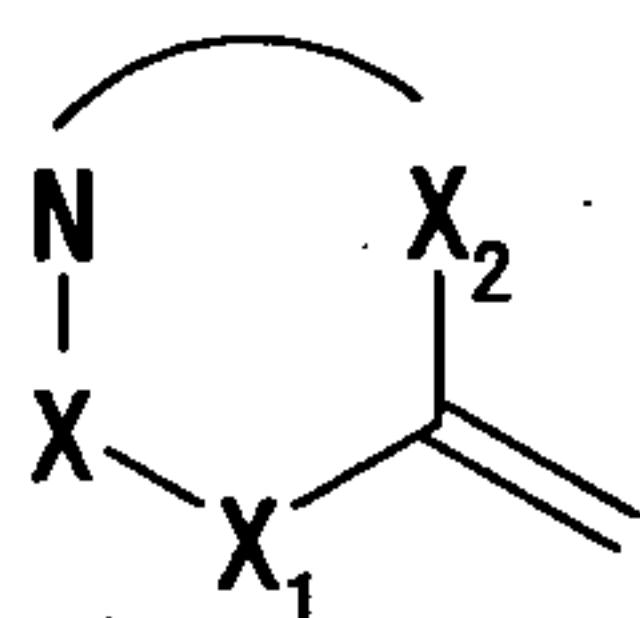
- (5) a group represented by the formula: =N-CO-OR'

wherein R' is as defined above; or

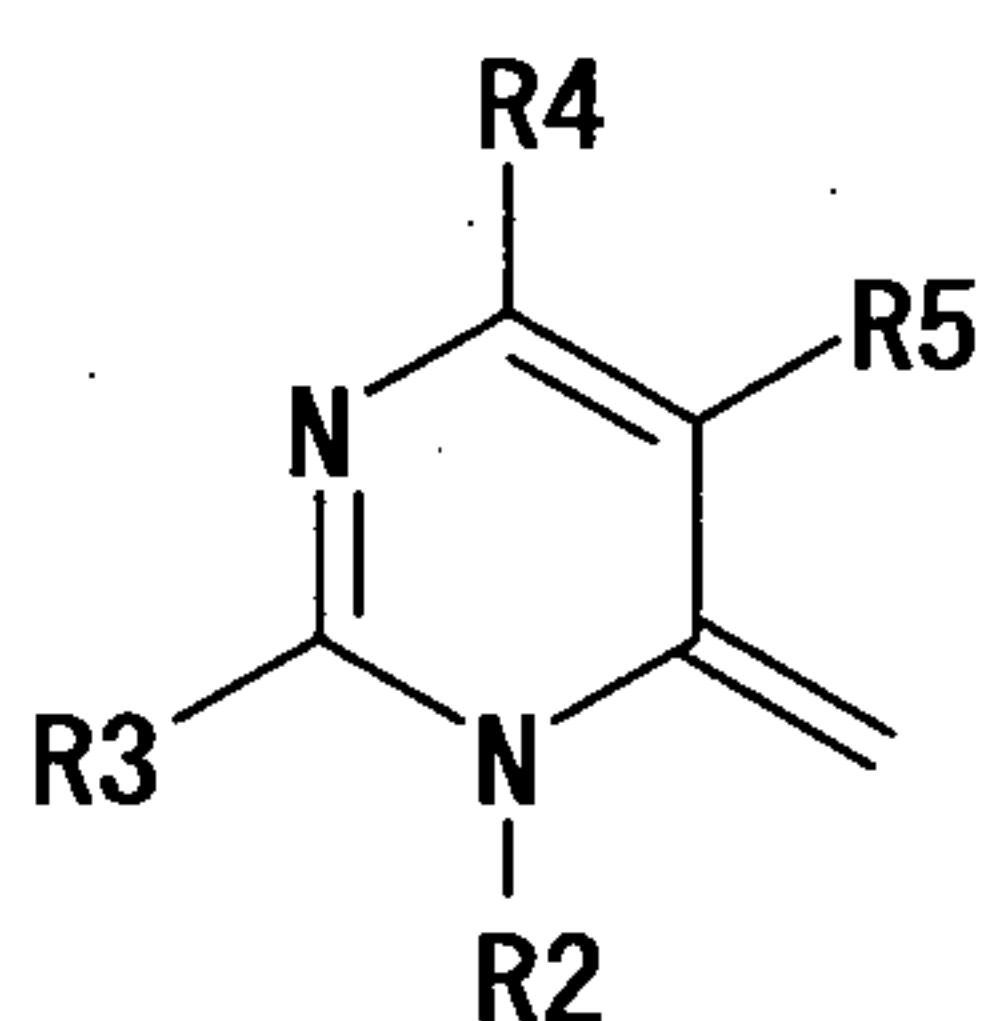
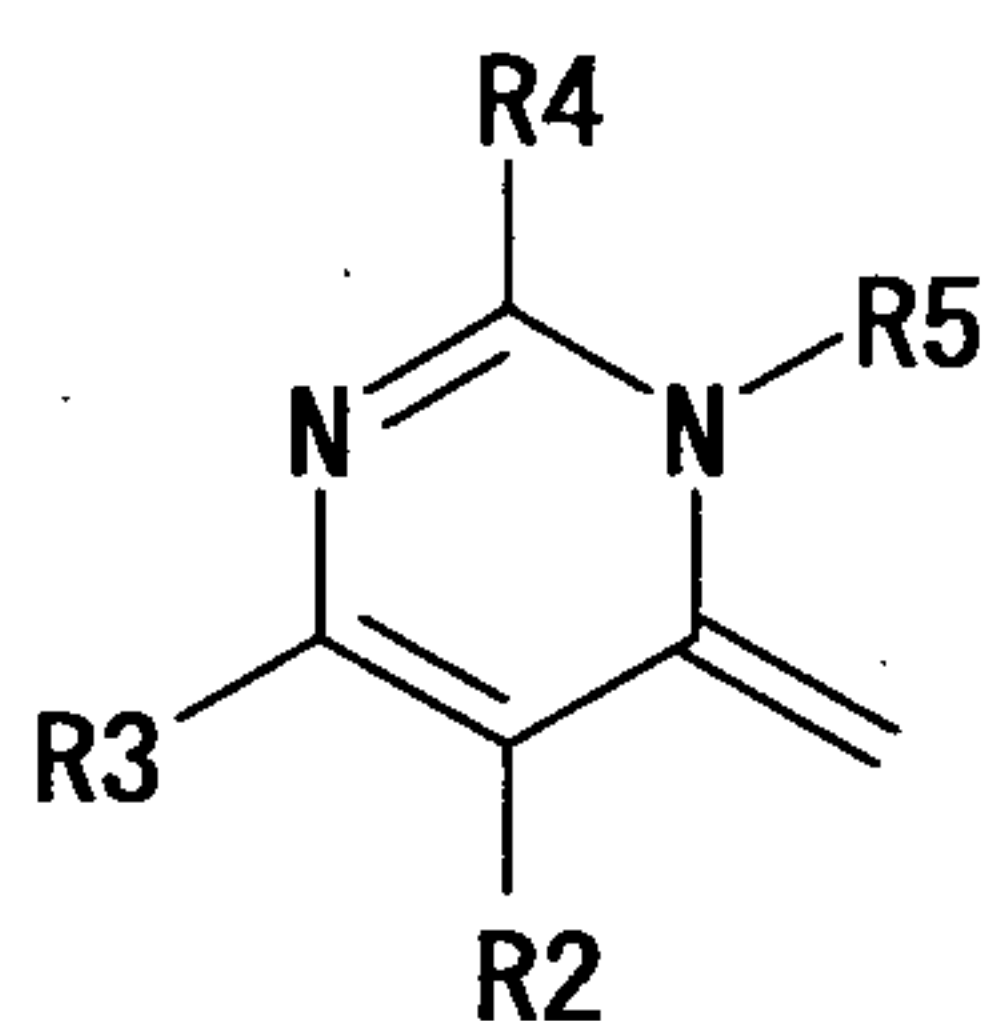
- (6) a group represented by the formula: =N-SO₂-R'

