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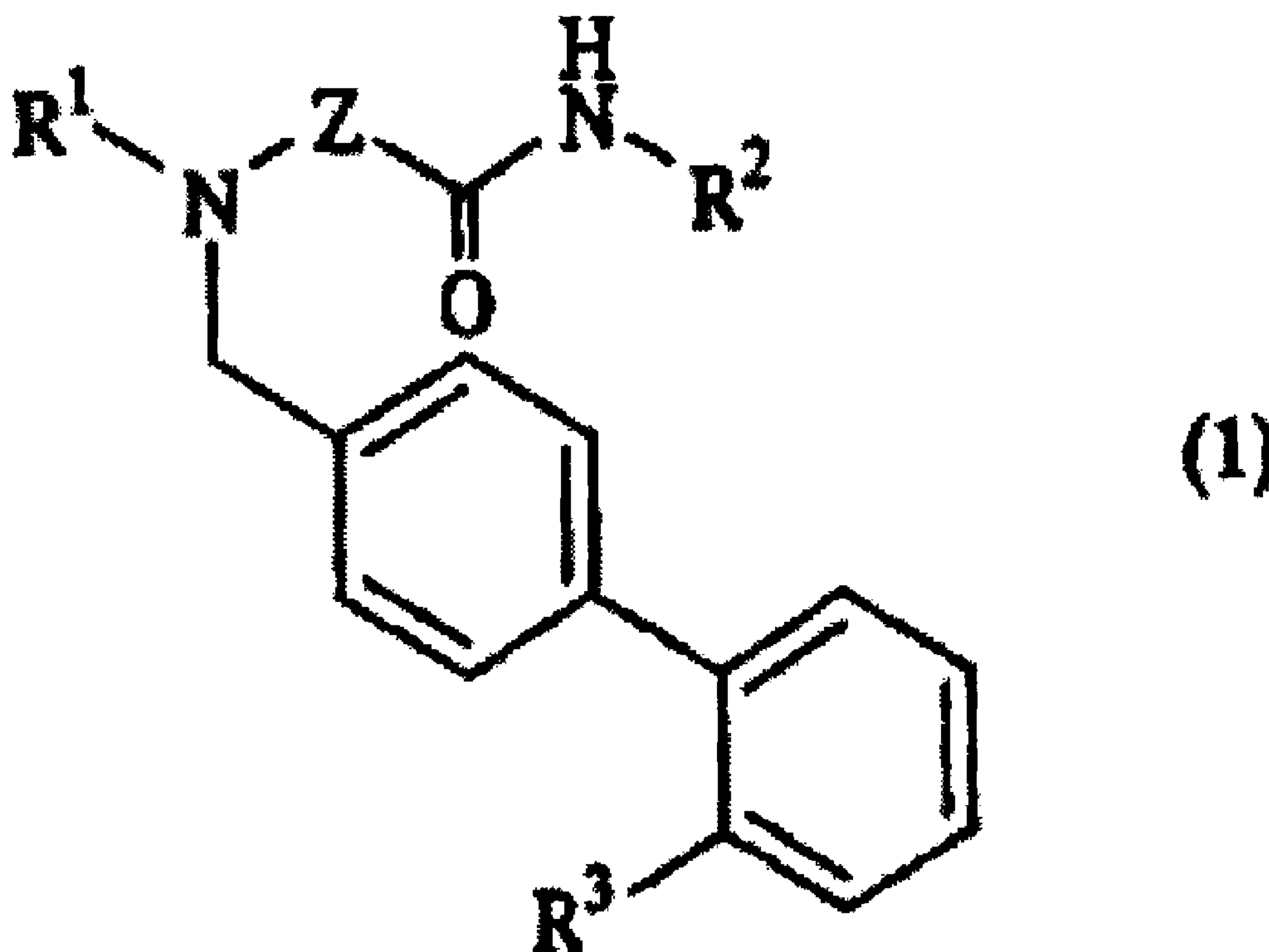
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(54) Titre : DERIVES DE BIPHENYLE

(54) Title: BIPHENYL DERIVATIVES



(57) Abrégé/Abstract:

Biphenyl derivatives represented by the following formula (1): (see formula 1) wherein R^1 represents a C_{5-7} alkyl group, R^2 represents a substituted or unsubstituted aromatic hydrocarbon, or cycloalkyl group, R^3 represents a tetrazolyl group, $-NHCOCF_3$, $-NHSO_2CF_3$ or $-SO_2NHCONHR^4$ in which R^4 represents a substituted or unsubstituted aromatic hydrocarbon group, and Z represents a single bond, a C_{1-4} alkylene group or $-SO_2NH-$, and salts thereof; and ACAT inhibitors and medicines containing them as active ingredients. The compounds according to the present invention possess excellent ACAT inhibitory activities, and are useful as preventives and/or therapeutics for diseases caused by the enhancement of ACAT activity, for example, hypercholesterolemia, atherosclerosis and the like.

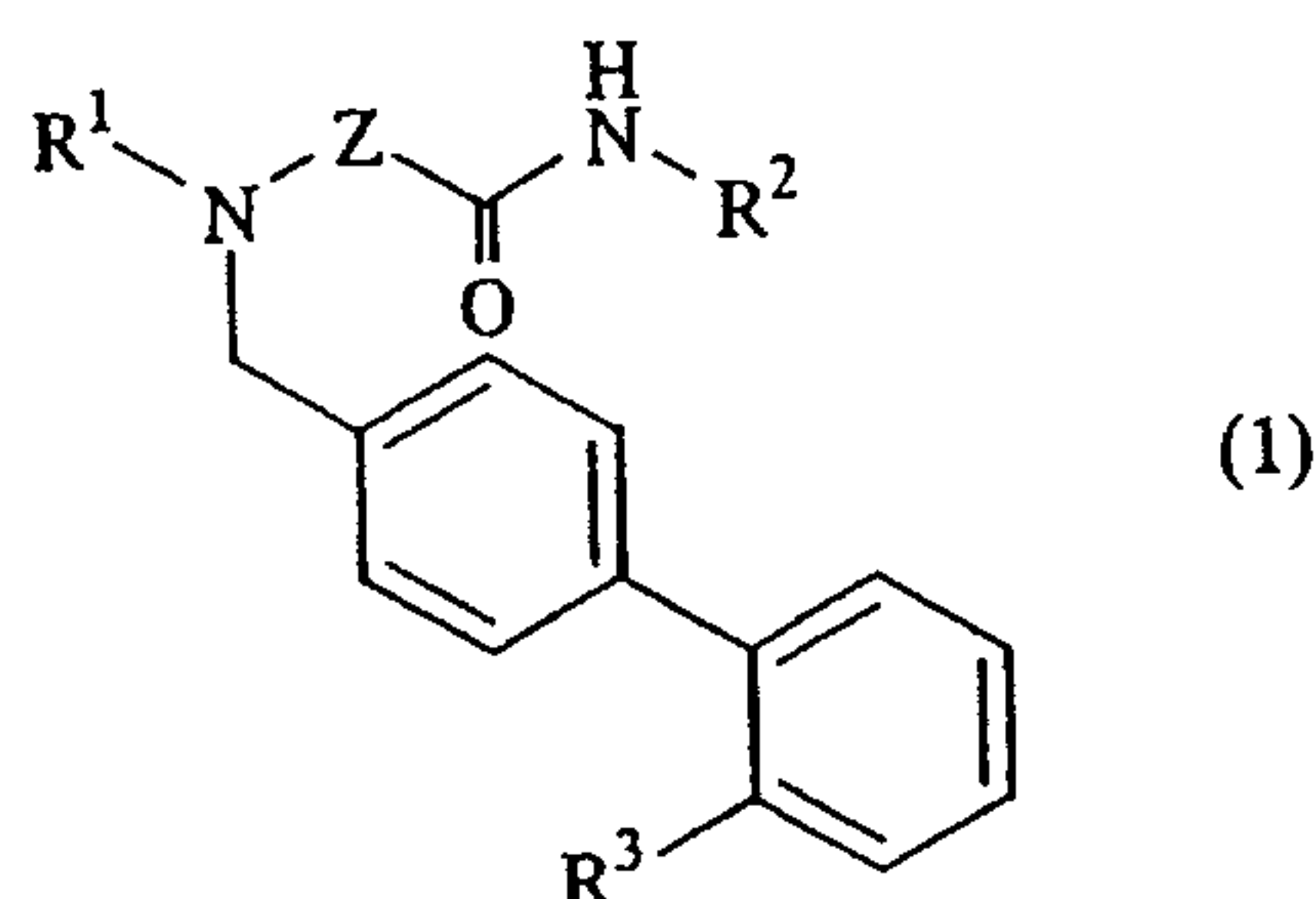
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ABSTRACT

Biphenyl derivatives represented by the following formula (1):



5 wherein R^1 represents a C_{5-7} alkyl group, R^2 represents a substituted or unsubstituted aromatic hydrocarbon, or cycloalkyl group, R^3 represents a tetrazolyl group, -
 NHCOCF₃, -NH₂SO₂CF₃ or -SO₂NHCONHR⁴ in which R^4 represents a
 substituted or unsubstituted aromatic hydrocarbon group,
 10 and Z represents a single bond, a C_{1-4} alkylene group or -
 SO₂NH-, and salts thereof; and ACAT inhibitors and
 medicines containing them as active ingredients.

The compounds according to the present invention
 possess excellent ACAT inhibitory activities, and are
 15 useful as preventives and/or therapeutics for diseases
 caused by the enhancement of ACAT activity, for example,
 hypercholesterolemia, atherosclerosis and the like.

DESCRIPTION**BIPHENYL DERIVATIVES****5 Technical Field**

 This invention relates to compounds possessing excellent acyl-CoA:cholesterol acyltransferase (hereinafter abbreviated as "ACAT") inhibitory activities, and also to medicines containing the same.

10

Background Art

 Free cholesterol has important physiological activities as a constituent of cell membranes and the precursor of bile acids, and also as a regulatory factor for the metabolism of cholesterol. In hyperlipidemia characterized by an extraordinarily high value of serum cholesterol or the like, however, it has been considered that atherosclerosis advances to result in an increase of the onset risk of coronary diseases. An increase of serum cholesterol has been, therefore, ranked as the greatest risk factor for coronary diseases.

20

 ACAT is an enzyme which catalyzes esterification of cholesterol in cells, and physiologically, plays an important role in the control of the free cholesterol levels in blood and cells. It has been reported that the

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physiological role of ACAT differs depending on the tissue and that ACAT takes part in the absorption of exogenous cholesterol in the small intestine, in the secretion of very-low-density lipoproteins (VLDL) in the liver, and in the accumulation of cholesterol esters in arterial walls. However, the enhanced ACAT activity leads to an onset and advancement of hyperlipidemia and arteriosclerosis due to the increase of serum lipids and the formation of foam cells based on the excessive accumulation of cholesterol esters in arterial walls.

The inhibition of ACAT activity is, therefore, expected to bring about lipid lowering effect on the basis of the suppression of cholesterol absorption through the digestive tracts and the suppression of VLDL secretion from the liver, and further, antiarteriosclerotic effect on the basis of the suppression of the formation of foam cells. Aiming at hyperlipidemia treatment agents and antiarteriosclerotic agents, a variety of substances having ACAT inhibitory activity has been developed accordingly. Under the current circumstances, however, these conventional ACAT inhibitors have not found practical utility yet, because, in clinical trials, they have not been able to obtain sufficient effect or have induced side effects such as hepatopathy, degeneration or necrosis of the adrenal

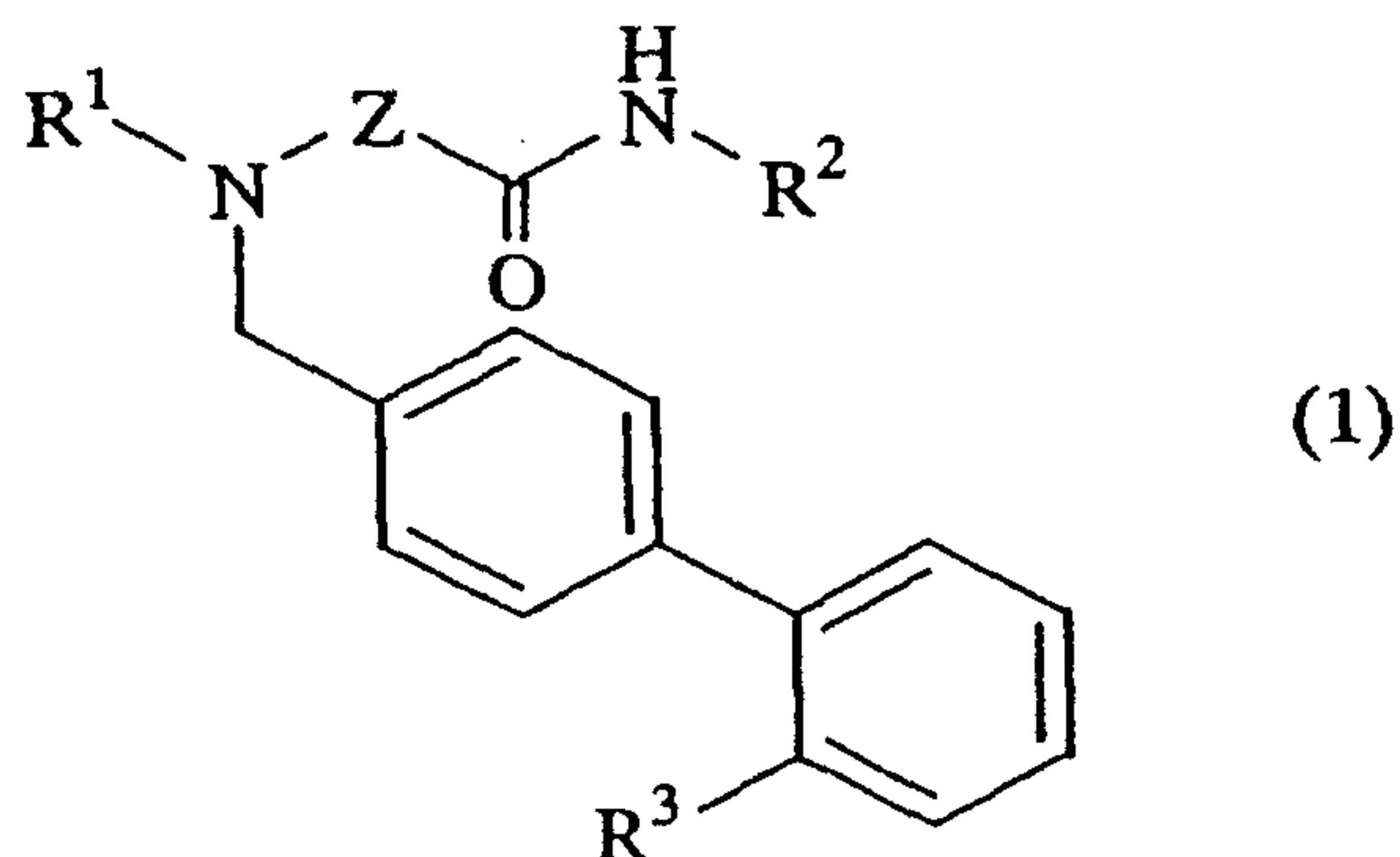
cortex, and diarrhea caused by the suppression of fat absorption.

An object of the present invention is, therefore, to provide a new substance having ACAT inhibitory activity and a medicine containing the same.

Disclosure of the Invention

With the foregoing circumstances in view, the present inventors have proceeded with an extensive investigation. As a result, it has been found that the compounds represented by the formula (1) described below and salts thereof have excellent ACAT inhibitory activities and are useful as preventives and/or therapeutics for diseases caused by the enhancement of ACAT activity, for example, hypercholesterolemia, atherosclerosis and the like, leading to the completion of the present invention.

Specifically, the present invention provides a biphenyl derivative represented by the following formula (1):



wherein R^1 represents a C_{5-7} alkyl group, R^2 represents a substituted or unsubstituted aromatic hydrocarbon, or a cycloalkyl group, R^3 represents a tetrazolyl group, -
 5 $NHCOCF_3$, $-NHSO_2CF_3$ or $-SO_2NHCONHR^4$ in which R^4 represents a substituted or unsubstituted aromatic hydrocarbon group, and Z represents a single bond, a C_{1-4} alkylene group or $-SO_2NH-$, or a salt thereof; and an ACAT inhibitor and medicine containing them as an active ingredient.

10 The present invention also provides a medicinal composition comprising the biphenyl derivative or the salt thereof and a pharmacologically acceptable carrier.

The present invention further provides a method for the treatment of a disease caused by the enhancement of
 15 ACAT activity, which comprises administering the biphenyl derivative or the salt thereof.

The present invention still further provides use of the biphenyl derivative or the salt thereof for the production of a medicine.