30 wherein R' is as defined above; and

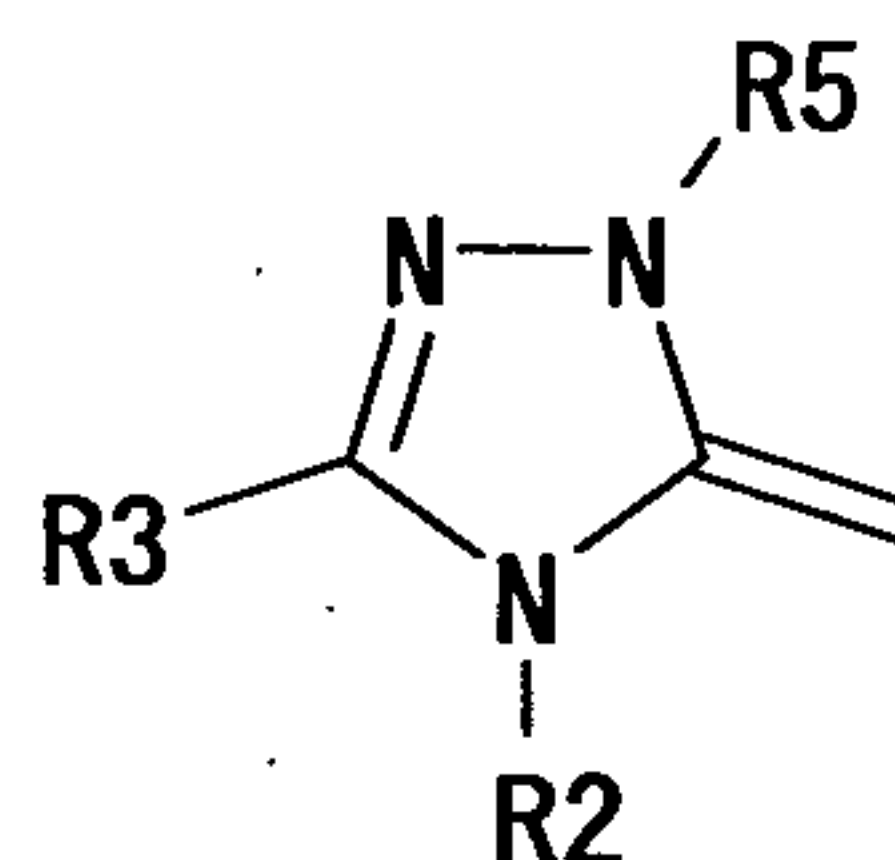
a group represented by the formula:



is

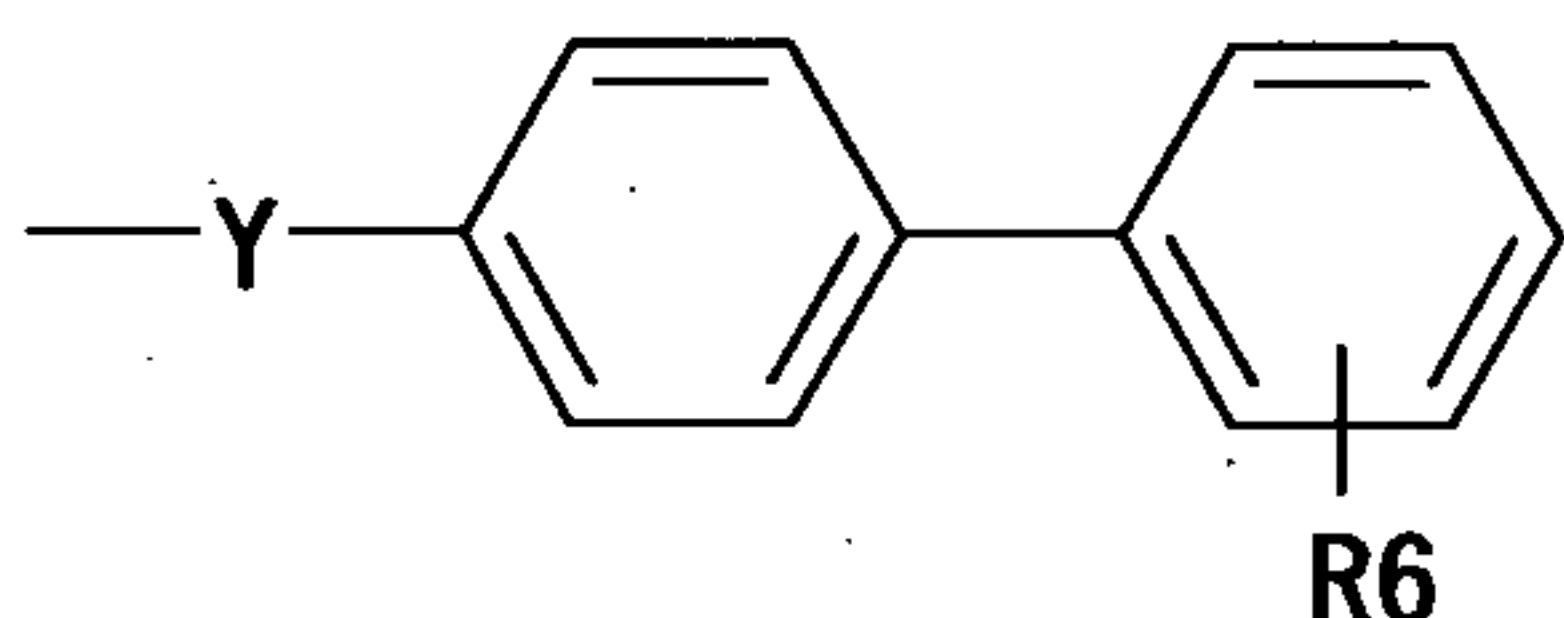


or

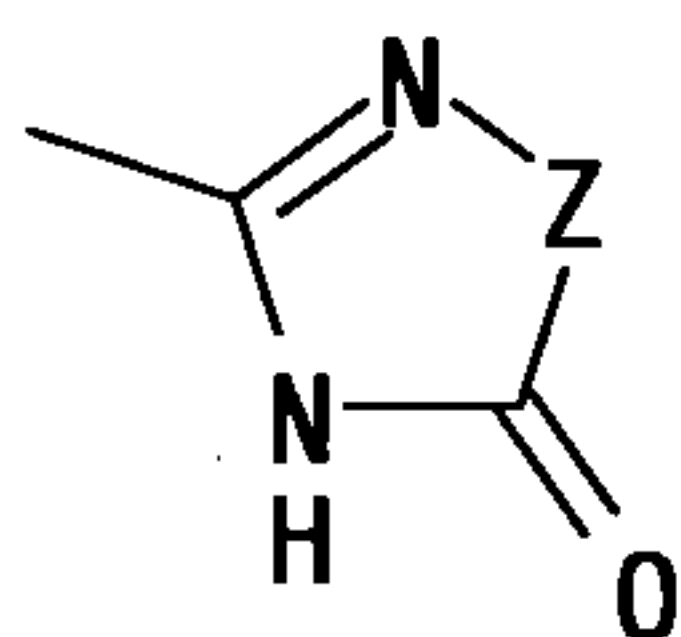


wherein

5 R2 is a group represented by the formula:



wherein R6 is a group represented by the formula:



wherein Z is O or S(O)_n (n is an integer of 0 to 2), and

10 Y is an optionally substituted C1-C4 alkylene group or a group represented by the formula: -O-W-, -W-O-, -N(Rd)-W- or -W-N(Rd)-

wherein W is a bond or an optionally substituted C1-C4 alkylene group, and Rd is an optionally substituted C1-C6 alkyl group or an optionally substituted C3-C6 cycloalkyl group (the biphenyl group is optionally further substituted); R3 and R4 are each independently