Best Modes for Carrying out the Invention

In the formula (1), the C₅₋₇ alkyl group represented by R¹ can be either linear or branched, although a linear alkyl group is preferred. Particularly preferred are n-pentyl, n-hexyl and n-heptyl from the standpoint of ACAT inhibitory activity.

As the aromatic hydrocarbons represented by R² and R⁴, C₆₋₁₀ aromatic hydrocarbon groups are preferred, with phenyl and naphthyl being more preferred and phenyl being particularly preferred. As the substituents which can substitute on the aromatic hydrocarbon groups, 1 to 3 substituents selected from halogen atoms and C₁₋₅ alkyl groups are preferred. Examples of the halogen atoms can include fluorine atom, chlorine atom, bromine atom and iodine atom, with fluorine atom being particularly preferred. The C₁₋₅ alkyl groups can be either linear or branched, and their specific examples can include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl and isopentyl. Among these, methyl, ethyl and isopropyl are particularly preferred.

As the cycloalkyl group represented by R², C₃₋₈, especially C₅₋₇ cycloalkyl groups are preferred. Specifically, cyclohexyl is particularly preferred.

Preferred as R² are C₆₋₁₀ aromatic hydrocarbon which may be substituted by 1 to 3 substituents selected from

halogen atoms and C₁₋₅ alkyl groups, or C₃₋₈ cycloalkyl groups, and more preferred are phenyl which may be substituted by 1 to 3 substituents selected from halogen atoms and C₁₋₅ alkyl groups, or C₅₋₇ cycloalkyl groups. Of these, particularly preferred specific examples of R² can include di- or trihalogenophenyl groups such as difluorophenyl and trifluorophenyl; di- or tri-C₁₋₅ alkylphenyl groups such as diisopropylphenyl and trimethylphenyl; and cyclohexyl.

Preferred as R⁴ are C₆₋₁₀ aromatic hydrocarbon groups which may be substituted by 1 to 3 substituents selected from halogen atoms and C₁₋₅ alkyl groups, and more preferred is a phenyl group which may be substituted by 1 to 3 substituents selected from halogen atoms and C₁₋₅ alkyl groups. Of these, particularly preferred specific examples of R⁴ can include di- or trihalogenophenyl groups such as difluorophenyl and trifluorophenyl; and di- or tri-C₁₋₅ alkylphenyl groups such as diisopropylphenyl and trimethylphenyl.

As the tetrazolyl group represented by R³, 5-tetrazolyl is particularly preferred. Particularly preferred examples of R³ can include tetrazolyl, -NHCOCF₃ and -NHSO₂CF₃.

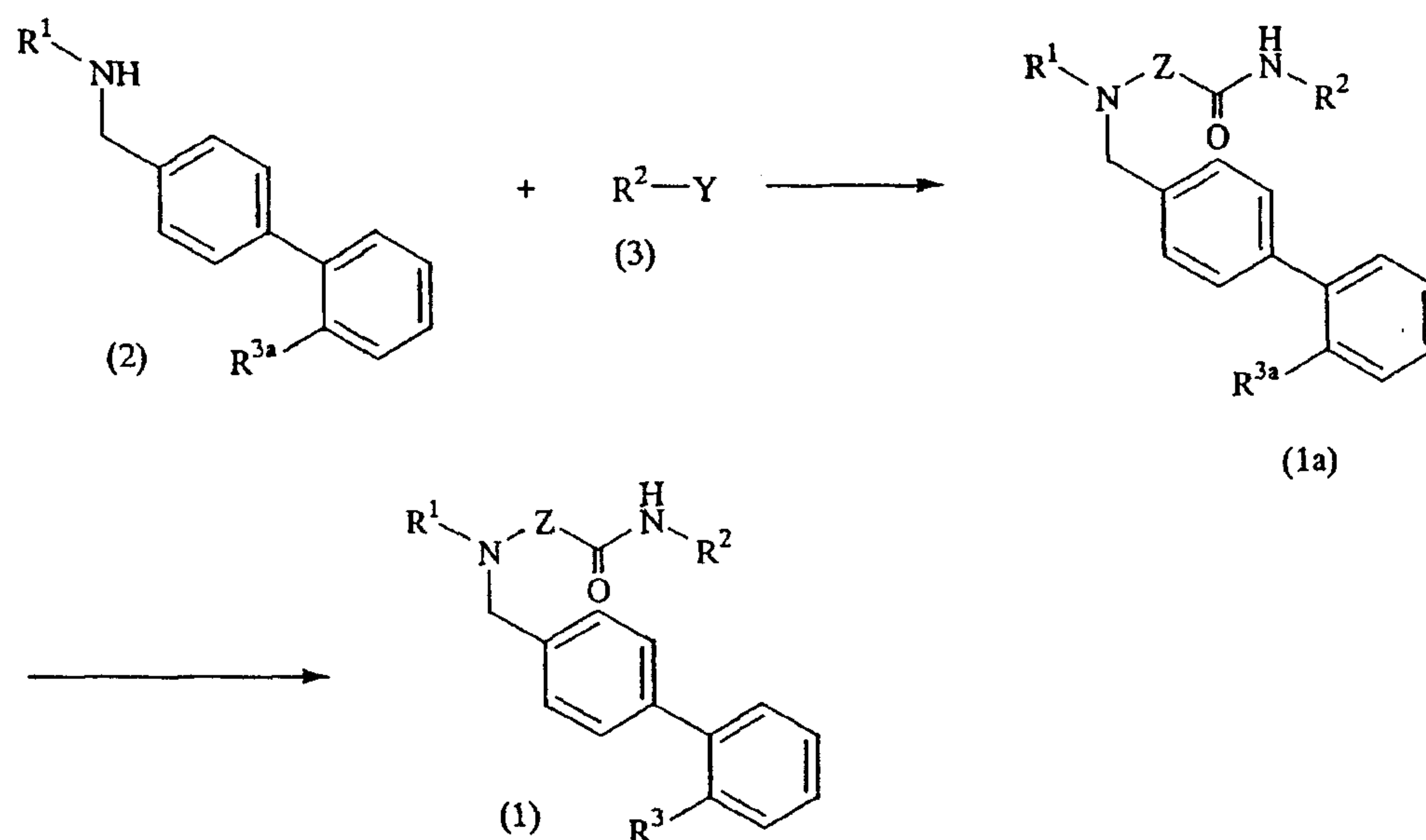
Illustrative of the C₁₋₄ alkylene group represented by Z are methylene, ethylene, 1-methylethylene,

trimethylene, and tetramethylene, with methylene being particularly preferred. Particularly preferred examples of Z can include a single bond, methylene and $-\text{SO}_2\text{NH}-$.

No particular limitation is imposed on the salt of
5 the biphenyl derivative represented by the formula (1) [the invention compound (1)], provided that it is physiologically acceptable. Preferred examples, however, can include mineral acid salts such as the hydrochloride, sulfate, phosphate and nitrate; organic acid salts such
10 as the citrate, oxalate, fumarate, maleate, formate, acetate, methanesulfonate, benzenesulfonate and paratoluenesulfonate; the carbonate; alkali metal salts such as the sodium and potassium salts; alkaline earth salts such as the calcium and magnesium salts; and the
15 ammonium salt.

In the present invention, the invention compound (1) or its salt includes its internal salts, adducts, complexes, solvates, hydrates and the like.

The invention compound (1) or its salt can be
20 produced, for example, in accordance with the following reaction scheme:



wherein R^{3a} represents a group, which can be converted into R^3 , or R^3 itself; Y represents $-NHCOOR^5$, $-NCO$, $-NHCOCH_2X^1$ or $-NHCONHSO_2X^2$ in which R^5 represents an alkyl or phenyl group and X^1 and X^2 represent halogen atoms; and R^1 , R^2 and Z have the same meanings as defined above.

Namely, the invention compound (1) can be obtained by reacting the compound (3) with the secondary amine (2) to obtain the compound (1a) and then converting R^{3a} into R^3 as needed.

The secondary amine (2) can be obtained, for example, by condensing an alkylamine with a substituted biphenyl methylhalide. As an alternative, it can also be obtained by reducing an N-alkanoyl-N-substituted biphenyl methylamine, which has been obtained by a reaction between a substituted biphenyl methylamine and a fatty acid halide, with a reducing agent such as lithium

aluminum hydride.

As the compound (3), on the other hand, the group described above can be mentioned. For a specific description, use of a carbamate ($R^2NHCOOR^5$) or isocyanate (R^2NCO) as the compound (3) affords a compound in which Z is a single bond, use of $R^2-NHCOCH_2X^1$ as the compound (3) yields a compound in which Z is a methylene group, and use of $R^2-NHCONHSO_2X^2$ as the compound (3) provides a compound in which Z is $-SO_2NH-$.

The condensation reaction between the secondary amine (2) and the compound (3) can be conducted, for example, in the presence of a base such as a tertiary amine or potassium carbonate, although the reaction conditions vary depending on the kind of Y in the compound (3).

As R^{3a} , N-protected tetrazolyl groups, nitro group and the like can be mentioned in addition to R^3 . As an illustrative N-protected tetrazolyl group, N-triphenylmethyln-tetrazolyl can be mentioned. The deprotection reaction of the protecting group can be conducted preferably by treatment with an acid such as hydrochloric acid. If R^{3a} is a nitro group, a compound in which R^3 is $-NHCOCF_3$ or $-NHSO_2CF_3$ can be obtained when, after conversion of the nitro group into an amino group by reduction, the amino group is trifluoroacetylated or

trifluoromethylsulfonylated.

It is to be noted that the production of the invention compound (1) is not limited to the reaction scheme relying upon the reaction between the secondary amine (2) and the compound (3). As any reaction scheme can be employed insofar as a biphenylmethyl group, R^1 and $-ZCONHR^2$ can bind together via a nitrogen atom, it is possible to introduce the biphenylmethyl group or R^1 into the nitrogen atom at last.

The salt of the invention compound (1) can be produced, for example, by mixing the invention compound (1) with an acid or base in a polar solvent and/or a non-polar solvent.

The invention compound (1) or the salt thereof, which has been obtained as described above, shows excellent ACAT inhibitory activity and hence, is useful as an ACAT activity inhibitor.

As an ACAT activity inhibitor can reduce the absorption of cholesterol from food, can suppress the secretion of VLDL from the liver and can decrease the accumulation of intracellular cholesterol esters in the walls of blood vessels such as arteries, it can lower the cholesterol level in blood and further, can prevent the formation of lesion parts due to atherosclerosis or the like. Accordingly, the invention compound (1) or its

salt is effective for diseases caused by the enhancement of ACAT activity, for example, hypercholesterolemia, atherosclerosis, and various diseases caused by such diseases in mammals (for example, men, mice, rats, rabbits, dogs, monkeys, and the like), and is effective as preventives and/or therapeutics for such diseases. Incidentally, specific examples of hypercholesterolemia, atherosclerosis, and various diseases caused by such diseases can include hyperlipidemia, arteriosclerosis, cervical or cerebral arteriosclerosis, cerebrovascular disease, cerebral infarction, stroke, reperfusion injuries, ischemic heart diseases, myocardial infarction, coronary sclerosis, nephrosclerosis, arteriosclerotic nephrosclerosis, arteriolar nephrosclerosis, malignant nephrosclerosis, ischemic enteropathy, acute mesenteric vessel occlusion, chronic intestinal angina, ischemic colitis, aortic aneurysm, arteriosclerosis obliterans (ASO), and fatty liver.

The medicine according to the present invention contains the invention compound (1) or its salt as an active ingredient, and can be used either singly or in combination with one or more other medicinal ingredients or one or more medicinal ingredients having different action mechanisms. Further, the invention compound (1) or its salt can also be administered as a medicinal

composition with a pharmacologically acceptable carrier added therein as needed, and hence, can be formulated into a medicinal composition (preparation). Namely, the medicinal composition according to the present invention is characterized in that it contains the compound represented by the formula (1) and/or its salt. Examples of the term "composition (preparation)" as used herein can include inhalations, injections, oral preparations, perrectal preparations, and transdermal preparations. Pharmacologically acceptable carriers which can be incorporated in these compositions are, for example, excipients, binders, coating materials, lubricants, sugarcoating materials, disintegrators, extenders, correctives, emulsifiers, solubilizers, dispersants, stabilizer, pH adjusters, and isotonicities.

The preferred dosage of the medicine according to the present invention differs depending on the condition, the kind of disease, the sex, the age, the physique and the like, but in terms of the invention compound (1) or its salt, it is generally preferred to administer 1 to 1,000 mg in one to several portions per adult and day.

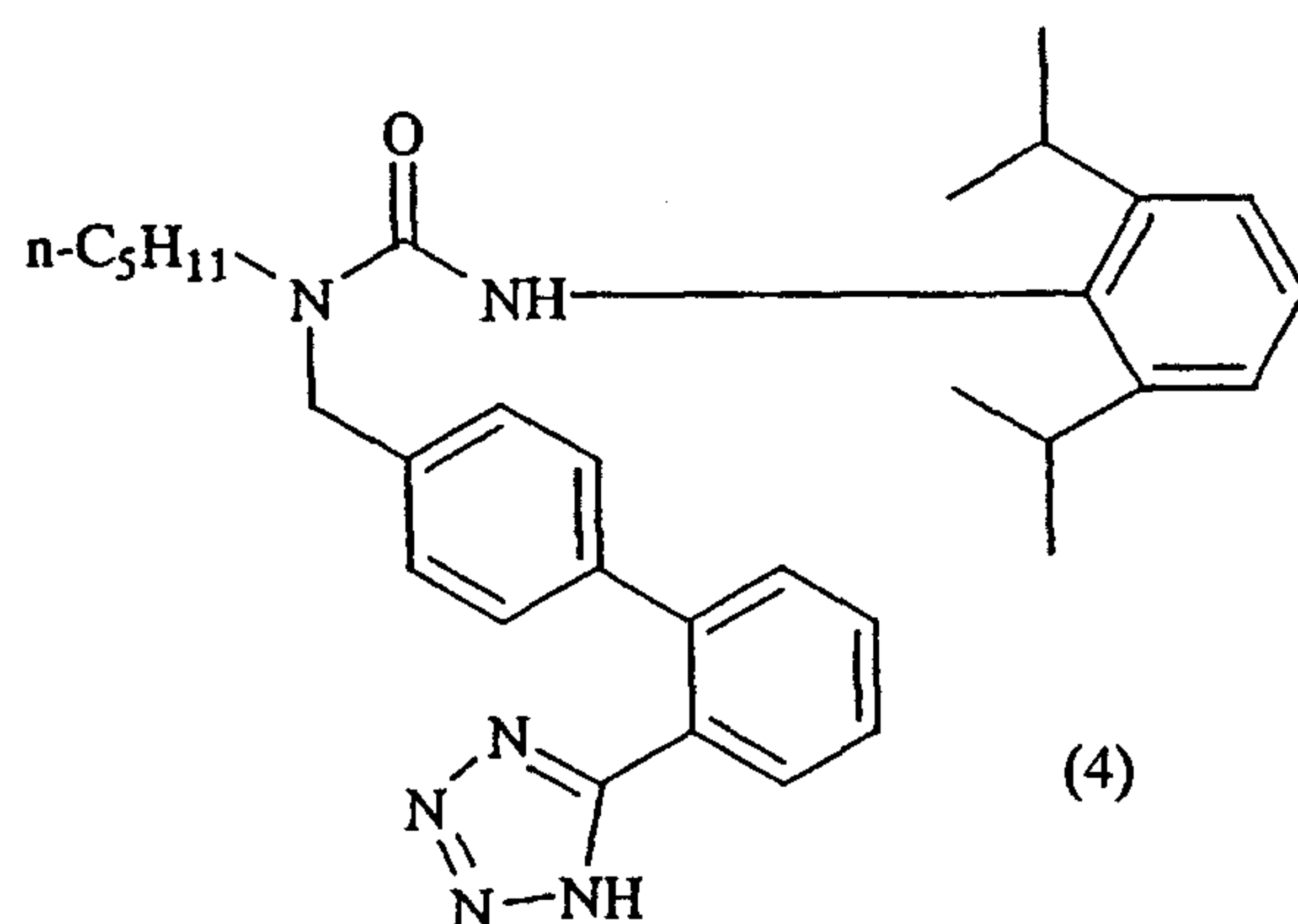
Examples

The present invention will hereinafter be described in further detail on the basis of Examples, needless to

say, the present invention shall by no means be limited only to the following Examples.

Example 1

5 N-(2,6-Diisopropylphenyl)-N'-pentyl-N'-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]urea



n-Pentylamine (129.6 mg) and triethylamine (170 mg) were dissolved in dimethylformamide (3 mL) and under ice bath cooling, [[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl] bromide (399.8 mg) was added, and then the mixture was stirred at room temperature. Forty-eight hours later, ethyl acetate (30 mL) was added, and the resulting mixture was washed three times with brine (50 mL, each). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue and phenyl 2,6-diisopropylphenylcarbamate (216.9 mg) were dissolved in toluene (10 mL), and the solution was heated under reflux. Two hours later, the reaction mixture was concentrated

under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford N-(2,6-diisopropylphenyl)-N'-pentyl-N'-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]urea (88.6 mg). Yield: 16%.