- (1) hydrogen,
- (2) an optionally substituted C1-C6 alkyl group,
- 20 (3) an optionally substituted C3-C6 cycloalkyl group,
- (4) an optionally substituted C1-C6 alkoxy group,
- (5) an optionally substituted C3-C6 cycloalkyloxy group,

(6) an optionally substituted C1-C6 alkylamino group,
 (7) an optionally substituted di(C1-C6)alkylamino group or
 (8) an optionally substituted C1-C6 alkylthio group; and
 R5 is

- 5 (1) hydrogen,
- (2) an optionally substituted C1-C6 alkyl group,
- (3) an optionally substituted C2-C6 alkenyl group,
- (4) an optionally substituted cyclic group,
- (5) a group represented by the formula: -CO-R8

10 wherein R8 is an optionally substituted C1-C6 alkyl group or
 an optionally substituted cyclic group, or

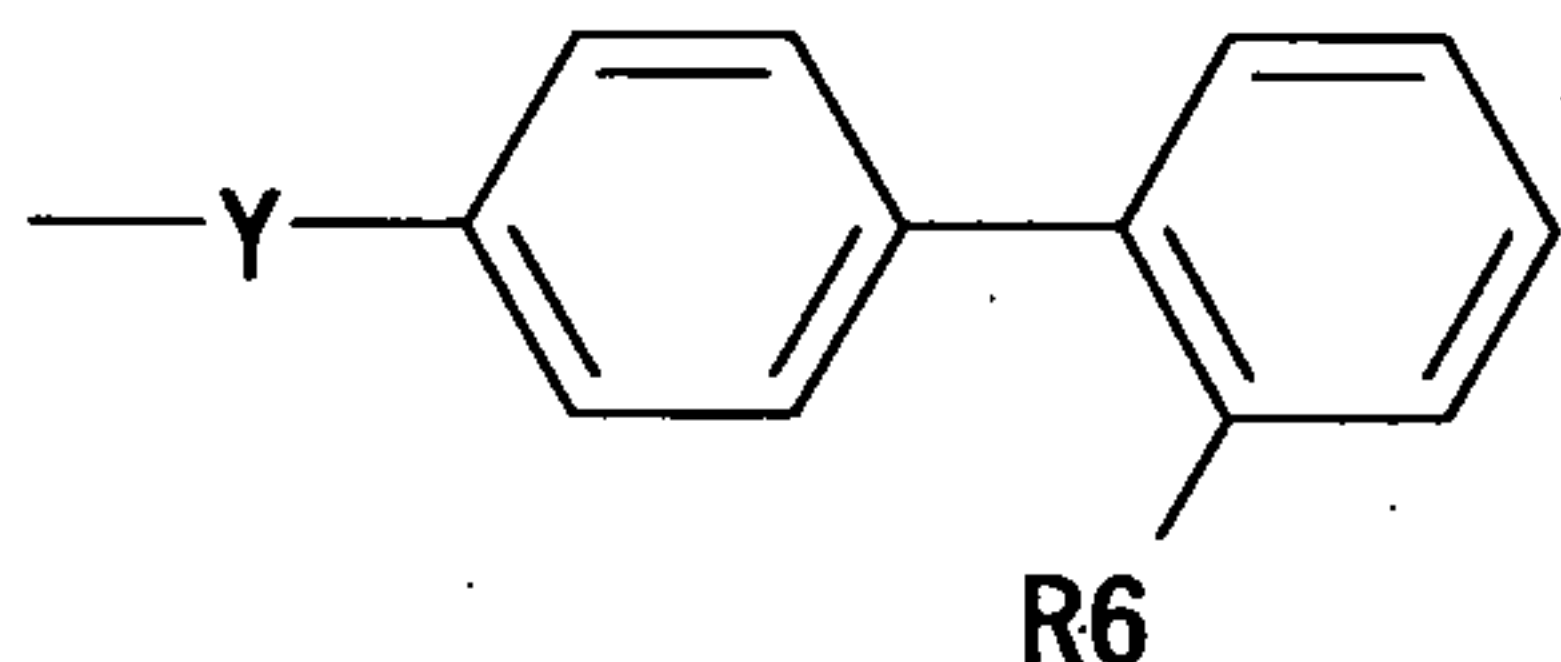
(6) a group represented by the formula: -O-R8'

wherein R8' is an optionally substituted C1-C6 alkyl group or
 an optionally substituted cyclic group,

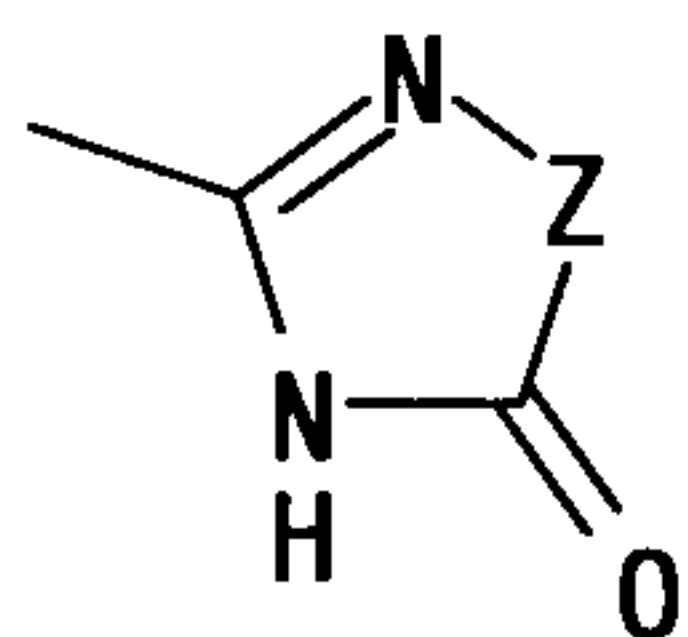
15 or a salt thereof.