¹H-NMR (CDCl₃, ppm):

0.83-0.98 (m, 6H), 1.23-1.42 (m, 13H),
1.62-1.70 (m, 2H), 2.90-3.03 (m, 2H),
3.33 (t, 2H, J=7.29Hz), 4.49 (s, 2H), 5.56 (s, 1H),
6.90-6.94 (m, 6H), 7.10-7.17 (m, 6H), 7.22-7.37 (m, 11H),
7.42-7.54 (m, 2H), 7.96 (dd, 1H, J=7.02Hz, J=2.43Hz).

N-(2,6-Diisopropylphenyl)-N'-pentyl-N'-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]urea (330 mg) was dissolved in tetrahydrofuran (4 mL). After addition of 10% hydrochloric acid (1.2 mL), the resulting mixture was stirred at room temperature. Seventeen hours later, the reaction mixture was concentrated at low temperature under reduced pressure. Water (10 mL) was added to the concentrate, followed by extraction three times with chloroform (12 mL, each). The organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (chloroform/methanol) to afford the compound represented

by the formula (4) (0.21 g). Yield: 93%.

$^1\text{H-NMR}$ (CDCl_3 , ppm):

0.91 (t, 3H, $J=6.75\text{Hz}$), 0.97–1.12 (m, 12H),
 1.31–1.42 (m, 4H), 1.60–1.78 (m, 2H), 2.91–3.01 (m, 2H),
 3.27 (t, 2H, $J=7.83\text{Hz}$), 4.45 (s, 2H), 5.71 (s, 1H),
 6.96–7.20 (m, 7H), 7.39–7.60 (m, 3H),
 7.81 (dd, 1H, $J=7.29\text{Hz}$, $J=1.62\text{Hz}$).

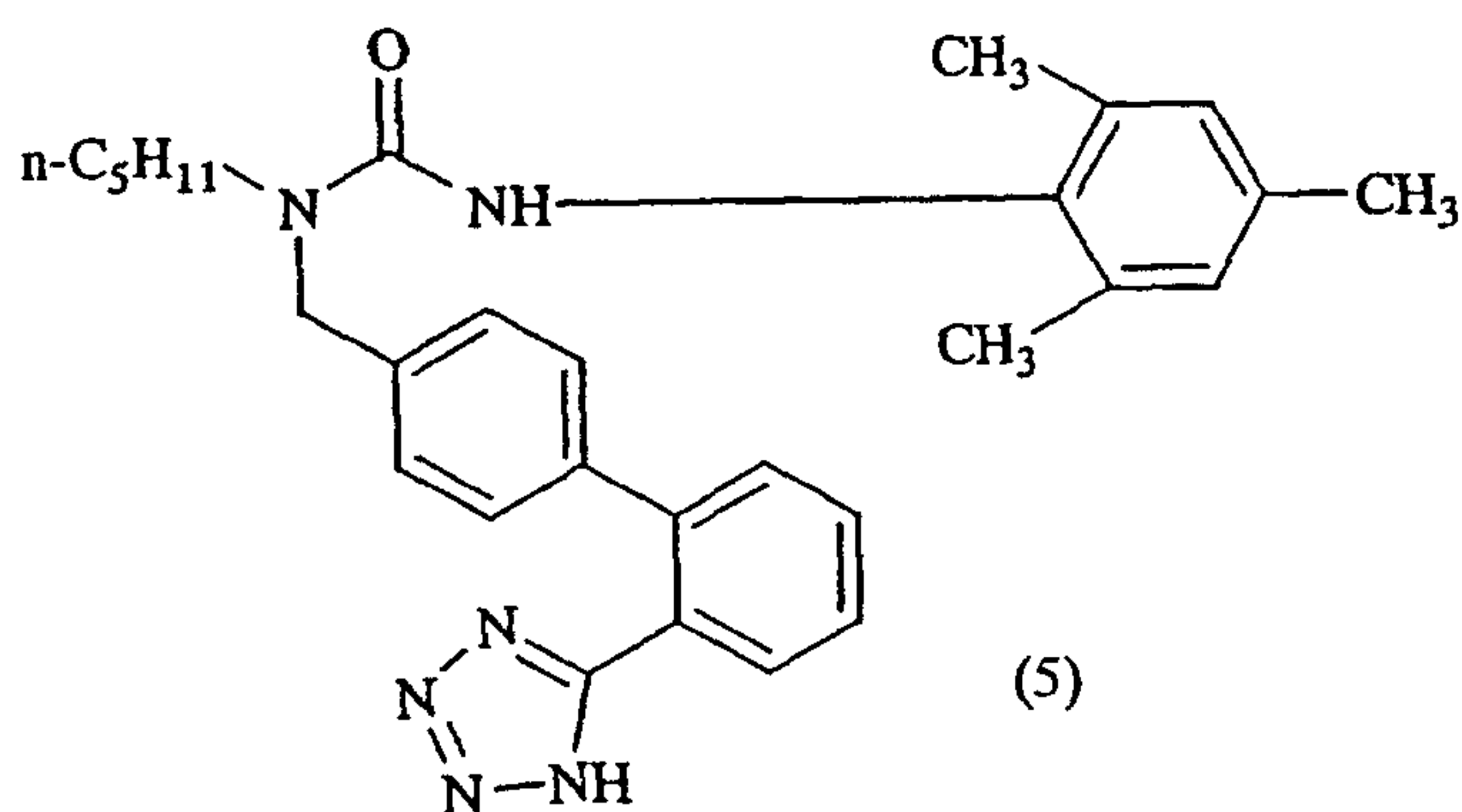
m.p. 129–132°C

IR (cm^{-1}) (KBr):

1255, 1510, 1609, 2868, 2930, 2960.

Example 2

N' -Pentyl- N' -[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]- N -(2,4,6-trimethylphenyl)urea



Using n -pentylamine (304.2 mg), triethylamine (442.2 mg), [[2'-[N -(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl] bromide (400 mg) and phenyl 2,4,6-trimethylphenylcarbamate (233.8 mg), N' -pentyl- N -(2,4,6-trimethylphenyl)- N' -[[2'-[N -(triphenylmethyl)tetrazol-5-

yl]-1,1'-biphenyl-4-yl)methyl]urea (113 mg) was obtained by a similar procedure as in Example 1. Yield: 22%.

¹H-NMR (CDCl₃, ppm):

0.88 (t, 3H, J=6.48Hz), 1.18-1.35 (m, 4H),
 1.61-1.69 (m, 2H), 2.05 (s, 3H), 2.23 (s, 6H),
 3.30 (t, 2H, J=7.29Hz), 4.49 (s, 2H), 5.54 (s, 1H),
 6.83-6.99 (m, 8H), 7.12-7.16 (m, 3H), 7.25-7.38 (m, 11H),
 7.44-7.92 (m, 2H),
 7.94 (dd, 1H, J=8.91Hz, J=2.16Hz).

N'-Pentyl-N-(2,4,6-trimethylphenyl)-N'-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]urea (113 mg) was treated with hydrochloric acid in a similar manner as in Example 1 to afford the compound represented by the formula (5) (61.8 mg).

Yield: 82%.

¹H-NMR (CDCl₃, ppm):

0.88 (t, 3H, J=6.75Hz), 1.22-1.35 (m, 4H),
 1.55-1.72 (m, 2H), 2.00 (s, 6H), 2.14 (s, 3H),
 3.21 (t, 2H, J=7.29Hz), 4.23 (s, 2H), 5.66 (s, 1H),
 6.55 (s, 2H), 7.07-7.29 (m, 5H), 7.44-7.62 (m, 2H),
 7.84 (dd, 1H, J=7.29Hz, J=1.35Hz).

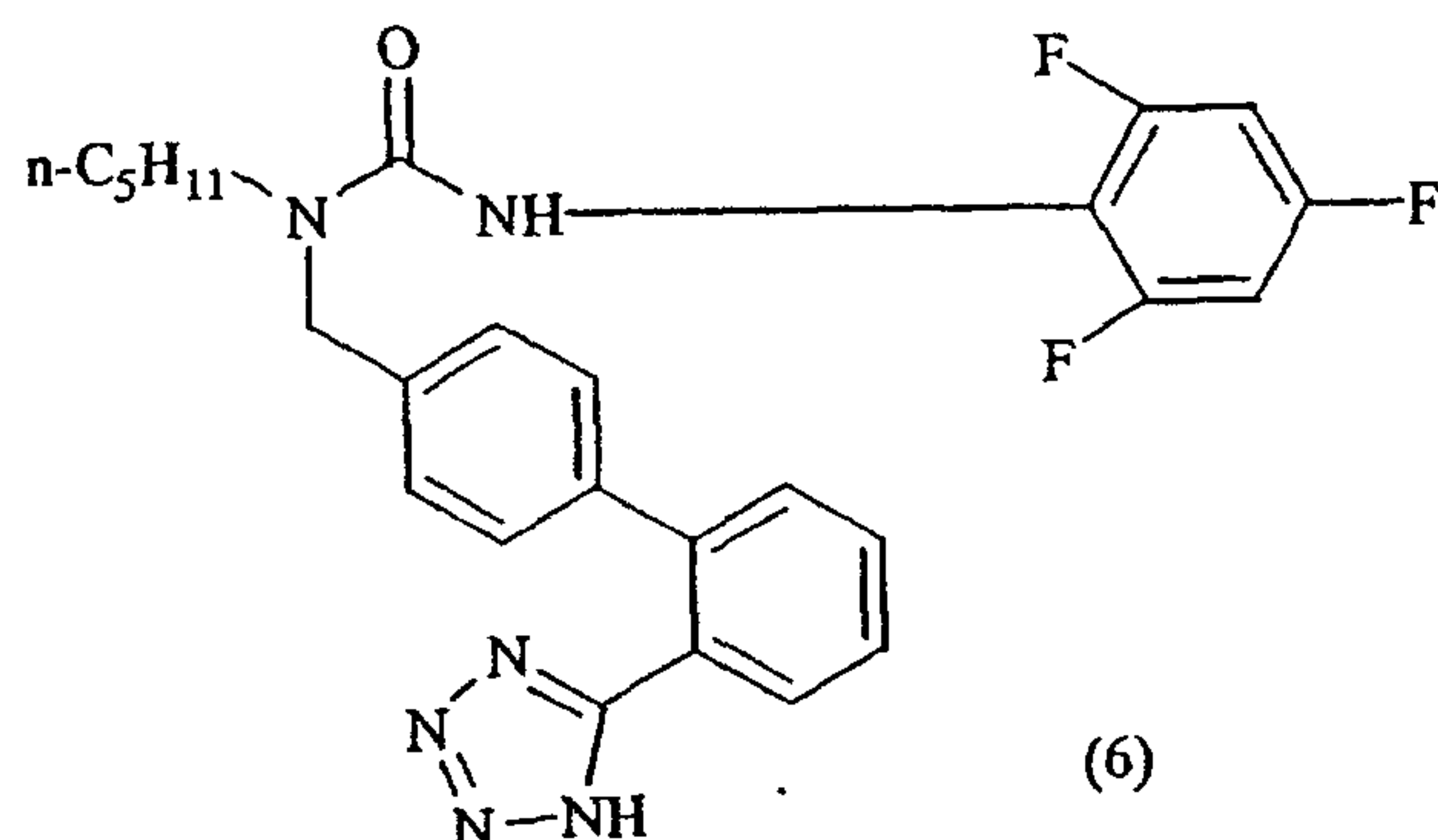
m.p. 106-109°C

IR (cm⁻¹) (KBr):

1240, 1466, 1600, 2928.

Example 3

N'-Pentyl-N'-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-N-(2,4,6-trifluorophenyl)urea



According to the procedure of Example 1, a
 5 secondary amine was produced from n-pentylamine (0.94 g)
 and [[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-
 biphenyl-4-yl]methyl] bromide (1.50 g). Using the
 secondary amine and phenyl 2,4,6-trifluorophenylcarbamate
 (0.72 g), N'-pentyl-N-(2,4,6-trifluorophenyl)-N'-[[2'-[N-
 10 (triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-
 yl]methyl]urea was afforded (0.50 g). Yield: 25%.

¹H-NMR (CDCl₃, ppm):

0.89 (t, 3H, J=6.48Hz), 1.23-1.36 (m, 4H),
 1.50-1.66 (m, 2H), 3.21 (t, 2H, J=7.56Hz), 4.49 (s, 2H),
 15 5.54 (s, 1H), 6.65-6.73 (m, 2H), 6.90-7.53 (m, 22H),
 7.94 (dd, 1H, J=7.02Hz, J=1.89Hz).

N'-Pentyl-N-(2,4,6-trifluorophenyl)-N'-[[2'-[N-
 (triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-
 yl]methyl]urea (173.2 mg) was treated with hydrochloric

acid in a similar manner as in Example 1 to afford the compound represented by the formula (6) (60.2 mg).

Yield: 52%.

$^1\text{H-NMR}$ (CDCl_3 , ppm):

5 0.89 (t, 3H, $J=6.48\text{Hz}$), 1.26-1.31 (m, 4H),
 1.55-1.65 (m, 2H), 3.28 (t, 2H, $J=7.02\text{Hz}$), 4.41 (s, 2H),
 6.14 (s, 1H), 6.51-6.57 (m, 2H), 6.90-7.65 (m, 7H),
 7.82 (d, 1H, $J=7.29\text{Hz}$).

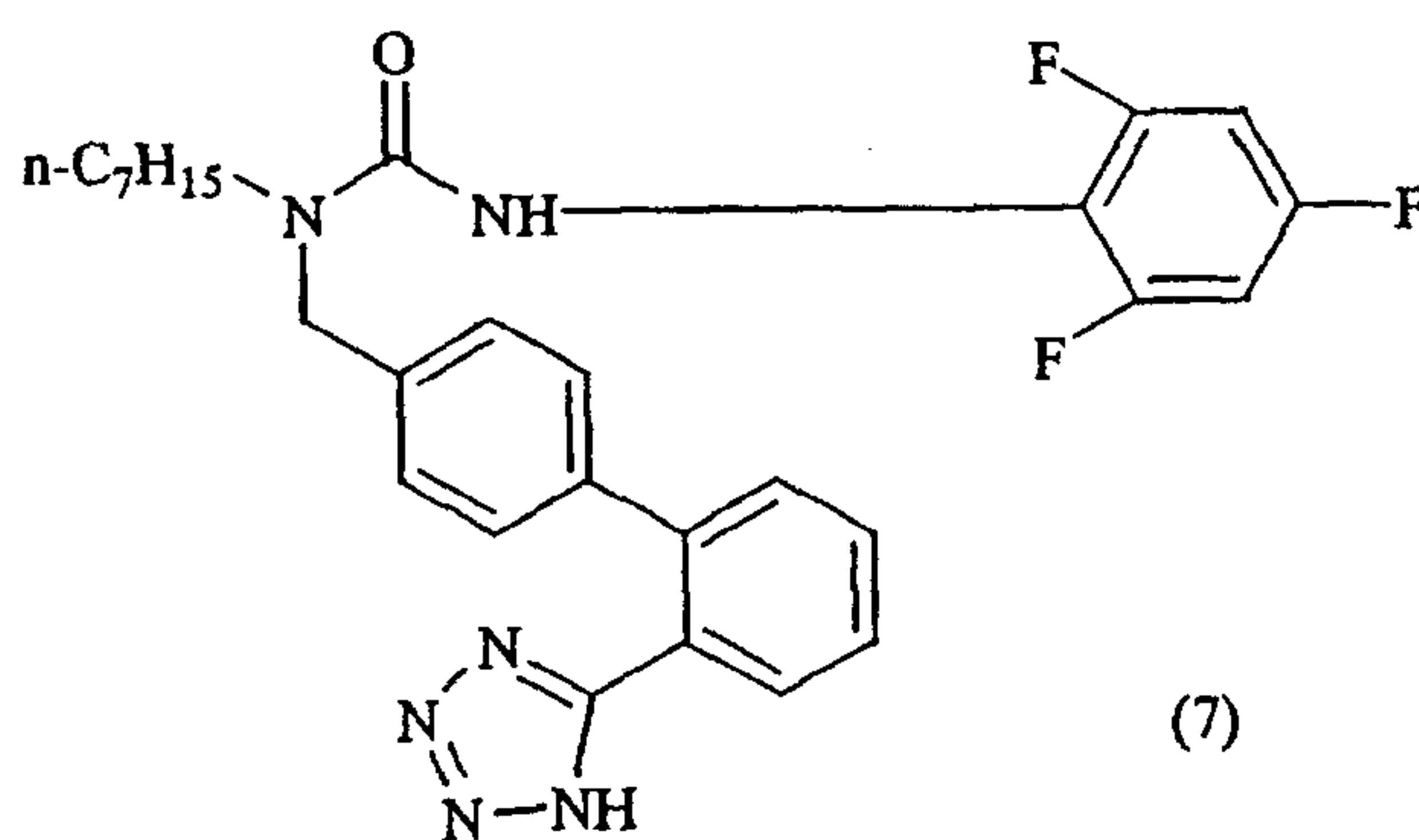
m.p. 103-107°C

10 IR (cm^{-1}) (KBr):

1449, 1521, 1612, 1629, 2931, 2958.