2. The compound of claim 1, wherein R1 is an oxo group.

3. The compound of claim 1, wherein R2 is a group represented
 20 by the formula:



wherein R6 is a group represented by the formula:

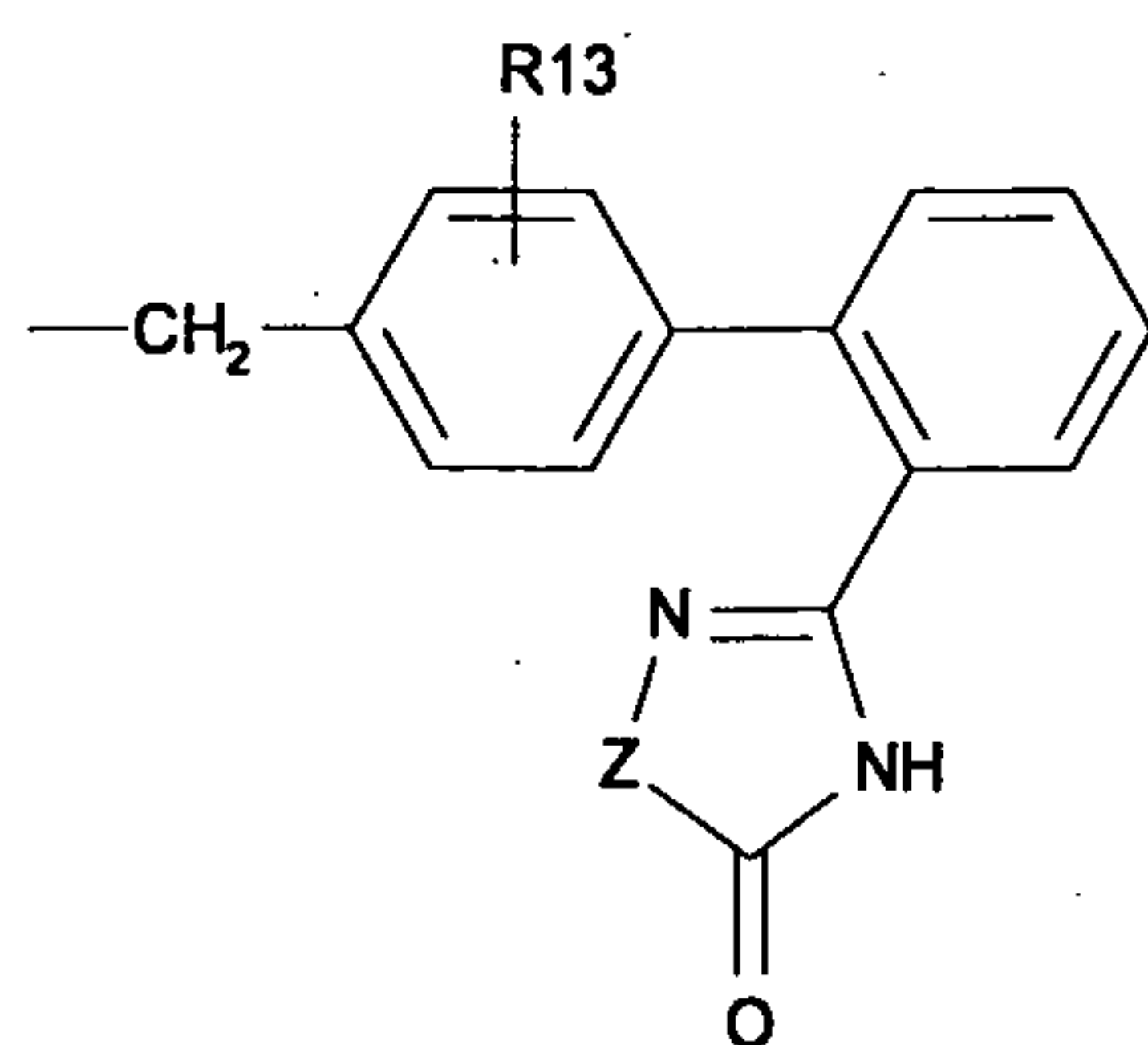


wherein Z is O or S(O)_n (n is an integer of 0 to 2), and

25 Y is a C1-C4 alkylene group,

(the biphenyl group is optionally further substituted).

4. The compound of claim 3, wherein R2 is a group represented
 by the formula:

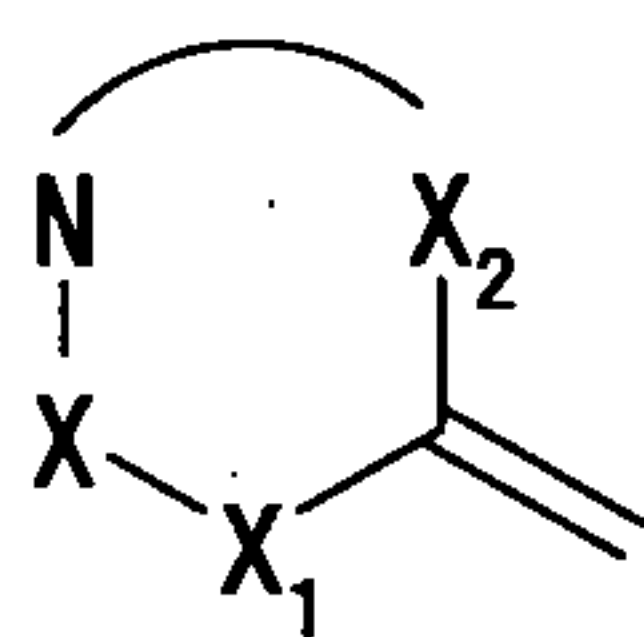


wherein R13 is

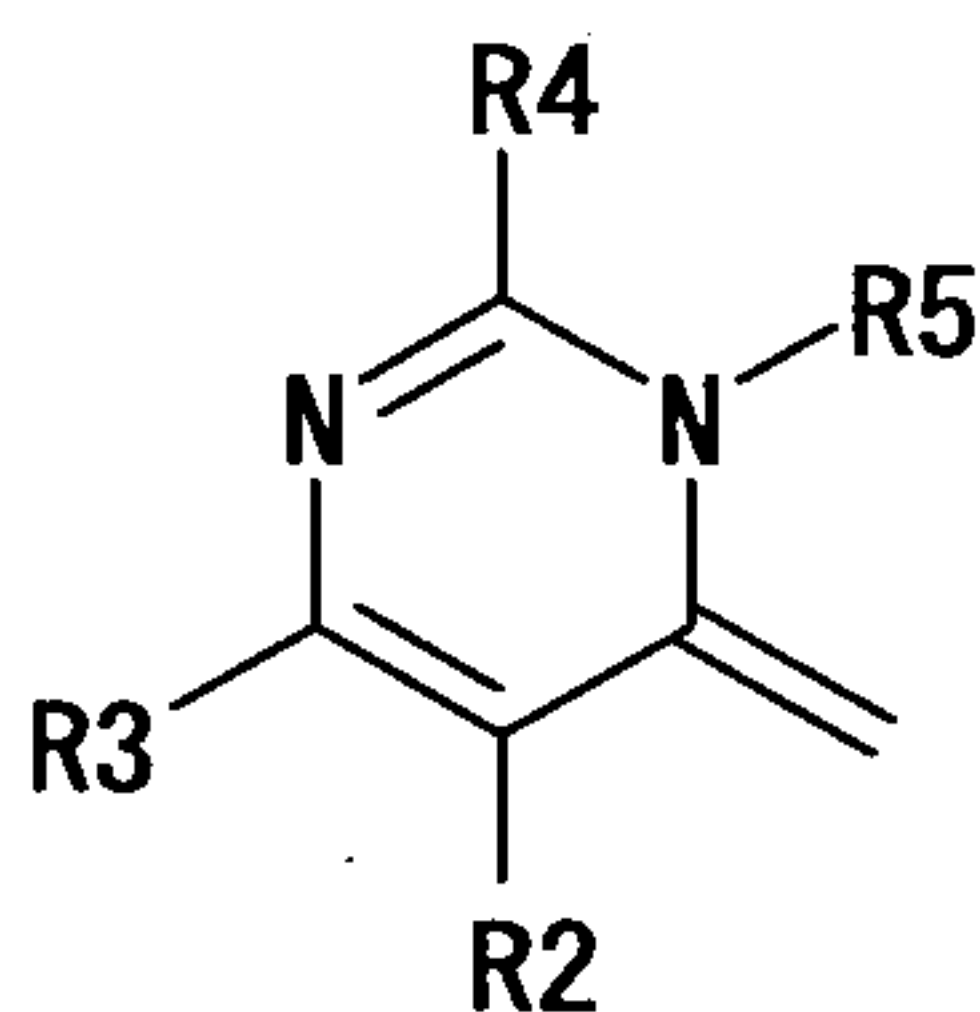
- (1) hydrogen,
- (2) halogen,
- 5 (3) a C1-C6 alkoxy group, or
- (4) a C1-C6 alkyl group optionally having 1 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group, and
- Z is O or S.

10

5. The compound of claim 1, wherein a group represented by the formula:



is



15

wherein R2, R3, R4 and R5 are as defined in claim 1.

6. The compound of claim 5, wherein R3 is

- (1) a C1-C6 alkyl group optionally substituted by 1 to 3
- 20 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;
- (2) a C3-C6 cycloalkyl group;

- (3) a C1-C6 alkoxy group; or
- (4) a C1-C6 alkylthio group.

7. The compound of claim 5, wherein R4 is

- 5 (1) hydrogen;
- (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group and a heterocyclic group;
- 10 (3) a C3-C6 cycloalkyl group;
- (4) a C1-C6 alkoxy group; or
- (5) a di(C1-C6)alkylamino group.

8. The compound of claim 5, wherein R5 is an optionally
15 substituted C1-C6 alkyl group or an optionally substituted cyclic group.

9. The compound of claim 8, wherein R5 is an optionally substituted C6-C14 aryl group.

20

10. The compound of claim 9, wherein R5 is a C6-C14 aryl group optionally substituted by 1 to 3 substituents selected from the group consisting of

- (i) halogen;
- 25 (ii) a hydroxy group;
- (iii) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group, a C1-C6 alkoxy group and a C1-C6 alkyl-carbonyl group;
- 30 (iv) a C2-C6 alkenyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group;
- (v) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of a C2-C6
35 alkynyl group, a C1-C6 alkoxy group, halogen, a cyano group, a

hydroxy group, a C3-C6 cycloalkyl group, a C1-C6 alkoxy-carbonyl group and a carbamoyl group;

(vi) a C2-C6 alkenyloxy group;

(vii) a C2-C6 alkynyloxy group;

5 (viii) a C1-C6 alkyl-carbonylamino group;

(ix) a C1-C6 alkylthio group;

(x) a C1-C6 alkylsulfinyl group;

(xi) a C1-C6 alkylsulfonyl group;

(xii) a C1-C6 alkyl-carbonyl group;

10 (xiii) a C1-C6 alkyl-carbamoyl group; and

(xiv) a di(C1-C6)alkyl-carbamoyl group.

11. 3-(4-Isopropoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-
15 4(3H)-one;

6-butyl-2-methoxy-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-phenylpyrimidin-4(3H)-one;

6-butyl-3-(3,4-dimethylphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
20 4(3H)-one;

6-butyl-3-[3-(1-hydroxy-1-methylethyl)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;

6-butyl-3-(4-ethoxyphenyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
25 3-[4-(1-ethylpropoxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;

3-(4-tert-butoxyphenyl)-2-ethyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-
30 4(3H)-one;

2-ethyl-3-[4-(2-hydroxy-1,1-dimethylethoxy)phenyl]-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one; or

35 2-ethyl-3-[4-(2-hydroxy-1,1-dimethylpropoxy)phenyl]-5-{[2'-(5-

oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl}-6-propylpyrimidin-4(3H)-one;
or a salt thereof.

5 12. The compound of claim 9, wherein R5 is a C6-C14 aryl group optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) a C3-C6 cycloalkyl group;

(ii) a C3-C10 cycloalkyloxy group optionally substituted by 1
10 to 3 substituents selected from the group consisting of halogen, an oxo group, a hydroxy group, a C1-C6 alkyl group, a C1-C6 alkoxy group optionally substituted by 1 to 3 halogens, a hydroxy-C1-C6 alkyl group and a C1-C6 alkoxy-C1-C6 alkyl group;

15 (iii) a C6-C14 aryloxy group;

(iv) a heterocyclyl-oxy group optionally substituted by 1 to 3 C1-C6 alkyl groups;

(v) a heterocyclyl-C1-C6 alkyloxy group; and

(vi) a heterocyclic group.

20

13. 3-[4-(Cyclobutyloxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]-6-propylpyrimidin-4(3H)-one;

3-[4-(cyclopropyloxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]-6-propylpyrimidin-4(3H)-one;

3-[4-(cyclopentyloxy)phenyl]-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]-6-propylpyrimidin-4(3H)-one;

30 2-ethyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]-6-propyl-3-[4-(tetrahydro-2H-pyran-4-yloxy)phenyl]pyrimidin-4(3H)-one;

2-ethyl-3-(4-{[(2R)-2-hydroxycyclopentyl]oxy}phenyl)-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl]-6-propylpyrimidin-4(3H)-one;

2-ethyl-3-{4-[(trans-4-hydroxycyclohexyl)oxy]phenyl}-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;

2-ethyl-3-{4-[(cis-4-hydroxycyclohexyl)oxy]phenyl}-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;

2-ethyl-3-{4-[(4-oxocyclohexyl)oxy]phenyl}-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;

3-(4-{[(2R,4s,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl]oxy}phenyl)-2-ethyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one; or

2-ethyl-3-{4-[(3-hydroxycyclohexyl)oxy]phenyl}-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;

or a salt thereof.

14. The compound of claim 8, wherein R5 is an optionally substituted heterocyclic group.

15. The compound of claim 14, wherein R5 is a heterocyclic group optionally substituted by 1 to 3 substituents selected from the group consisting of

- (i) halogen;
- (ii) an oxo group;
- (iii) a hydroxy group;
- (iv) an amino group;
- (v) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C1-C6 alkoxy group;
- (vi) a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a hydroxy group and a C3-C6 cycloalkyl group;
- (vii) a heterocycl-yl-oxy group;

- (viii) a C1-C6 alkyl-carbonylamino group; and
 (ix) a C1-C6 alkoxy-carbonyl group.

16. 6-Butyl-2-cyclopropyl-3-(2,3-dihydro-1-benzofuran-5-yl)-5-
 5 { [2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
 yl]methyl}pyrimidin-4(3H)-one;
 6-butyl-3-(2,3-dihydro-1-benzofuran-5-yl)-2-isopropyl-5-{ [2'-(
 (5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
 yl]methyl}pyrimidin-4(3H)-one;
 10 6-butyl-3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-
 methyl-5-{ [2'-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-
 yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 3-(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-2-methyl-5-{ [2'-(
 (5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-
 15 6-propylpyrimidin-4(3H)-one;
 3-(4-hydroxy-2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)-2-
 methyl-5-{ [2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-
 yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;
 6-butyl-3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-
 20 methyl-5-{ [2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-
 yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 2-methyl-3-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)-5-{ [2'-(5-
 oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-
 propylpyrimidin-4(3H)-one;
 25 3-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-methyl-5-
 { [2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
 yl]methyl}-6-propylpyrimidin-4(3H)-one; or
 3-(7-fluoro-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-
 methyl-5-{ [2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-
 30 yl)biphenyl-4-yl]methyl}-6-propylpyrimidin-4(3H)-one;
 or a salt thereof.