Example 4

N' -Heptyl- N' -[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]- N -(2,4,6-trifluorophenyl)urea



15

2,4,6-Trifluorobenzoic acid (148.8 mg),
 diphenylphosphoryl azide (223.3 mg) and triethylamine
 (105.1 mg) were added to benzene (8 mL) and the mixture
 was heated under reflux. Fifty minutes later, a solution

of N-heptyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-
1,1'-biphenyl-4-yl]methyl]amine (393.7 mg) in benzene (3
mL) was added to the reaction mixture, and under reflux,
heating was continued. Upon elapsed time of 45 minutes
5 after the addition of the solution, the reaction mixture
was concentrated under reduced pressure. Ethyl acetate
(40 mL) was added to the residue, and the resulting
mixture was washed successively with 5% hydrochloric acid,
water, a saturated sodium bicarbonate solution and brine
10 (40 mL, each). The organic layer was dried over
anhydrous sodium sulfate, and then concentrated under
reduced pressure. The residue was subjected to
chromatography on a silica gel column (hexane/ethyl
acetate) to afford N'-heptyl-N-(2,4,6-trifluorophenyl)-
15 N'-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-
4-yl]methyl]urea as a colorless amorphous mass (369.1 mg).
Yield: 74%.

¹H-NMR (CDCl₃, ppm):

0.87 (t, 3H, J=6.21Hz), 1.15-1.35 (m, 8H),
20 1.50-1.60 (m, 2H), 3.20 (t, 2H, J=7.29Hz), 4.48 (s, 2H),
5.62 (s, 1H), 6.62-6.76 (m, 2H), 6.89-6.98 (m, 6H),
7.06-7.16 (m, 4H), 7.22-7.53 (m, 12H),
7.93 (dd, 1H, J=7.02Hz, J=1.62Hz).

N'-Heptyl-N-(2,4,6-trifluorophenyl)-N'-[[2'-[N-
25 (triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-

yl]methyl]urea (437.5 mg) was treated with hydrochloric acid in a similar manner as in Example 1 to afford the compound represented by the formula (7) (219.1 mg).

Yield: 73%.

5 $^1\text{H-NMR}$ (CDCl_3 , ppm):

0.88 (t, 3H, $J=6.48\text{Hz}$), 1.15-1.47 (m, 8H),
1.55-1.75 (m, 2H), 3.10 (t, 2H, $J=7.56\text{Hz}$), 4.54 (s, 2H),
5.89 (s, 1H), 6.58 (dd, 2H, $J=7.29\text{Hz}$, $J=8.37\text{Hz}$),
7.11-7.26 (m, 4H), 7.40-7.61 (m, 3H),
10 7.93 (dd, 1H, $J=7.29\text{Hz}$, $J=1.62\text{Hz}$).

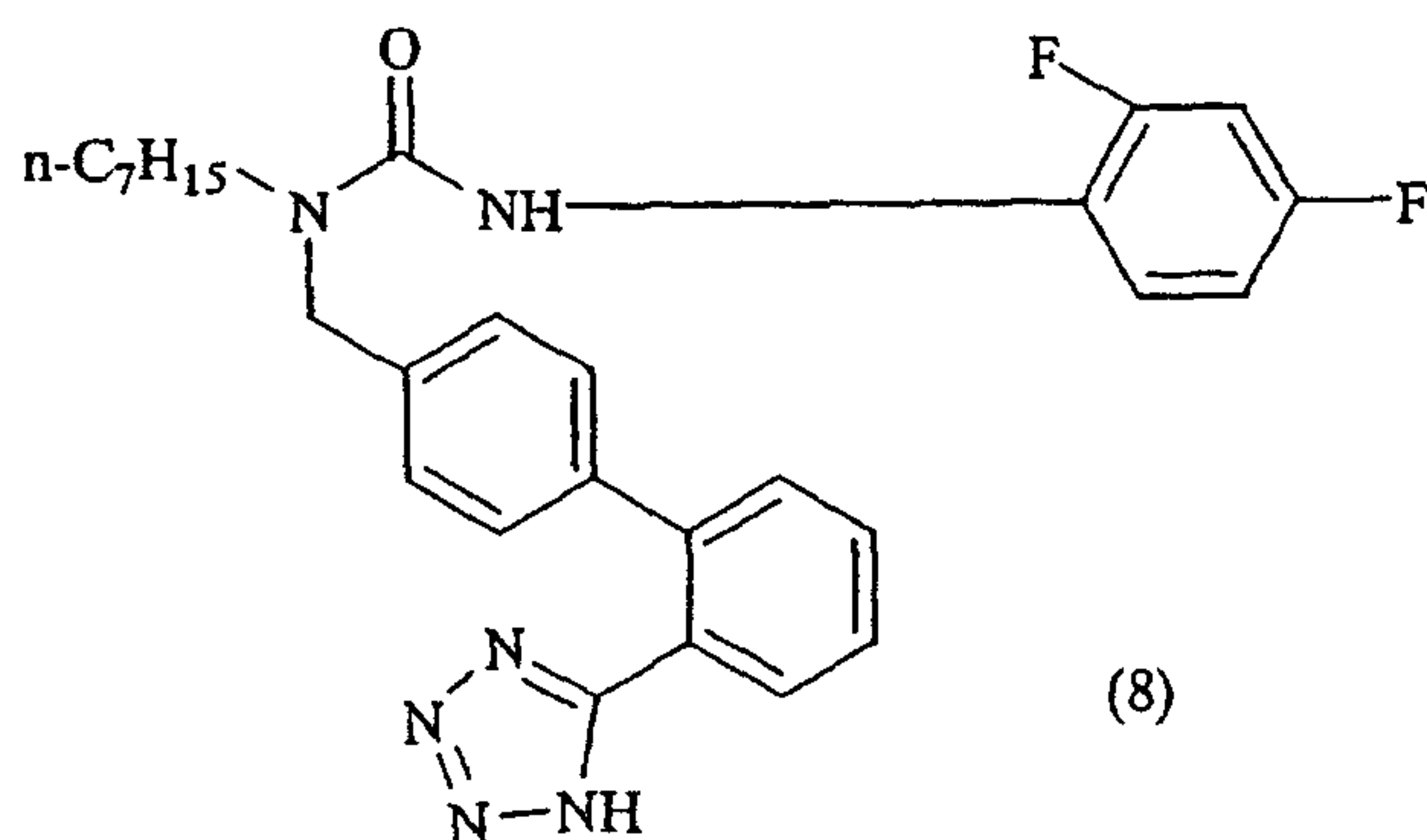
m.p. 86-89°C

IR (cm^{-1}) (KBr):

1521, 1615, 1625, 2929.

Example 5

15 N-(2,4-Difluorophenyl)-N'-heptyl-N'-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]urea



n-Heptylamine (3.96 g) and potassium carbonate (0.91 g) were added to dimethylformamide (60 mL), and

under ice cooling, [[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl] bromide (4.00 g) was added. The resulting mixture was stirred at the same temperature for a while, and was then stirred at room temperature.

5 Forty-five hours later, ethyl acetate (150 mL) was added. The mixture was washed once with water (500 mL) and four times with brine (500 mL, each), dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. Toluene (100 mL) and 2,4-difluorophenyl

10 isocyanate (1.33 g) were added to the residue and the mixture was heated under reflux. Eighty minutes later, the mixture was diluted with toluene (100 mL), and then washed successively with a saturated sodium bicarbonate solution (100 mL) and brine (100 mL). The organic layer

15 was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford N-(2,4-difluorophenyl)-N'-heptyl-N'-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]urea as a pale yellow oil (3.15 g). Yield: 59%.

¹H-NMR (CDCl₃, ppm):

0.88 (t, 3H, J=6.48Hz), 1.15-1.35 (m, 8H),
1.57-1.60 (m, 2H), 3.19 (t, 2H, J=7.29Hz), 4.46 (s, 2H),
25 6.37 (d, 1H, J=3.24Hz), 6.73-6.93 (m, 11H),

7.04-7.53 (m, 13H), 7.94 (dd, 1H, J=7.56Hz, J=1.62Hz),
8.02-8.11 (m, 1H).

N-(2,4-Difluorophenyl)-N'-heptyl-N'-[[2'-(N-(triphenylmethyl)tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]urea (1.05 g) was treated with hydrochloric acid in a similar manner as in Example 1 to afford the compound represented by the formula (8) (0.34 g). Yield: 59%.

¹H-NMR (CDCl₃, ppm):

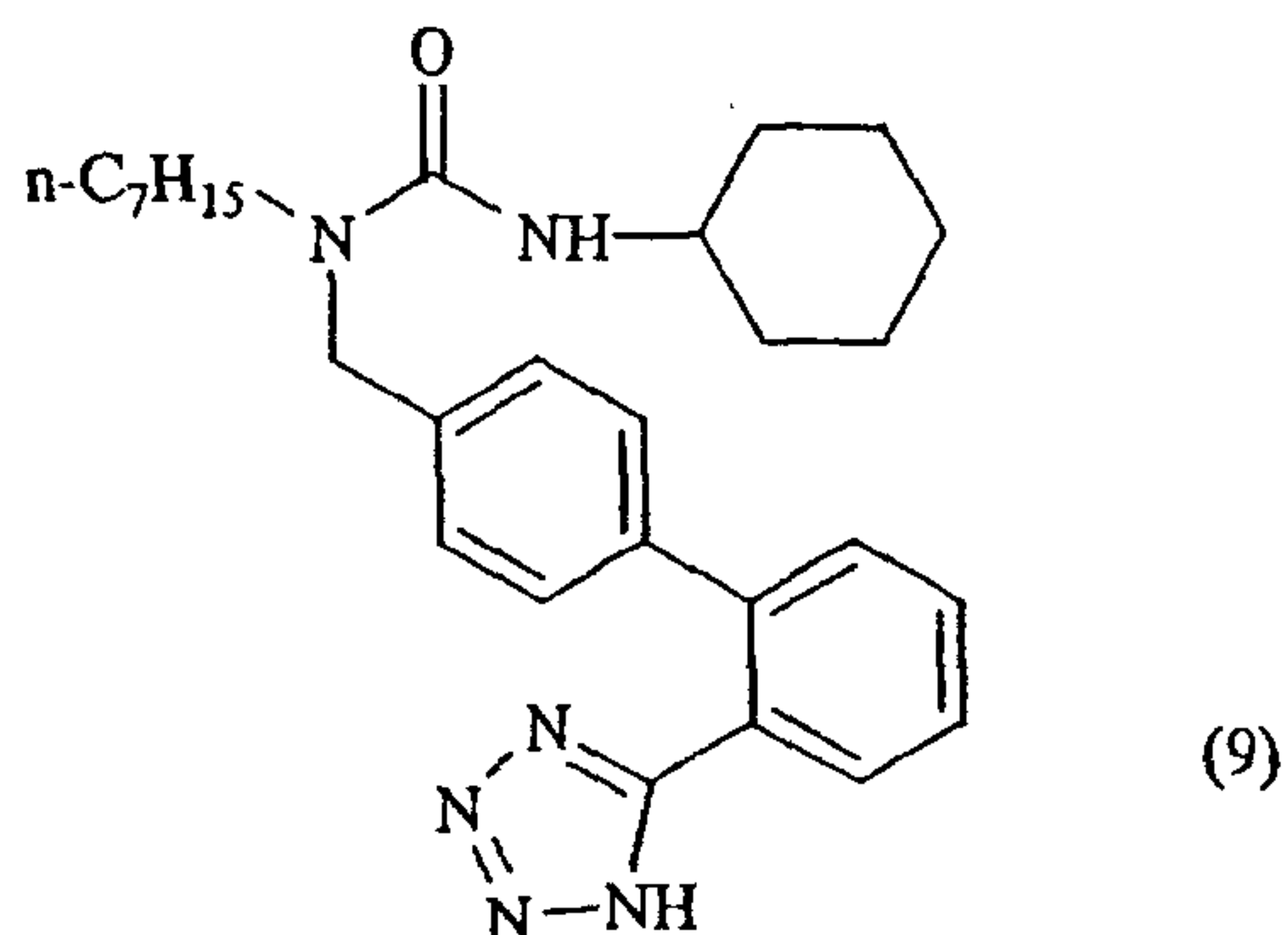
0.88 (t, 3H, J=6.48Hz), 1.22-1.33 (m, 8H),
1.58-1.75 (m, 2H), 3.30 (t, 2H, J=7.83Hz), 4.53 (s, 2H),
6.45 (d, 1H, J=3.51Hz), 6.70-6.87 (m, 2H),
7.14-7.32 (m, 4H), 7.34-7.65 (m, 3H), 7.76-7.85 (m, 1H),
7.98 (d, 1H, J=7.56Hz).

IR (cm⁻¹) (KBr):

1516, 1624, 1612.

Example 6

N-Cyclohexyl-N'-heptyl-N'-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]urea



Using n-heptylamine (192 mg), [[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl] bromide (843 mg) and cyclohexyl isocyanate (230 mg), N-cyclohexyl-N'-heptyl-N'-[[2'-[N-(triphenylmethyl)tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]urea (0.53 g) was obtained in a similar manner as in Example 5. Yield: 49%.

¹H-NMR (CDCl₃, ppm):

0.87 (t, 3H, J=6.75Hz), 0.94-1.40 (m, 12H),
 1.48-1.62 (m, 6H), 1.85-1.90 (m, 2H),
 3.06 (t, 2H, J=7.83Hz), 3.61-3.71 (m, 1H), 4.13 (d, 1H),
 4.34 (s, 2H), 6.86-6.94 (m, 6H), 7.00-7.12 (m, 4H),
 7.17-7.53 (m, 12H), 7.91 (dd, 1H, J=6.75Hz, J=1.35Hz).

N-Cyclohexyl-N'-heptyl-N'-[[2'-[N-(triphenylmethyl)tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]urea (0.53 g) was treated with hydrochloric acid in a similar manner as in Example 1 to afford the compound represented by the formula (9) (0.24 g). Yield:

69%.

$^1\text{H-NMR}$ (CDCl_3 , ppm):

0.87 (t, 3H, $J=6.75\text{Hz}$), 0.93-1.38 (m, 15H),

1.51-1.66 (m, 3H), 1.72-1.80 (m, 2H),

5 3.06 (t, 2H, $J=7.83\text{Hz}$), 3.35-3.52 (m, 1H),

4.14 (d, 1H, $J=7.29\text{Hz}$), 4.37 (s, 2H), 7.12 (s, 4H),

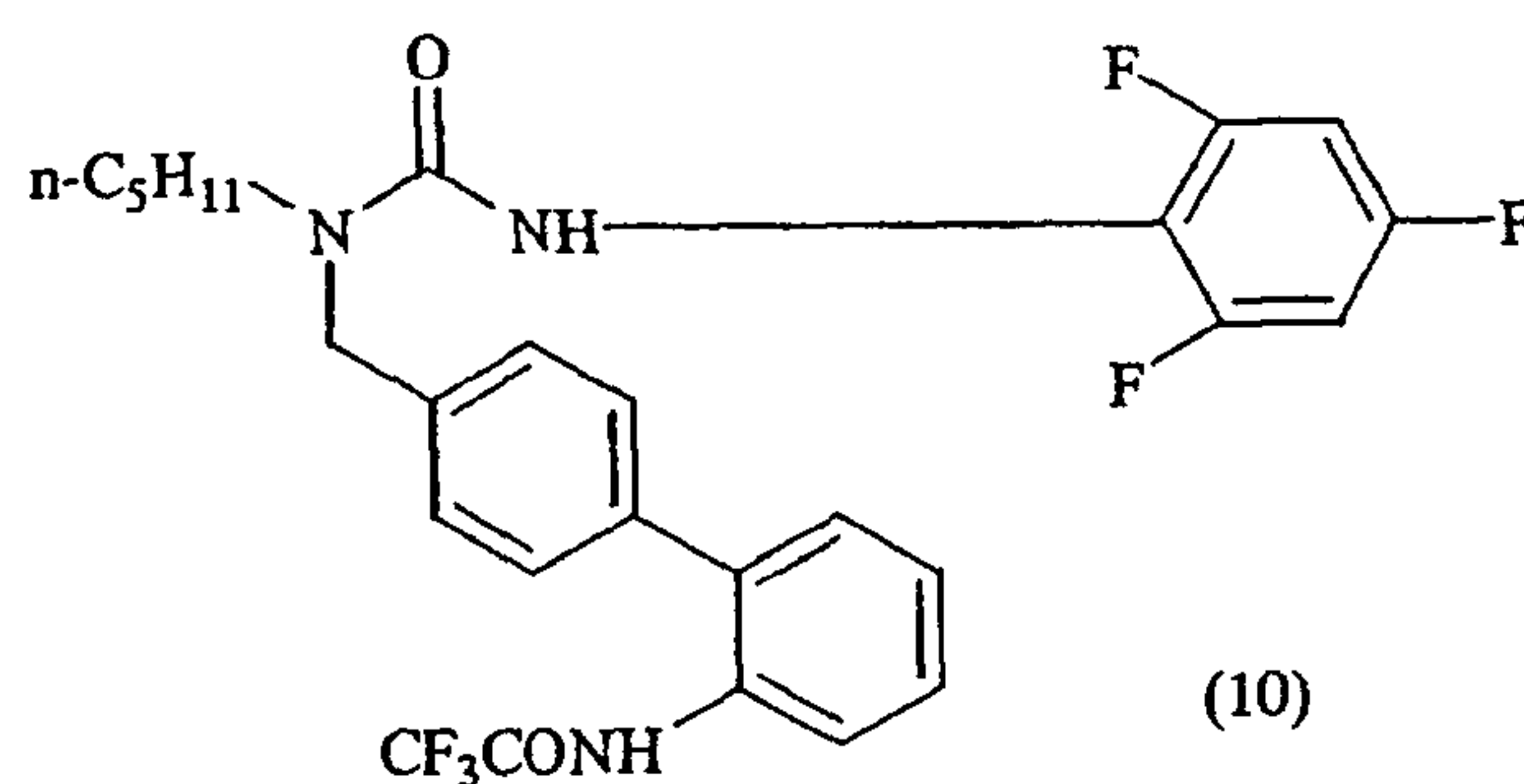
7.42-7.65 (m, 3H), 7.90 (dd, 1H, $J=6.75\text{Hz}$, $J=1.35\text{Hz}$).