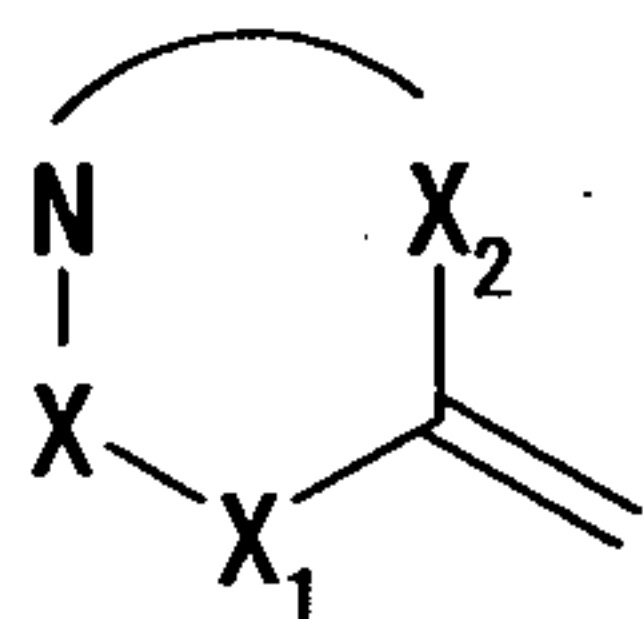
17. The compound of claim 8, wherein R5 is an optionally
 substituted C1-C6 alkyl group.

18. The compound of claim 17, wherein R5 is a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of

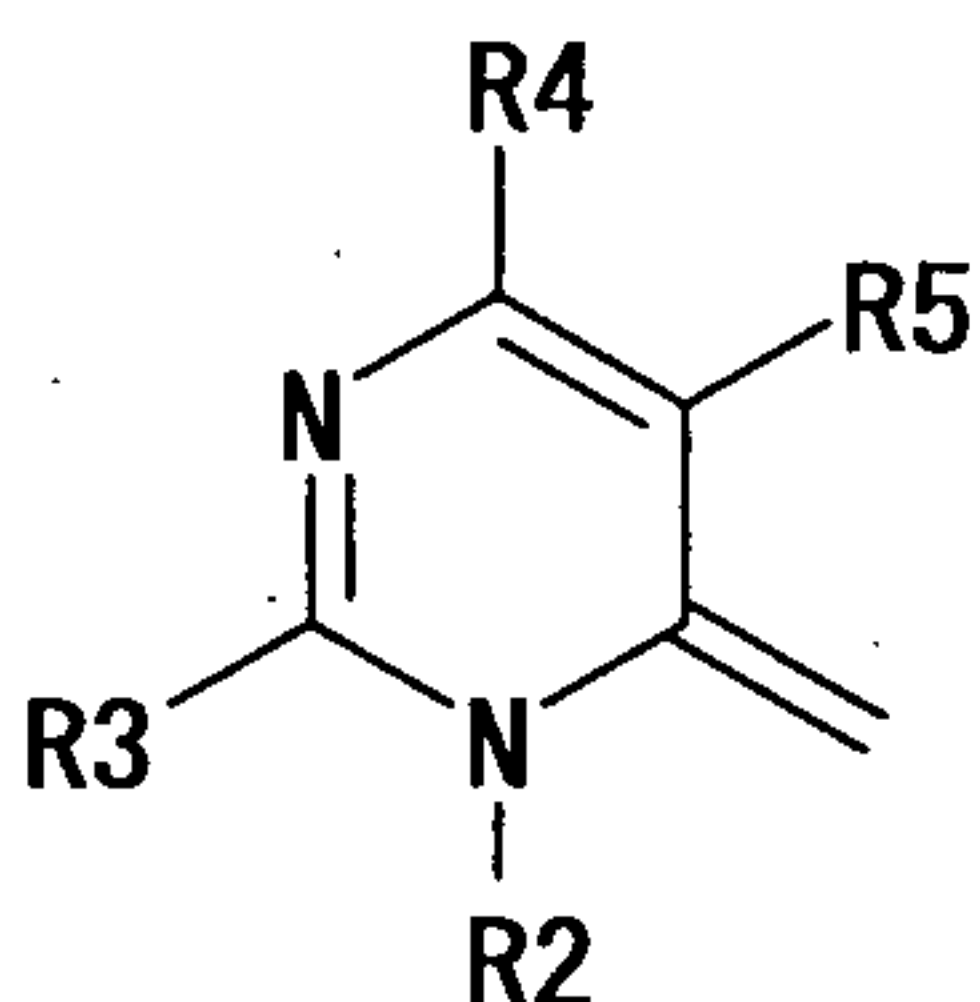
- (i) a hydroxy group;
- 5 (ii) a carboxy group;
- (iii) a C1-C6 alkoxy-carbonyl group;
- (iv) a C1-C6 alkyl-carbonyl group;
- (v) a C3-C10 cycloalkyl-carbonyl group;
- (vi) a C6-C14 aryl-carbonyl group optionally substituted by 1
- 10 to 3 substituents selected from the group consisting of halogen and a C1-C6 alkoxy group;
- (vii) a heterocyclyl-carbonyl group;
- (viii) a C1-C6 alkyl-carbamoyl group;
- (ix) a C3-C6 cycloalkyl group;
- 15 (x) an adamantyl group;
- (xi) a C6-C14 aryl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, a
- 20 hydroxy group and a C1-C6 alkoxy group; a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group; a C1-C6 alkylsulfonyl group; a carboxy group; a C1-C6 alkoxy-carbonyl group; a C1-C6 alkyl-carbonyl group; and a heterocyclyl-
- 25 carbonyl group;
- (xii) a heterocyclic group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen; a hydroxy group; a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of
- 30 halogen, a hydroxy group and a C1-C6 alkoxy group; a C6-C14 aryl group; a C7-C16 aralkyl group; a heterocyclic group; and a C1-C6 alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen and a hydroxy group; and
- 35 (xiii) a C1-C6 alkoxyimino group.

19. 6-Butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(2-thienylmethyl)pyrimidin-4(3H)-one;
- 5 6-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
- 3-benzyl-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
- 10 6-butyl-3-(cyclohexylmethyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
- 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-(pyridin-2-ylmethyl)pyrimidin-
- 15 4(3H)-one;
- 6-butyl-3-(4-methoxybenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
- 3-(1,3-benzothiazol-2-ylmethyl)-6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-
- 20 yl]methyl}pyrimidin-4(3H)-one;
- 2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-6-propyl-3-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one;
- 25 6-butyl-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-3-[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]pyrimidin-4(3H)-one; or
- 6-butyl-3-(2,6-difluorobenzyl)-2-methyl-5-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-
- 30 4(3H)-one;
- or a salt thereof.

20. The compound of claim 1, wherein the group represented by the formula:



is a group represented by the formula:



wherein R2, R3, R4 and R5 are as defined in claim 1.

5

21. The compound of claim 20, wherein R3 is

- (1) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, halogen, a hydroxy group and a C3-C6 cycloalkyl group;
- (2) a C3-C6 cycloalkyl group;
- (3) a C1-C6 alkoxy group; or
- (4) a C1-C6 alkylthio group.