IR (cm^{-1}) (KBr):

1532, 2930.

10 Example 7

N'-Pentyl-N'-[[2'-[[[(trifluoromethyl)carbonyl]-
amino]-1,1'-biphenyl-4-yl]methyl]-N-(2,4,6-
trifluorophenyl)urea



15 n-Amylamine (0.54 g) and potassium carbonate (0.98
g) were suspended in dimethylformamide (3.5 mL), and
[[2'-nitro-1,1'-biphenyl-4-yl]methyl] bromide (0.51 g)
was added in portions. Four hours later, ethyl acetate
(20 mL) was added, and the resulting mixture was washed
20 once with water (40 mL) and twice with brine (90 mL,

each). The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (chloroform/ethyl acetate) to afford N-[(2'-nitro-1,1'-biphenyl-4-yl)methyl]-N-pentylamine as a
5 yellow oil (0.40 g). Yield: 77%.

Using 2,4,6-trifluorobenzoic acid (0.43 g), diphenylphosphoryl azide (0.68 g), triethylamine (0.25 g) and N-[(2'-nitro-1,1'-biphenyl-4-yl)methyl]-N-pentylamine
10 (0.40 g), N'-[(2'-nitro-1,1'-biphenyl-4-yl)methyl]-N'-pentyl-N-(2,4,6-trifluorophenyl)urea (0.60 g) was obtained by a similar procedure as in Example 4. Yield: 95%.

¹H-NMR (CDCl₃, ppm):

15 0.94 (t, 3H, J=7.02Hz), 1.20-1.49 (m, 4H),
1.59-1.75 (m, 2H), 3.42 (t, 2H, J=7.83Hz), 4.64 (s, 2H),
5.74 (s, 1H), 6.64-6.87 (m, 4H), 7.09-7.65 (m, 6H).

N'-[(2'-Nitro-1,1'-biphenyl-4-yl)methyl]-N'-pentyl-N-(2,4,6-trifluorophenyl)urea (196.0 mg) and anhydrous
20 tin(II) chloride (401.6 mg) were added to ethanol (4 mL), and the mixture was heated under reflux. One hour later, the solvent was distilled off, and ethyl acetate (15 mL) and a saturated sodium bicarbonate solution (15 mL) were added to the residue. The resultant precipitate was
25 filtered off through Celite*. The filtrate was extracted

* Trade-mark

with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford N'-[(2'-amino-1,1'-biphenyl-4-yl)methyl]-N'-pentyl-N-(2,4,6-trifluorophenyl)urea (179.2 mg). Yield: 94%.

N'-[(2'-Amino-1,1'-biphenyl-4-yl)methyl]-N'-pentyl-N-(2,4,6-trifluorophenyl)urea (179.2 mg) was dissolved in pyridine (1.5 mL), and after addition of trifluoroacetic anhydride (0.15 mL), the mixture was stirred at room temperature. Thirty minutes later, ethyl acetate (15 mL) was added, and the resulting mixture was washed successively with water (15 mL), brine (30 mL), a saturated sodium bicarbonate solution (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford the compound represented by the formula (10) as a colorless amorphous mass (129.5 mg). Yield: 58%.

¹H-NMR (CDCl₃, ppm):

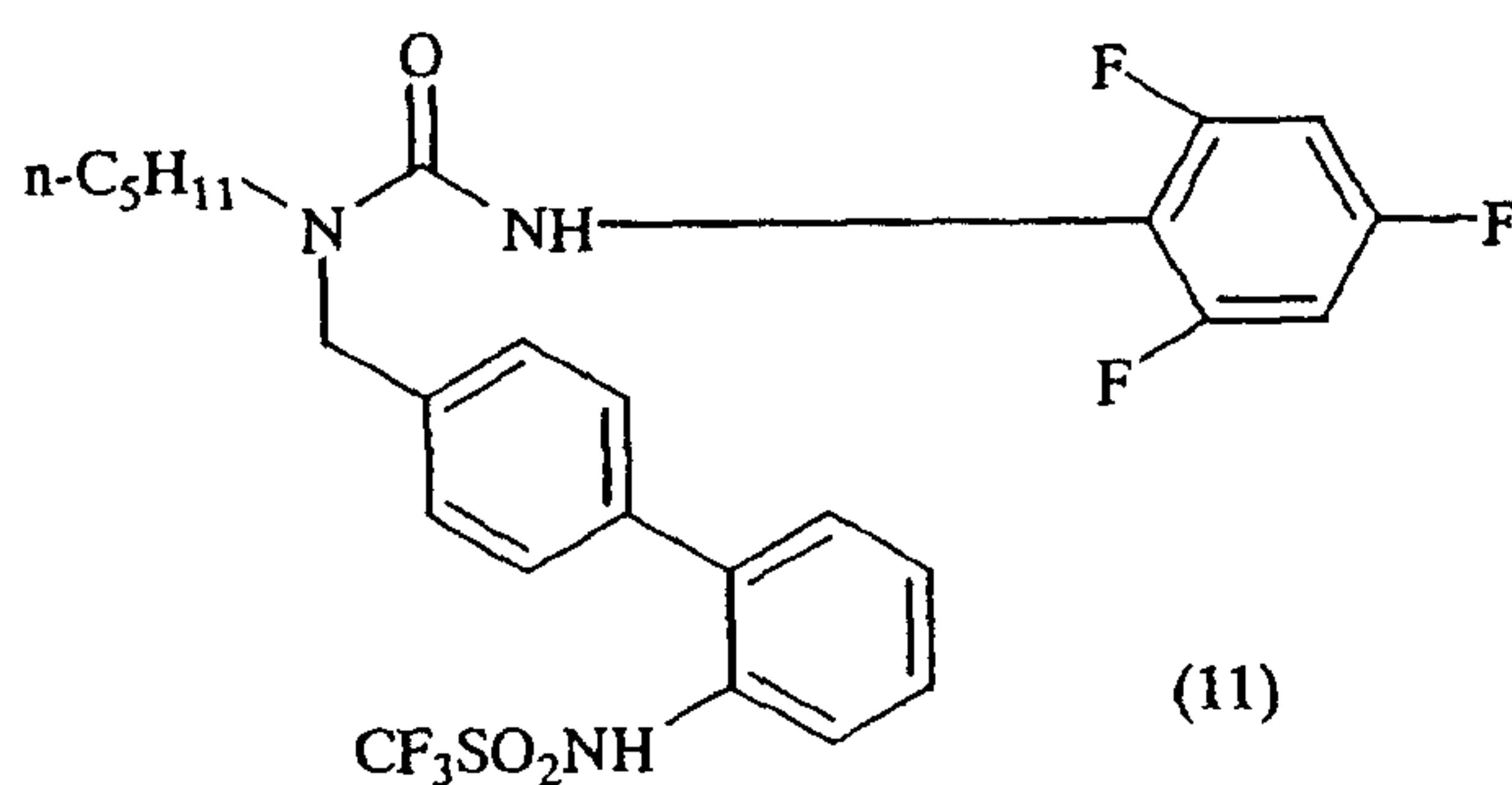
0.94 (t, 3H, J=7.02Hz), 1.32-1.78 (m, 4H),
1.62-1.72 (m, 2H), 3.41 (t, 2H, J=7.29Hz), 4.68 (s, 2H),
5.73 (s, 1H), 6.66-6.77 (m, 2H), 7.20-7.49 (m, 7H),
7.95 (bs, 1H), 8.23 (d, 1H, J=8.10Hz).

IR (cm⁻¹) (KBr):

1202, 1521, 1636.

Example 8

N'-Pentyl-N'-[[2'-[[[(trifluoromethyl)sulfonyl]-
amino]-1,1'-biphenyl-4-yl]methyl]-N-(2,4,6-
trifluorophenyl)urea



N'-[(2'-Amino-1,1'-biphenyl-4-yl)methyl]-N'-pentyl-
N-(2,4,6-trifluorophenyl)urea (100 mg) was dissolved in
dichloromethane (2 mL), and while maintaining the
solution at -10 to -5°C, a solution of
trifluoromethanesulfonic acid anhydride (70 mg) in
dichloromethane (2 mL) was added dropwise. After the
resulting mixture was stirred at the same temperature for
4 hours, chloroform (20 mL) was added and the mixture was
washed with a saturated sodium bicarbonate solution (20
mL). The aqueous layer was extracted further with
chloroform (10 mL). The combined organic layers were
dried over anhydrous sodium sulfate and then concentrated
under reduced pressure. The residue was purified by
chromatography on a silica gel column

(chloroform/methanol) to afford the compound represented by the formula (11) (60 mg). Yield: 46%.

$^1\text{H-NMR}$ (CDCl_3 , ppm):

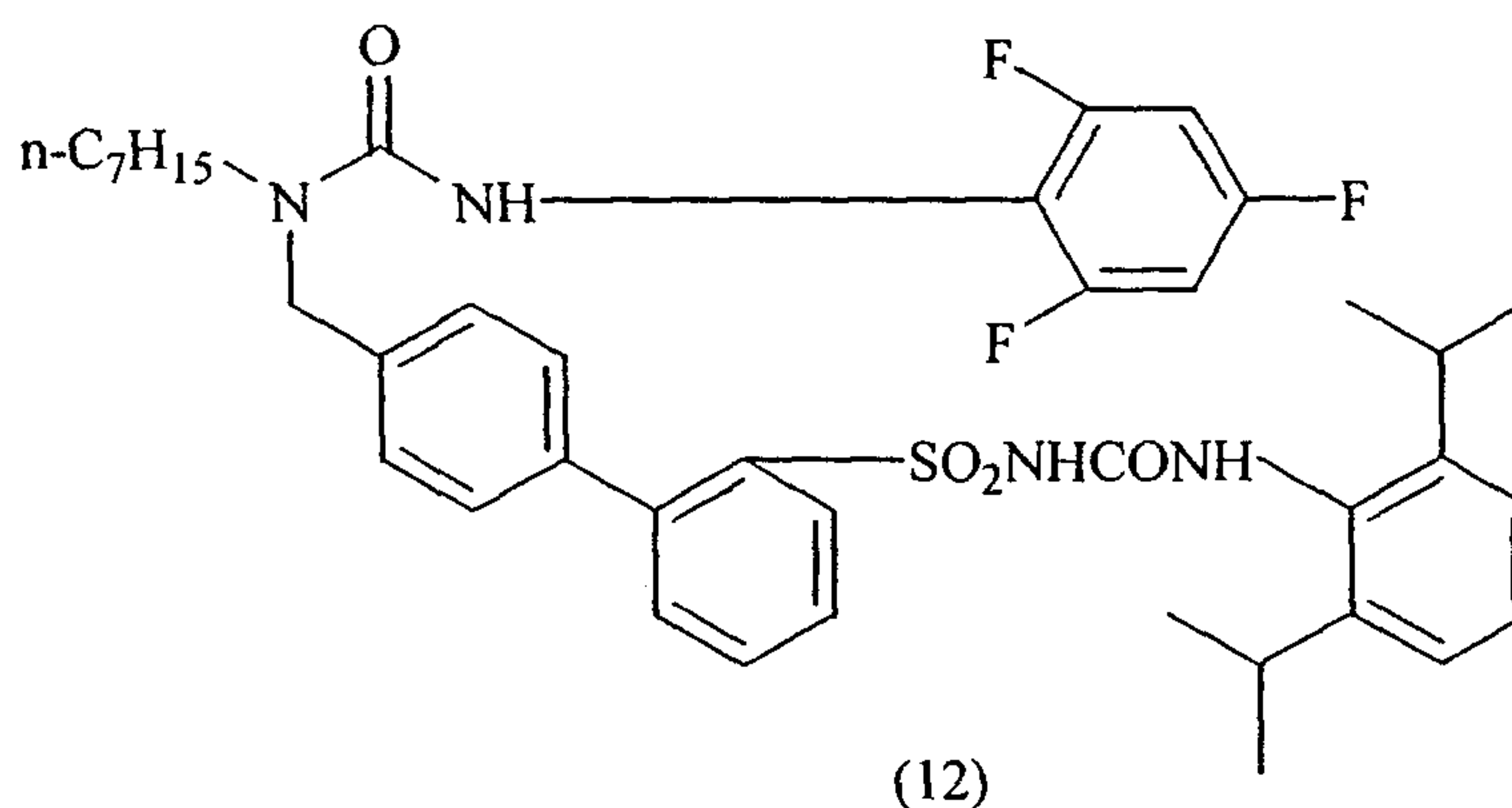
0.92 (t, 3H, $J=6.75\text{Hz}$), 1.32-1.38 (m, 4H),
 1.68-1.78 (m, 2H), 3.41 (t, 2H, $J=7.56\text{Hz}$), 4.68 (s, 2H),
 5.73 (s, 1H), 6.66-6.77 (m, 2H), 7.31-7.49 (m, 7H),
 7.95 (s, 1H), 8.28 (d, 1H, $J=7.83\text{Hz}$).

IR (cm^{-1}) (KBr):

1202, 1521, 1636.

Example 9

N' -[[2'-[[[[(2,6-Diisopropylphenyl)amino]-carbonyl]amino]sulfonyl]-1,1'-biphenyl-4-yl]methyl]- N' -heptyl- N -(2,4,6-trifluorophenyl)urea



[[2'-[(*t*-Butylamino)sulfonyl]-1,1'-biphenyl-4-yl]methyl] bromide (0.94 g), *n*-heptylamine (0.28 g) and potassium carbonate (0.35 g) were added to dimethylformamide and the mixture was stirred at room temperature. Sixteen hours and 30 minutes later, ethyl acetate (30 mL) was added, and the resulting mixture was

washed three times with brine (100 mL, each). The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (chloroform/ethyl acetate) to afford N-[[2'-[(t-butylamino)sulfonyl]-1,1'-biphenyl-4-yl]methyl]-N-heptylamine as a yellow oil (0.43 g). Yield: 42%.

¹H-NMR (CDCl₃, ppm):

0.89 (t, 3H, J=7.02Hz), 0.99 (s, 9H), 1.22-1.31 (m, 6H),
1.45-1.60 (m, 4H), 2.64 (t, 2H, J=6.75Hz), 3.56 (s, 1H),
4.86 (s, 2H), 7.30-7.65 (m, 7H),
8.17 (dd, 1H, J=7.83Hz, J=1.35Hz).

Using 2,4,6-trifluorobenzoic acid (0.27 g), diphenylphosphoryl azide (0.44 g), triethylamine (0.17 g) and N-[[2'-[(t-butylamino)sulfonyl]-1,1'-biphenyl-4-yl]methyl]-N-heptylamine (0.43 g), N'-[[2'-[(t-butylamino)sulfonyl]-1,1'-biphenyl-4-yl]methyl]-N'-heptyl-N-(2,4,6-trifluorophenyl)urea was afforded as colorless crystals (0.49 g) by a similar procedure as in Example 4. Yield: 81%.