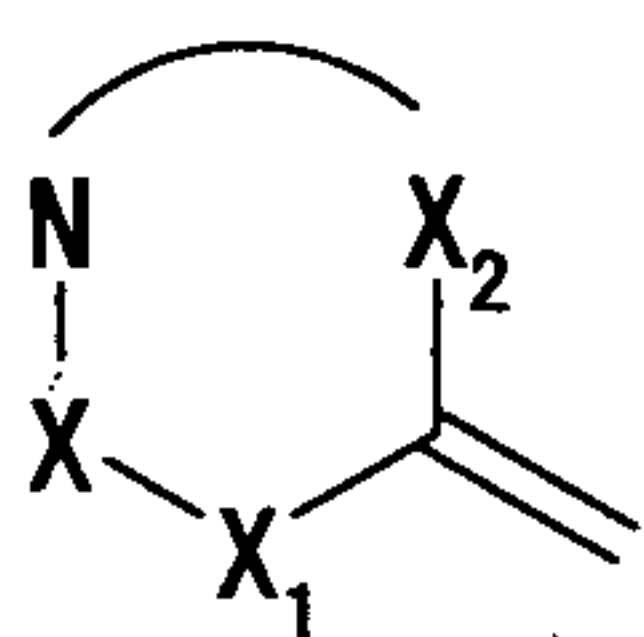
15 22. The compound of claim 20, wherein R4 is

- (1) hydrogen;
- (2) a C1-C6 alkyl group optionally substituted by 1 to 3 substituents selected from the group consisting of a C1-C6 alkoxy group, a hydroxy group, halogen, a cyclic hydrocarbon group and a heterocyclic group;
- (3) a C3-C6 cycloalkyl group;
- (4) a C1-C6 alkoxy group; or
- (5) a di(C1-C6)alkylamino group.

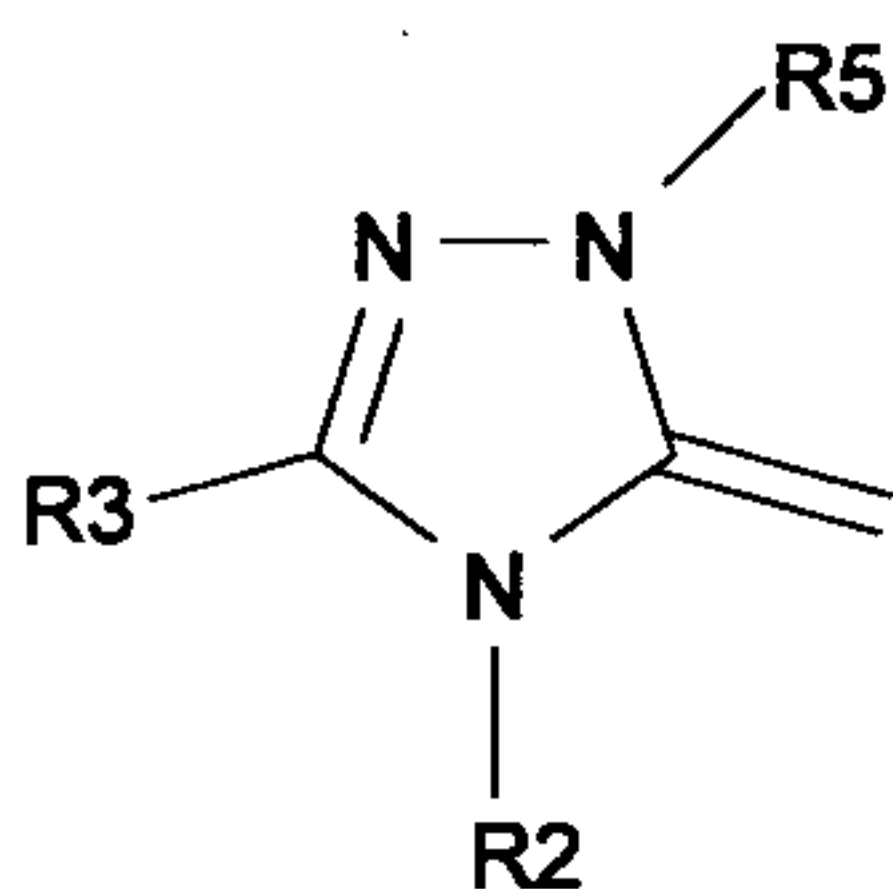
25 23. The compound of claim 20, wherein R5 is an optionally substituted C1-C6 alkyl group or an optionally substituted cyclic group.

24. 5-Benzyl-2-ethoxy-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propyl-5-(tetrahydro-2H-pyran-2-ylmethyl)pyrimidin-4(3H)-one;
 5-(4-isopropoxyphenyl)-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one;
 5-benzyl-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one;
 2-butyl-5-[hydroxy(phenyl)methyl]-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 5-benzoyl-2-butyl-6-methyl-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one;
 6-ethyl-5-(morpholin-4-ylmethyl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one;
 6-ethyl-5-(1-hydroxy-2-methylpropyl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one;
 6-ethyl-5-(6-isopropoxypyridin-3-yl)-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one; or
 6-ethyl-5-[4-(2-hydroxy-1,1-dimethylethoxy)phenyl]-3-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-2-propylpyrimidin-4(3H)-one;
 or a salt thereof.

25. The compound of claim 1, wherein the group represented by the formula:



is a group represented by the formula:



wherein R2, R3 and R5 are as defined in claim 1.

5 26. The compound of claim 25, wherein R3 is a C1-C6 alkyl group.

27. The compound of claim 25, wherein R5 is an optionally substituted C1-C6 alkyl group or an optionally substituted
10 cyclic group.

28. 3-(4'-{[3-Butyl-1-(2,2-dimethylpropyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one;

15 3-(4'-{[3-butyl-1-(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one;

3-(4'-{[3-butyl-5-oxo-1-(2-phenylethyl)-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one;

20 3-{4'-[(3-butyl-1-sec-butyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)methyl]biphenyl-2-yl}-1,2,4-oxadiazol-5(4H)-one;

3-{4'-[(3-butyl-5-oxo-1-phenyl-1,5-dihydro-4H-1,2,4-triazol-4-yl)methyl]biphenyl-2-yl}-1,2,4-oxadiazol-5(4H)-one;

3-(4'-{[3-butyl-5-oxo-1-(tetrahydro-2H-pyran-2-yl)methyl]-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one;

3-[4'-({3-butyl-1-[2-(4-fluorophenyl)-2-oxoethyl]-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)methyl}biphenyl-2-yl]-1,2,4-oxadiazol-5(4H)-one;

30 3-[4'-({3-butyl-1-[2-(4-methoxyphenyl)-2-oxoethyl]-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)methyl}biphenyl-2-yl]-1,2,4-

oxadiazol-5(4H)-one; or

3-(4'-{[3-butyl-1-(3,3-dimethyl-2-oxobutyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]methyl}biphenyl-2-yl)-1,2,4-oxadiazol-5(4H)-one;

5 or a salt thereof.

29. A prodrug of the compound of claim 1.

30. A pharmaceutical agent comprising the compound of claim 1
10 or a prodrug thereof as an active ingredient.

31. The pharmaceutical agent of claim 30, which has an
angiotensin II receptor inhibitory activity and/or a
peroxisome proliferator-activated receptor agonistic activity.

15

32. The pharmaceutical agent of claim 30, which is an agent
for the prophylaxis or treatment of circulatory diseases,
metabolic diseases and/or central nervous system diseases.

20 33. The pharmaceutical agent of claim 30, which is an agent
for the prophylaxis or treatment of hypertension, cardiac
disease, arteriosclerosis, kidney disease, cerebral apoplexy,
hyperlipidemia, obesity, diabetes, dementia and/or Alzheimer's
disease.

25

34. A method for inhibiting an angiotensin II receptor and/or
activating a peroxisome proliferator-activated receptor in a
mammal, which comprises administering the compound of claim 1
or a prodrug thereof to said mammal.