¹H-NMR (CDCl₃, ppm):

0.89 (t, 3H, J=7.02Hz), 0.95 (s, 9H), 1.22-1.35 (m, 4H),
1.52-1.58 (m, 2H), 1.66-1.78 (m, 2H),
3.39 (t, 2H, J=8.10Hz), 3.56 (s, 1H), 4.66 (s, 2H),
5.74 (s, 1H), 6.66-6.77 (m, 2H), 7.20-7.65 (m, 7H),

8.17 (dd, 1H, J=7.29Hz, J=1.08Hz).

N'-[[2'-[(t-Butylamino)sulfonyl]-1,1'-biphenyl-4-yl]methyl]-N'-heptyl-N-(2,4,6-trifluorophenyl)urea (0.49 g) was dissolved in trifluoroacetic acid (8 mL), and
5 after addition of anisole (0.36 mL), the resulting mixture was stirred at room temperature. Twenty-four hours later, ethyl acetate (40 mL) was added to the reaction mixture, and the mixture was washed with a saturated sodium bicarbonate solution (60 mL) and brine
10 (60 mL). The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford N'-[[2'-aminosulfonyl]-1,1'-biphenyl-4-yl]methyl]-N'-
15 heptyl-N-(2,4,6-trifluorophenyl)urea (0.40 g) as a colorless amorphous mass. Yield: 90%.

¹H-NMR (CDCl₃, ppm):

0.89 (t, 3H, J=6.48Hz), 1.23-1.35 (m, 8H),
1.65-1.73 (m, 2H), 3.41 (t, 2H, J=7.29Hz), 4.25 (s, 2H),
20 4.66 (s, 2H), 5.81 (s, 1H), 6.66-6.72 (m, 2H),
7.31-7.63 (m, 7H), 8.14 (dd, 1H, J=7.83Hz, J=1.08Hz).

N'-[[2'-Aminosulfonyl]-1,1'-biphenyl-4-yl]methyl]-N'-heptyl-N-(2,4,6-trifluorophenyl)urea (0.40 g) and 2,6-diisopropylphenyl isocyanate (0.22 g) were added to
25 acetone (15 mL) and the mixture was heated under reflux.

Fifty minutes later, the reaction mixture was concentrated under reduced pressure and an aqueous solution of potassium dihydrogenphosphate was added to the residue to adjust the pH to 4 to 5. The resulting mixture was extracted with ethyl acetate (40 mL), and the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford the compound represented by the formula (12) in the form of a colorless amorphous mass (0.41 g). Yield: 74%.

$^1\text{H-NMR}$ (CDCl_3 , ppm):

0.88 (t, 3H, $J=6.75\text{Hz}$), 0.99 (d, 12H, $J=6.75\text{Hz}$),
1.23-1.34 (m, 8H), 1.62-1.78 (m, 2H), 2.51 (m, 2H),
3.43 (t, 2H, $J=7.56\text{Hz}$), 4.67 (s, 2H), 5.76 (s, 1H),
6.63-6.74 (m, 2H), 7.07 (d, 2H, $J=8.10\text{Hz}$),
7.16-7.66 (m, 8H), 8.25 (d, 1H, $J=7.02\text{Hz}$).

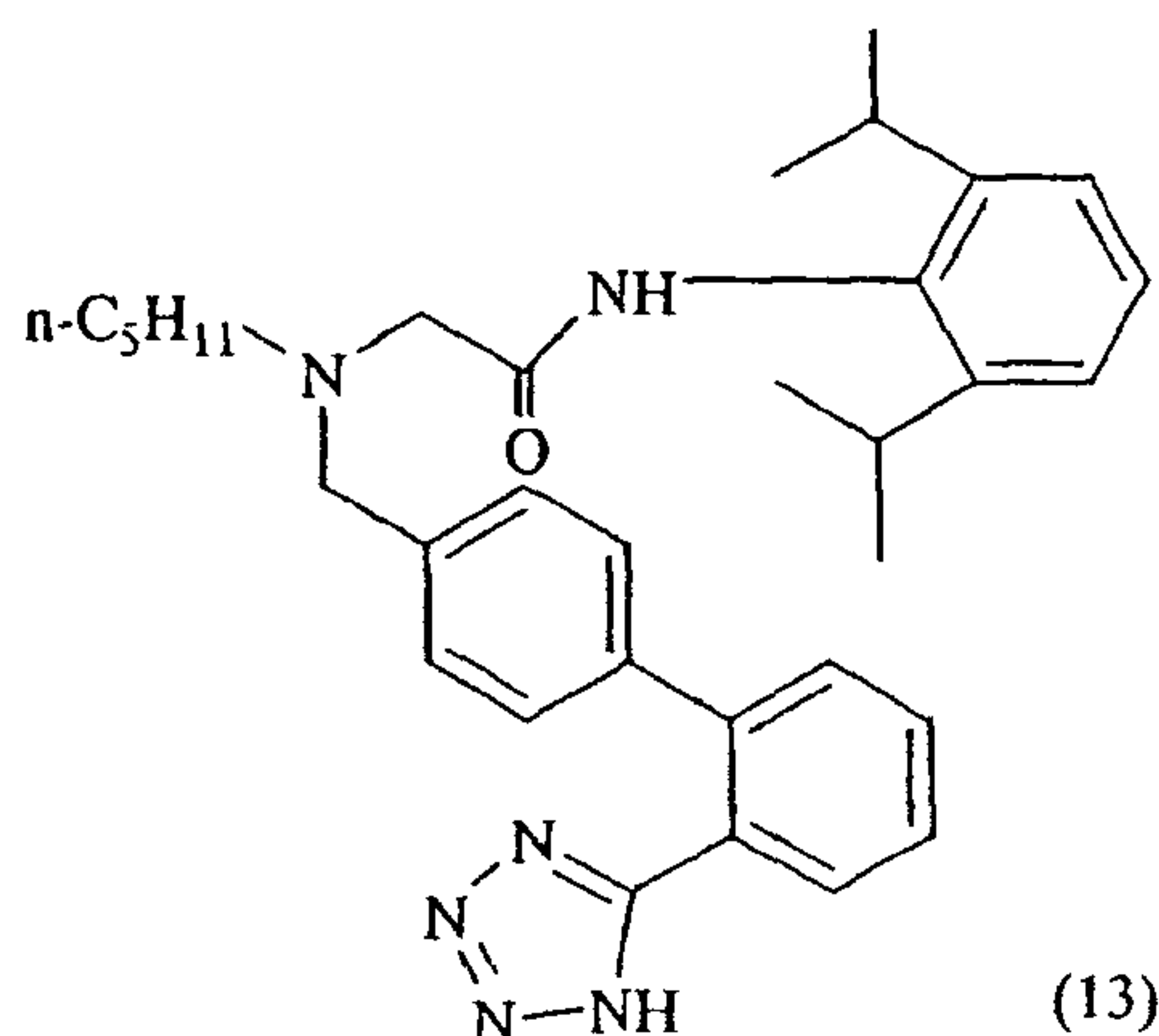
m.p. 89-93°C

IR (cm^{-1}) (KBr):

1121, 1502, 1521, 1636.

Example 10

N-[[[(2,6-Diisopropylphenyl)amino]carbonyl]methyl]-
N-pentyl-N-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-
yl]methyl]amine



[[2'-[N-(Triphenylmethyl)tetrazol-5-yl)-1,1'-
biphenyl-4-yl]methyl] bromide (2.32 g) and sodium azide
(0.59 g) were suspended in a mixed solution of
5 dimethylformamide (8 mL) and water (0.4 mL), and then the
mixture was stirred at room temperature. Twenty-two
hours later, ethyl acetate (100 mL) was added, and the
resulting mixture was washed three times with brine (300
mL, each). The organic layer was dried over anhydrous
10 sodium sulfate and concentrated under reduced pressure.
The residue was dissolved in tetrahydrofuran (40 mL), and
under ice bath cooling, lithium aluminum hydride (322.0
mg) was added. The mixture was stirred at room
temperature for 1 hour, and under ice bath cooling, water
15 (8 mL), a 10% aqueous solution of sodium hydroxide (8 mL)
and water (8 mL) were added successively. The resulting
precipitate was filtered off, and the filtrate was
concentrated under reduced pressure. Water (80 mL) was
added to the residue, and the mixture was extracted twice

with chloroform (60 mL, each). The organic layers were combined and then washed with brine (100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in dichloromethane (30 mL), and after addition of triethylamine (1500 mg) and valeroyl chloride (1.80 g), the mixture was stirred under ice bath cooling. Forty minutes later, chloroform (50 mL) was added to the reaction mixture, and the resulting mixture was washed with a saturated sodium bicarbonate solution (100 mL) and brine (100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford N-pentanoyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine as colorless crystals (1.61 g). Yield: 67%.

¹H-NMR (CDCl₃, ppm):

0.90 (t, 3H, J=7.29Hz), 1.23-1.37 (m, 2H),
1.55-1.66 (m, 2H), 2.10 (t, 2H, J=8.10Hz),
4.32 (d, 2H, J=5.40Hz), 5.41 (bs, 1H), 6.88-7.53 (m, 22H),
7.96 (dd, 1H, J=6.75Hz, J=2.16Hz).

N-Pentanoyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine (1.61 g) was dissolved in tetrahydrofuran (40 mL) and at room

temperature, lithium aluminum hydride (340.1 mg) was added, and then the mixture was heated under reflux. Ninety minutes later, water (5 mL), a 10% aqueous solution of sodium hydroxide (5 mL) and water (5 mL) were
5 added successively under ice bath cooling. The organic layer was separated, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. As water remained to the residue, ethyl acetate was added to conduct extraction twice from the remaining water. The
10 organic layer was dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to afford N-pentyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine (1.57 g). Yield: 100%.

N-(Chloroacetyl)-2,6-diisopropylaniline (196.3 mg),
15 N-pentyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine (430.0 mg), potassium iodide (70 mg) and triethylamine (0.6 g) were suspended in dimethylformamide (3 mL). The resulting mixture was heated to about 80°C, and then stirred at that
20 temperature. Three hours later, the reaction mixture was cooled, ethyl acetate (30 mL) was added, and the mixture was washed four times with brine (50 mL, each). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was
25 subjected to chromatography on a silica gel column

(hexane/ethyl acetate) to afford N-[[[(2,6-diisopropylphenyl)amino]carbonyl]methyl]-N-pentyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine (196.4 mg). Yield: 33%.

5 ¹H-NMR (CDCl₃, ppm):

0.90 (t, 3H, J=7.02Hz), 1.13 (d, 12H, J=7.02Hz),
1.24-1.41 (m, 4H), 1.55-1.65 (m, 2H),
2.60 (t, 2H, J=7.83Hz), 2.63-2.98 (m, 2H), 3.24 (s, 2H),
3.62 (s, 2H), 6.90-6.94 (m, 6H), 7.07-7.55 (m, 19H),
10 7.93 (dd, 1H, J=6.48Hz, J=1.08Hz), 8.63 (s, 1H).

N-[[[(2,6-Diisopropylphenyl)amino]carbonyl]methyl]-
N-pentyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-
biphenyl-4-yl]methyl]amine (278.3 mg) was dissolved in
tetrahydrofuran (10 mL), and after addition of 10%
15 hydrochloric acid (3.0 mL), the resulting mixture was
stirred at room temperature. Nineteen hours later, the
solvent was distilled off, and to the residue, water (30
mL) was added. The mixture so obtained was extracted
twice with chloroform (30 mL, each). The organic layer
20 was dried over anhydrous sodium sulfate and concentrated
under reduced pressure. The residue was subjected to
chromatography on a silica gel column
(chloroform/methanol) to afford N-[[[(2,6-
diisopropylphenyl)amino]carbonyl]methyl]-N-pentyl-N-[[2'-
25 (1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]amine

hydrochloride as pale yellow crystals (190.6 mg). Yield: 93%.

^1H -NMR (CDCl_3 , ppm):

0.90 (t, 3H, $J=6.48\text{Hz}$), 1.12 (d, 12H, $J=7.02\text{Hz}$),
5 1.25-1.43 (m, 4H), 1.85 (bs, 2H), 2.89-2.99 (m, 2H),
3.20 (bs, 2H), 3.83 (bs, 2H), 4.32 (bs, 2H),
7.10-7.16 (m, 4H), 7.25-7.31 (m, 1H), 7.39-7.59 (m, 5H),
7.91 (dd, 1H, $J=7.29\text{Hz}$, $J=1.35\text{Hz}$), 9.23 (bs, 1H).

m.p. 102-107°C

10 IR (cm^{-1}) (KBr):

1459, 1471, 1687, 2869, 2930, 2962.

N-[[[(2,6-Diisopropylphenyl)amino]carbonyl]methyl]-
N-pentyl-N-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-
yl]methyl]amine hydrochloride (140.4 mg) was suspended in
15 a saturated sodium bicarbonate solution (5 mL) and the
mixture was stirred for 1 hour. The mixture was adjusted
to pH 3 with dilute hydrochloric acid, and then extracted
with ethyl acetate (30 mL). The organic layer was washed
with brine. The organic layer was dried over anhydrous
20 sodium sulfate and concentrated under reduced pressure to
afford the compound represented by the formula (13) as a
colorless solid (107.3 mg). Yield: 82%.

^1H -NMR (CDCl_3 , ppm):

0.90 (t, 3H, $J=6.75\text{Hz}$), 1.11 (d, 12H, $J=7.02\text{Hz}$),
25 1.23-1.34 (m, 4H), 2.74 (t, 2H, $J=7.29\text{Hz}$),

2.86-2.96 (m, 2H), 3.33 (s, 2H), 3.85 (s, 2H),
 7.07-7.16 (m, 4H), 7.25-7.31 (m, 3H), 7.38-7.41 (m, 1H),
 7.47-7.60 (m, 2H), 7.99 (dd, 1H, $J=7.29\text{Hz}$, $J=1.35\text{Hz}$),
 8.77 (s, 1H).

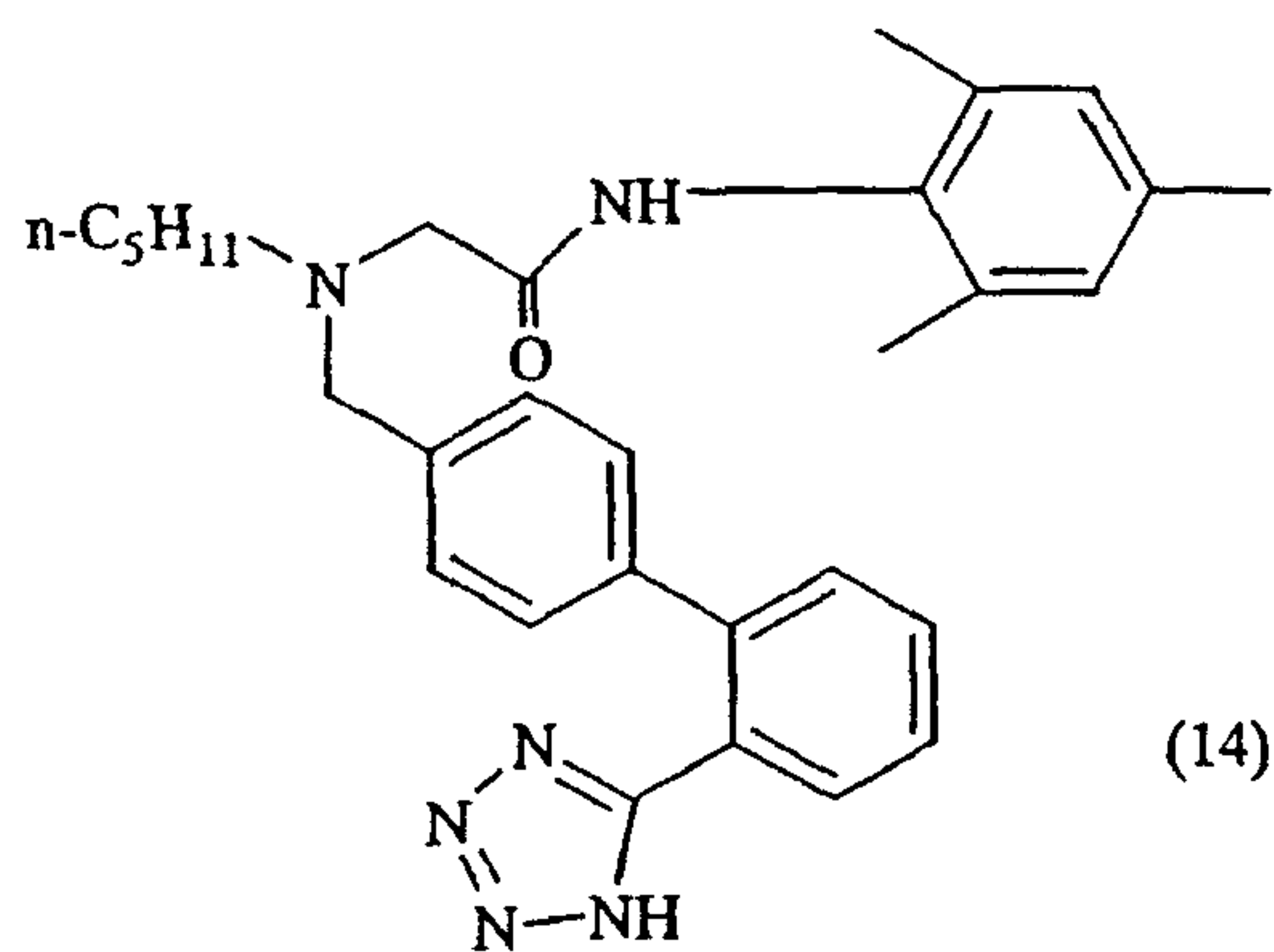
5 m.p. 74-80°C

IR (cm^{-1}) (KBr):

1459, 1505, 1658, 2869, 2930.

Example 11

N-Pentyl-N-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-N-[[[(2,4,6-trimethylphenyl)amino]-carbonyl]methyl]amine



N-(Chloroacetyl)-2,4,6-trimethylaniline (443.2 mg),
 N-pentyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-
 15 biphenyl-4-yl]methyl]amine (780.0 mg), potassium iodide
 (129.1 mg) and triethylamine (1.15 g) were suspended in
 dimethylformamide (6 mL). The resulting mixture was
 heated to about 80°C, and then stirred at that
 temperature. Three hours later, the reaction mixture was

cooled, ethyl acetate (50 mL) was added, and the mixture was washed four times with brine (100 mL, each). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was
5 subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford N-pentyl-N-[[[(2,4,6-trimethylphenyl)amino]carbonyl]methyl]-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine (395.4 mg). Yield: 39%.

10 ¹H-NMR (CDCl₃, ppm):

0.89 (t, 3H, J=7.02Hz), 1.23-1.31 (m, 4H),
1.45-1.65 (m, 2H), 2.08 (s, 6H), 2.26 (s, 3H),
2.59 (t, 2H, J=7.83Hz), 3.24 (s, 2H), 3.62 (s, 2H),
6.89-7.54 (m, 24H), 7.92 (dd, 1H, J=7.02Hz, J=1.89Hz),
15 8.59 (s, 1H).

N-Pentyl-N-[[[(2,4,6-trimethylphenyl)amino]-carbonyl]methyl]-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine (395.4 mg) was dissolved in tetrahydrofuran (25 mL), and after addition
20 of 10% hydrochloric acid, the resulting mixture was stirred for 18 hours and 30 minutes. The solvent was then distilled off under reduced pressure. To the residue, water (45 mL) was added, and the mixture was extracted twice with ethyl acetate (45 mL, each). The
25 organic layer was dried over anhydrous sodium sulfate and

concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (chloroform/methanol). Relevant fractions (the hydrochloride) were concentrated, and after addition of a small amount of methanol to the residue, the mixture was stirred together with a saturated sodium bicarbonate solution (6 mL) for 1 hour. Under ice bath cooling, the solution was adjusted to pH 3 with dilute hydrochloric acid. Ethyl acetate (30 mL) was added, and the resulting mixture was washed six times with brine (50 mL, each). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (chloroform/methanol) to afford the compound represented by the formula (14) as colorless crystals (188.4 mg). Yield: 69%.

^1H -NMR (CDCl_3 , ppm):

0.89 (t, 3H, $J=6.75\text{Hz}$), 1.23-1.43 (m, 4H),
1.56-1.72 (m, 2H), 2.02 (s, 6H), 2.22 (s, 3H),
2.69 (t, 2H, $J=7.29\text{Hz}$), 3.24 (s, 2H), 3.78 (s, 2H),
6.81 (s, 2H), 7.04 (d, 2H, $J=7.83\text{Hz}$),
7.22-7.57 (m, 5H), 7.95 (d, 1H, $J=7.29\text{Hz}$), 8.68 (s, 1H).

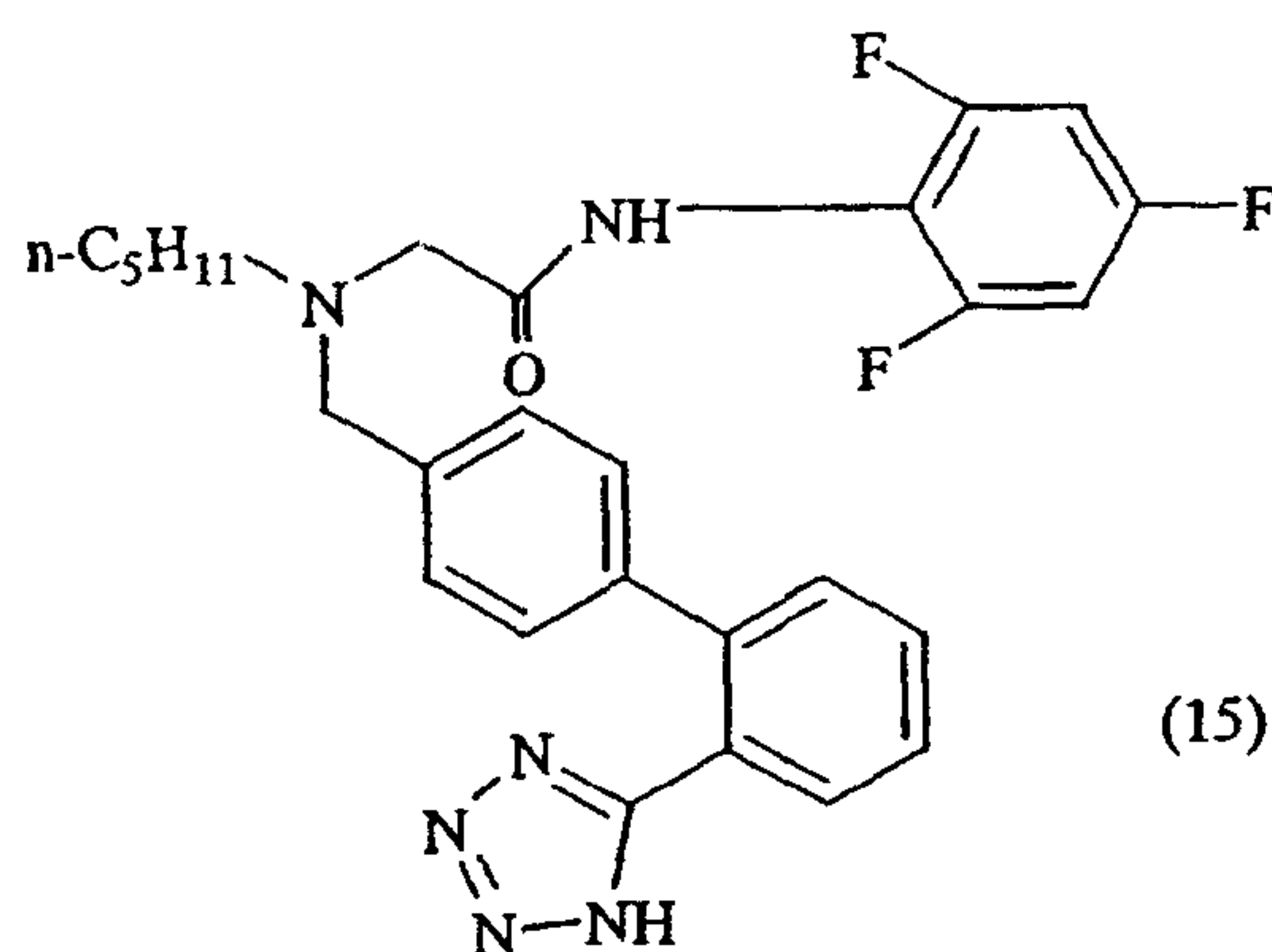
m.p. 73-77°C

IR (cm^{-1}) (KBr):

1505, 1659, 2928, 2956.

Example 12

N-Pentyl-N-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-N-[[[(2,4,6-trifluorophenyl)amino]carbonyl]methyl]amine



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N-(Chloroacetyl)-2,4,6-trifluoroaniline (313.0 mg), N-pentyl-N-[[2'-[N-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine (780.0 mg), potassium iodide (230 mg) and triethylamine (2.1 g) were suspended in dimethylformamide (12 mL). The resulting mixture was heated to about 80°C, and then stirred at that temperature. Three hours later, the reaction mixture was cooled, ethyl acetate (100 mL) was added, and the mixture was washed four times with brine (200 mL, each). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford N-pentyl-N-[[[(2,4,6-trifluorophenyl)amino]carbonyl]methyl]-N-[[2'-[N-

10

15

(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]amine (434.8 mg). Yield: 42%.

¹H-NMR (CDCl₃, ppm):

0.88 (t, 3H, J=7.02Hz), 1.18-1.38 (m, 4H),
1.48-1.60 (m, 2H), 2.54 (t, 2H, J=7.56Hz), 3.23 (s, 2H),
3.61 (s, 2H), 6.71-6.77 (m, 2H), 6.89-6.92 (m, 6H),
7.05-7.13 (m, 4H), 7.21-7.51 (m, 11H),
7.92 (d, 1H, J=5.94Hz), 7.93 (d, 1H, J=5.94Hz),
8.63 (s, 1H).

10 N-Pentyl-N-[[[(2,4,6-trifluorophenyl)amino]-
carbonyl]methyl]-N-[[2'-[N-(triphenylmethyl)tetrazol-5-
yl]-1,1'-biphenyl-4-yl)methyl]amine (425.8 mg) was
dissolved in tetrahydrofuran (25 mL), and after addition
of 10% hydrochloric acid, the resulting mixture was
15 stirred for 18 hours and 30 minutes. The solvent was
then distilled off under reduced pressure. To the
residue, water (45 mL) was added, and the mixture was
extracted twice with ethyl acetate (45 mL, each). The
organic layer was dried over anhydrous sodium sulfate and
20 concentrated under reduced pressure. The residue was
subjected to chromatography on a silica gel column
(chloroform/methanol). Relevant fractions (the
hydrochloride) were concentrated, and after addition of a
small amount of methanol to the residue, the mixture was
25 stirred together with a saturated sodium bicarbonate

solution (6 mL) for 1 hour. Under ice bath cooling, the solution was then adjusted to pH 3 with dilute hydrochloric acid. Ethyl acetate (30 mL) was added, and the resulting mixture was washed six times with brine (50 mL, each). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (chloroform/methanol) to afford the compound represented by the formula (15) (185.3 mg). Yield: 63%.

¹H-NMR (CDCl₃, ppm):

0.88 (t, 3H, J=6.48Hz), 1.15-1.50 (m, 4H),
1.51-1.75 (m, 2H), 2.73 (t, 2H, J=7.83Hz), 3.31 (s, 2H),
3.80 (s, 2H), 6.65-6.74 (m, 2H), 7.04 (d, 2H, J=7.83Hz),
7.21-7.27 (m, 2H), 7.38-7.57 (m, 3H),
7.90 (dd, 1H, J=7.83Hz, J=1.08Hz), 8.93 (s, 1H).

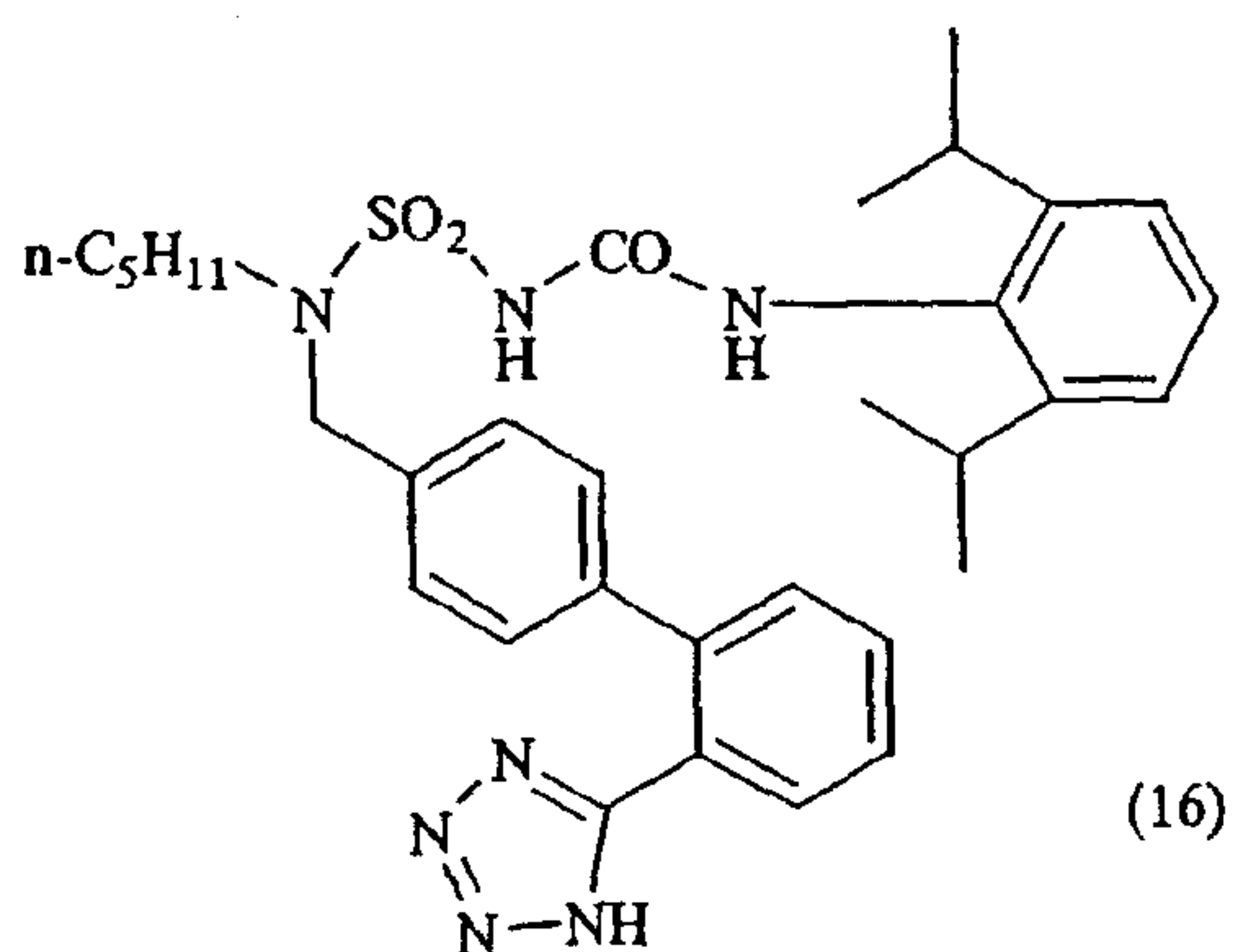
m.p. 69-73°C

IR (cm⁻¹) (KBr):

1449, 1521, 1610, 2932, 2957.

Example 13

N-[[[(2,6-Diisopropylphenyl)amino]carbonyl]-
amino]sulfonyl]-N-pentyl-N-[2'-[(1H-tetrazol-5-yl)-
1,1'-biphenyl-4-yl]methyl]amine



Chlorosulfonyl isocyanate (2.43 g) was dissolved in diethyl ether (10 mL), and at -15°C , the solution was added dropwise to a solution of 2,6-diisopropylaniline in diethyl ether (15 mL). After the mixture was stirred at the same temperature for 1 hour and 30 minutes, the resulting precipitates were collected by filtration and then washed with hexane. Colorless crystals so obtained were dried to afford [[[(2,6-diisopropylphenyl)amino]carbonyl]amino]sulfonyl chloride (4.11 g). Yield: 75%.

^1H -NMR (CDCl_3 , ppm):

1.22 (s, 6H), 1.25 (s, 6H), 3.13 (m, 2H),
7.20-7.39 (m, 3H), 7.76 (s, 1H)

m.p. $131-133^{\circ}\text{C}$

[[2'-[N-(Triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl] bromide (1.08 g), n-pentylamine (0.18 g) and potassium carbonate (0.45 g) were added to N,N-dimethylformamide (7 mL) and the mixture was stirred

at room temperature. Sixteen hours later, ethyl acetate (40 mL) was added. The organic layer was washed with brine (140 mL x 3 times). The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. To the residue, triethylamine (0.20 g) and tetrahydrofuran (11 mL) were added. Into the mixture, a solution of [[[2,6-diisopropylphenyl)amino]carbonyl]amino]sulfonyl chloride (4.11 g) in tetrahydrofuran (9 mL) was added dropwise at room temperature. Two hours later, ethyl acetate (80 mL) was added, and the resulting mixture was washed with water (80 mL) and brine (40 mL). The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane/ethyl acetate) to afford N-[[[[(2,6-diisopropylphenyl)amino]carbonyl]amino]sulfonyl]-N-pentyl-N-[[[2'-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine as a colorless amorphous mass (0.32 g). Yield: 20%.