30

35. A method for preventing or treating circulatory diseases,
metabolic diseases and/or central nervous system diseases in a
mammal, which comprises administering the compound of claim 1
or a prodrug thereof to said mammal.

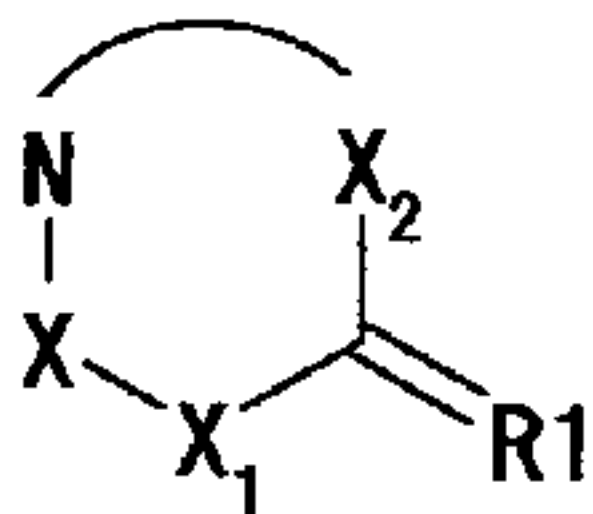
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36. A method for preventing or treating hypertension, cardiac disease, arteriosclerosis, kidney disease, cerebral apoplexy, hyperlipidemia, obesity, diabetes, dementia and/or Alzheimer's disease in a mammal, which comprises administering the
5 compound of claim 1 or a prodrug thereof to said mammal.

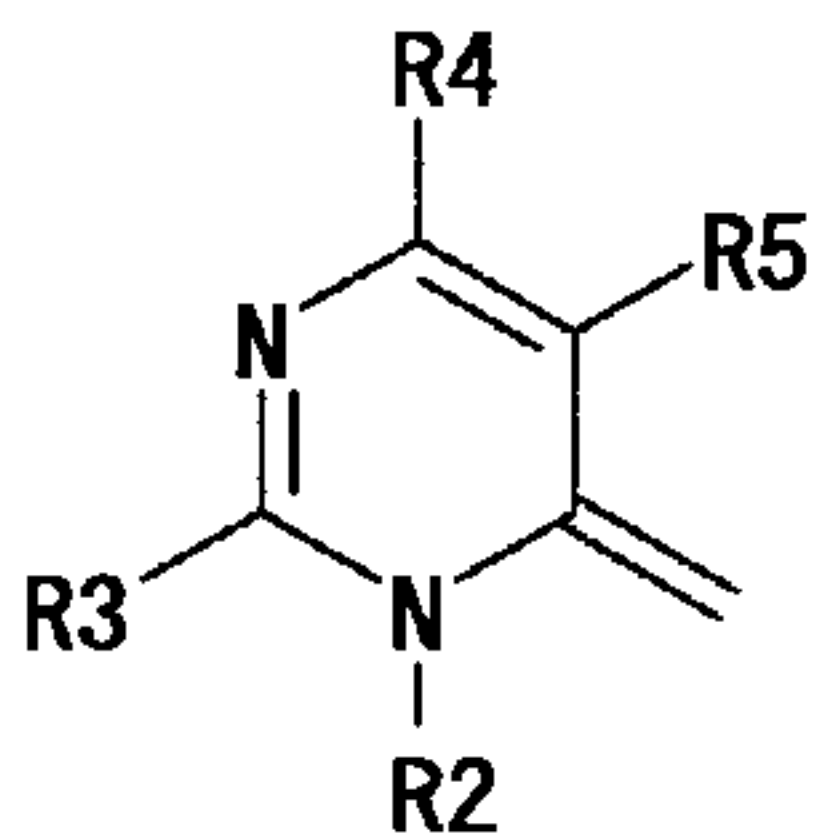
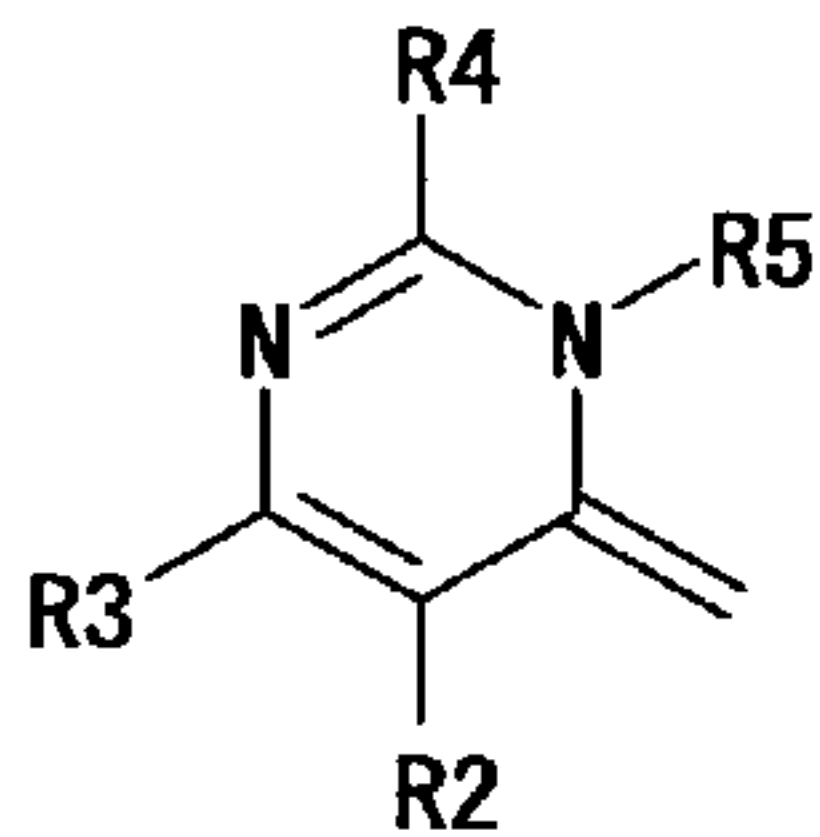
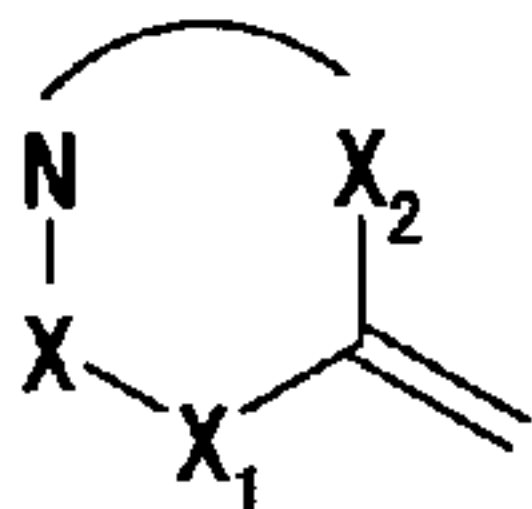
37. Use of the compound of claim 1 or a prodrug thereof for the production of an agent which has an angiotensin II receptor inhibitory activity and/or a peroxisome proliferator-
10 activated receptor agonistic activity.

38. Use of the compound of claim 1 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of circulatory diseases, metabolic diseases and/or central
15 nervous system diseases.

39. Use of the compound of claim 1 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of hypertension, cardiac disease, arteriosclerosis, kidney
20 disease, cerebral apoplexy, hyperlipidemia, obesity, diabetes, dementia and/or Alzheimer's disease.



(I)



or