¹H-NMR (CDCl₃, ppm):

0.83 (t, 3H, J=6.5Hz), 1.09-1.29 (m, 18H),
3.05-3.29 (m, 4H), 4.39 (s, 1H), 4.52 (s, 1H),
6.87-6.99 (m, 6H), 7.15-7.51 (m, 20H),
7.92 (dd, 1H, J=2.2, 5.4Hz).

N-[[[(2,6-Diisopropylphenyl)amino]carbonyl]amino]-sulfonyl]-N-pentyl-N-[[[2'-(triphenylmethyl)tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]amine (0.32 g) was dissolved in tetrahydrofuran (11 mL). At room temperature, 10% hydrochloric acid was added, and the resulting mixture was stirred. Seventeen hours later, ethyl acetate (60 mL) was added, and the mixture was washed with water (60 mL) and brine (60 mL). The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (chloroform/methanol) and further, purified by preparative thin-layer chromatography (chloroform/methanol). The thus-obtained crystals were suspended in diisopropyl ether. Crystals were collected by filtration, suspended in diethyl ether, and then collected again by filtration to afford the compound represented by the formula (16) (0.5 g).

$^1\text{H-NMR}$ (CDCl_3 , ppm):

0.97 (t, 3H, $J=6.8\text{Hz}$), 1.20 (s, 6H), 1.23 (s, 6H),
1.40-1.42 (m, 4H), 1.76-1.83 (m, 2H), 3.00-3.16 (m, 1H),
3.52 (t, 2H, $J=7.0\text{Hz}$), 4.52 (s, 2H), 4.61 (s, 1H),
7.13-7.31 (m, 5H), 7.39-7.65 (m, 6H).

IR (cm^{-1}) (KBr):

1517, 1521, 2962.

Test (Evaluation of ACAT inhibitory activity)

(1) Preparation of the enzyme (ACAT)

(1-1) Each rat was reared for about 3 weeks on high-cholesterol feed (solid feed prepared by adding 1% of cholesterol, 0.3% of sodium cholate, 0.1% of propylthiouracil and 3% of lard to a conventional feed MF).

(1-2) The liver of the rat reared in (1-1) was collected and shredded. 10 mM HEPES buffer (pH 7.4) which contained 0.25 M of sucrose and 1 mM of EDTA was added in an amount about three times as much as the weight of the liver to suspend the latter. The liver was then homogenized by a glass-Teflon homogenizer.

(1-3) The homogenized liver was centrifuged for 15 minutes under 22000 x g, and the supernatant was collected.

(1-4) The supernatant was centrifuged further for 60 minutes under 100000 x g. To the precipitates, 10 mM HEPES buffer (pH 7.4) containing 0.25 M of sucrose and 1 mM of EDTA therein was added in about a half of the volume used in (1-2), and the precipitates were suspended again.

(1-5) The suspension was again centrifuged for 60 minutes under 100000 x g, and the resulting precipitates were collected. 10 mM HEPES buffer (pH 7.4) containing

0.25 M of sucrose and 2 mM of DTT therein was added to suspend the precipitates. The suspension was stored at -80°C.

(2) Preparation of reagents

5 (2-1) Reaction buffer

0.75 M Phosphate buffer (pH 7.4), 800 μ M BSA and 100 mM DTT were mixed together in amounts of 1.0 mL, 0.5 mL and 0.1 mL, respectively, and ultrapure water (3.4 mL) was added.

10 (2-2) ACAT

A refrigerated sample of the enzyme was diluted with the "reaction buffer" described above to 2.5 mg protein/mL.

(2-3) Test samples

15 10^{-3} M Solutions of the compounds to be evaluated were prepared with methanol. 3×10^{-4} M Solutions were each prepared by adding 50% methanol (700 μ L) to the corresponding 10^{-3} M solution (300 μ L). 10^{-4} M Solutions were each prepared by adding 50% methanol (600 μ L) to the
20 corresponding 3×10^{-3} M solution (300 μ L). Up to 10^{-7} M solutions (serial 3-fold dilutions), the solutions were prepared by a similar procedure.

(3) Assay method of ACAT activity

(3-1) ACAT (20 μ L), the reaction buffer (20 μ L) and
25 desired one (5 μ L) of test samples were placed in a 1.5

mL test tube and incubated at 30°C for 10 minutes (the resulting solution will hereinafter be called "I").

(3-2) Reaction substrate [^{14}C]-oleoyl CoA (5 μL) was added into "I", and was allowed to react at 30°C for 5 4 minutes.

(3-3) Four minutes later, methanol (250 μL) was added to terminate the reaction, and then, a lipid mixture (40 μL), recovery-percentage-correcting [^3H]-cholesteryl oleate (10 μL) and hexane (700 μL) were added 10 into the test tube (this solution will hereinafter be called "II").

(3-4) "II" was stirred in a mixer, and the hexane layer (500 μL) was collected and transferred into another test tube (this solution will hereinafter be called 15 "III").

(3-5) "III" was evaporated to dryness, dissolved in chloroform (10 μL), and then spotted on a TLC plate. At that time, cholesteryl oleate was also spotted.

(3-6) After the spots were dried, they were 20 developed with a 85:15:0.5 mixture of hexane, diethyl ether and acetic acid as a developer solvent, and then stained with iodine. A plate section corresponding to the spot of cholesteryl oleate was cut out and placed in a vial. At the same time, the reaction substrate [^{14}C]- 25 oleoyl CoA (5 μL) and the recovery-percentage-correcting

[³H]-cholesteryl oleate (10 µL) were spotted on the TLC plate, and similarly, plate sections were cut out and placed in vials, respectively.

(3-7) Subsequently, "Aquazole II" (about 10 mL) was
5 added to the vials. After the vials were allowed to stand for a while, they were measured for [¹⁴C] and [³H] radioactivities.

Using the radioactivities, the % recovery of [¹⁴C]-cholesteryl oleate formed by the enzymatic reaction was
10 calculated from the radioactivity of [³H], and from the radioactivity of [¹⁴C], the yield of cholesteryl oleate was calculated. From the results, a concentration-response curve was prepared, and using the nonlinear least square method, a pIC₅₀ value was calculated and was
15 used as an index for ACAT inhibitory activity.

The pIC₅₀ values so calculated are shown in Table 1.

Table 1

Compound	PIC ₅₀
Compound of the formula (4)	5.72
Compound of the formula (5)	5.65
Compound of the formula (6)	5.52
Compound of the formula (7)	6.23
Compound of the formula (8)	5.49
Compound of the formula (9)	5.18
Compound of the formula (10)	6.57
Compound of the formula (11)	5.71
Compound of the formula (12)	6.40
Compound of the formula (13)	5.39
Compound of the formula (14)	5.23
Compound of the formula (15)	5.21
Compound of the formula (16)	5.51

It is understood from the above-described pIC₅₀ values that the compounds according to the present invention possess excellent ACAT inhibitory activities.

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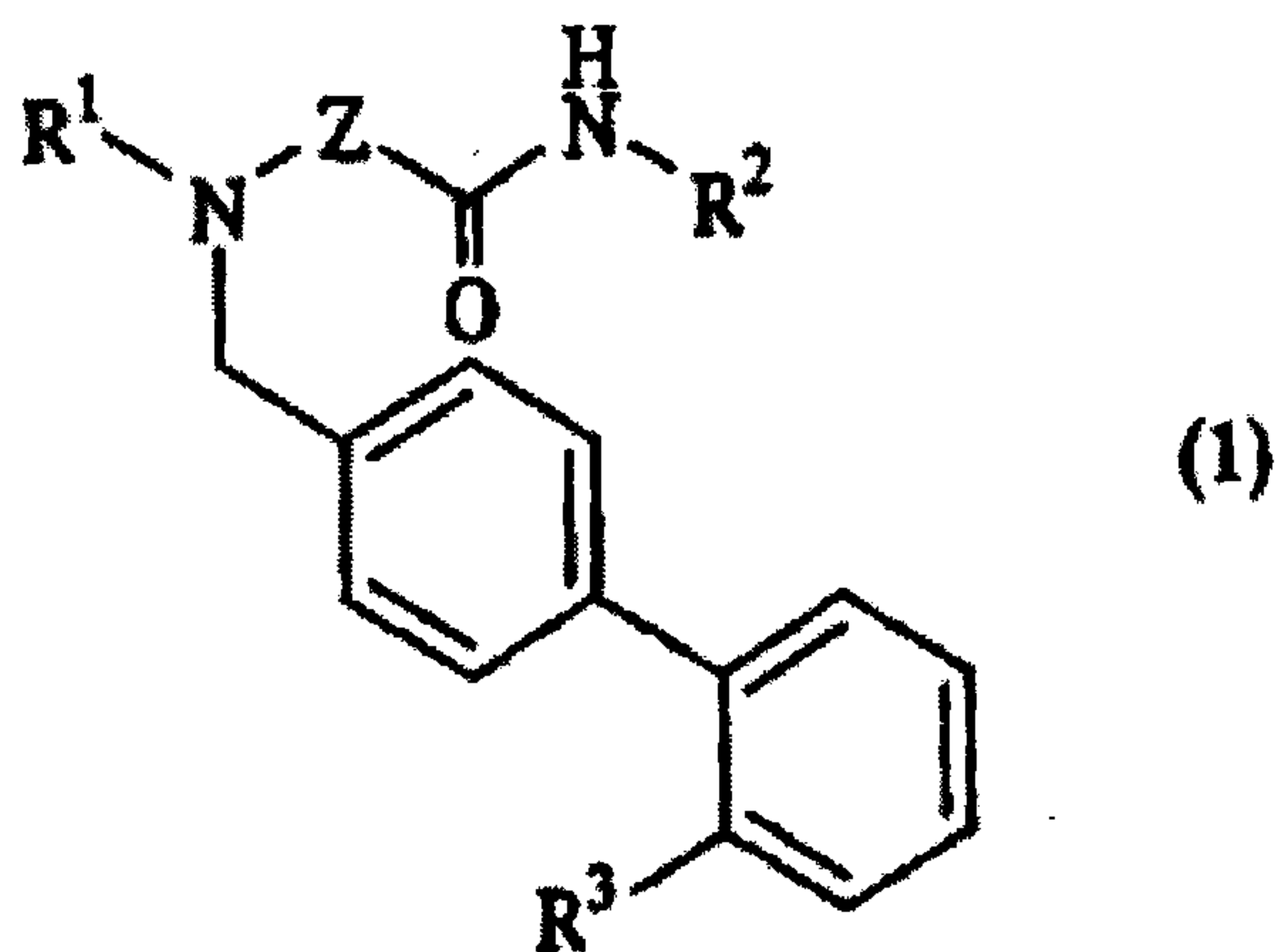
Industrial Applicability

The invention compounds (1) have excellent ACAT inhibitory activities and are useful as preventives and/or therapeutics for diseases caused by the enhancement of ACAT activity, for example, hypercholesterolemia, atherosclerosis and the like.

10

CLAIMS:

1. A biphenyl derivative or a salt thereof represented by the following formula (1):



wherein

R^1 represents a C_{5-7} alkyl group;

R^2 represents a C_{6-10} aromatic hydrocarbon which may be substituted by 1 to 3 substituents selected from halogen atoms, C_{1-5} alkyl groups, and C_{3-8} cycloalkyl group;

R^3 represents $-NHCOCF_3$, $-NHSO_2CF_3$ or $-SO_2NHCONHR^4$ in which R^4 represents a C_{6-10} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from halogen atoms and C_{1-5} alkyl groups, and

Z represents a single bond, a C_{1-4} alkylene group or $-SO_2NH-$.

2. A biphenyl derivative or a salt thereof as defined in claim 1, wherein

R^2 represents a phenyl group which may be substituted by 1 to 3 substituents selected from halogen atoms, C_{1-5} alkyl groups, and C_{5-7} cycloalkyl groups, and

R^4 represents a phenyl group which may be substituted by 1 to 3 substituents selected from halogen atoms and C_{1-5} alkyl groups.

3. An acyl-CoA:cholesterol acyltransferase inhibitor comprising as active ingredient a compound as defined in claim 1 or 2.

4. A medicine comprising as active ingredient a compound as defined in claim 1 or 2, which is a preventive and/or therapeutic for a disease caused by the enhancement of acyl-CoA:cholesterol acyltransferase activity.

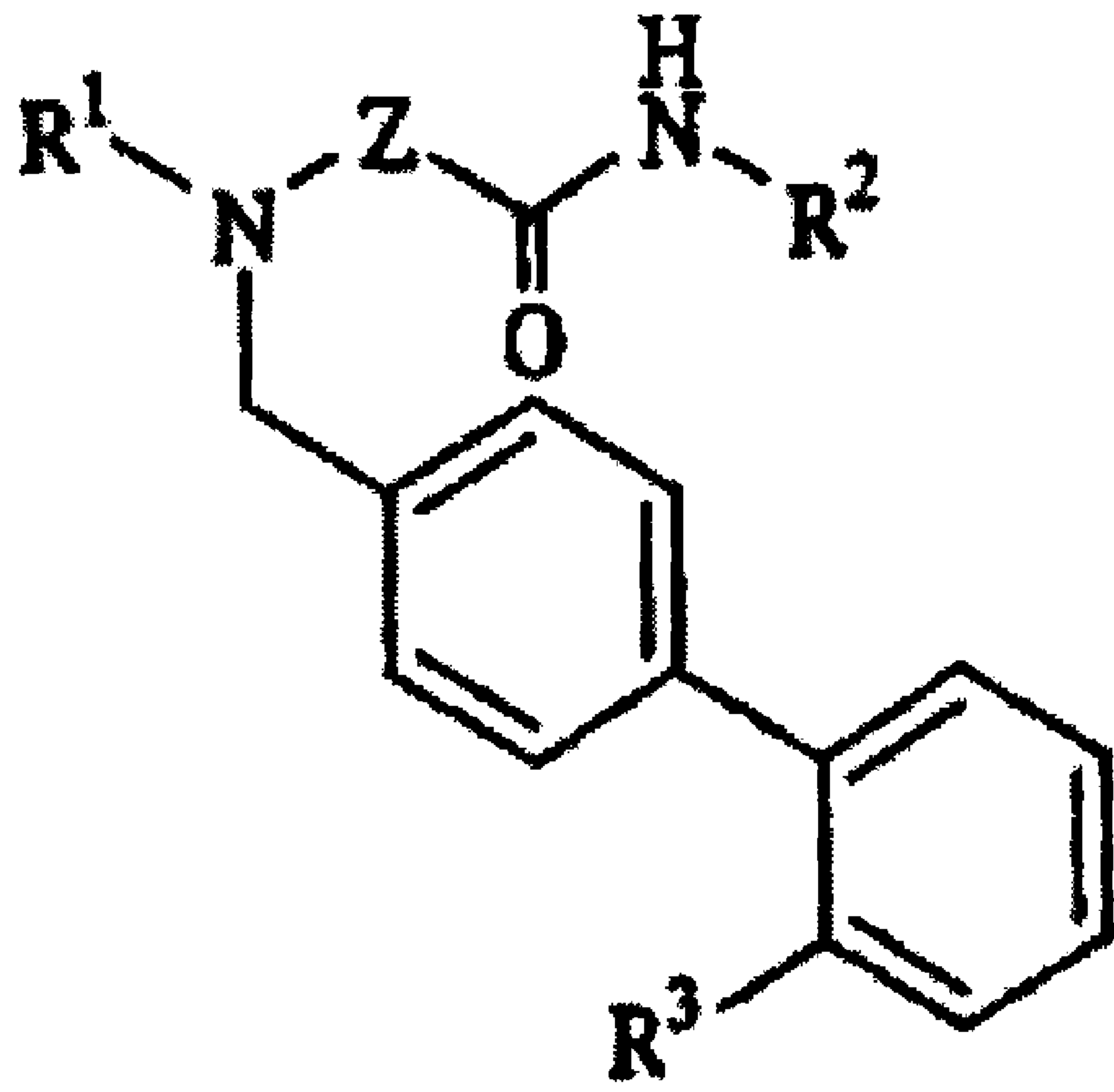
5 5. A medicine as defined in claim 4, which is a preventive and/or therapeutic for hypercholesterolemia or atherosclerosis.

6. A medicinal composition comprising a compound as defined in claim 1 or 2 and a pharmacologically acceptable carrier.

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7. Use of a compound as defined in claim 1 or 2 for the production of a medicine, wherein the medicine is a preventive and/or therapeutic for a disease caused by the enhancement of acyl-CoA:cholesterol acyltransferase activity.

15 8. Use of a compound as defined in claim 1 or 2 for the treatment of a disease caused by the enhancement of acyl-CoA:cholesterol acyltransferase activity.



(1)